of relatively increased hepatic arterial flow as a factor in the portal hypertension of cirrhosis associated with alcoholism. The investigations reported here were based upon their early studies and imply similar conclusions.

Moreno et al. (1) and Burchell et al. (9) have studied portal and hepatic arterial blood flow at laparotomy for portacaval anastomosis. They demonstrated an elevated setpoint for portal pressure of 40 cm of water since this pressure was found despite wide variation in portal blood flow (10). Attempts to correlate portal or hepatic arterial flow measured before or immediately after portacaval anastomosis with prognosis failed (9).

After our initial publications, Reynolds (50) attempted and failed to correlate wedge hepatic venous pressure measured after portacaval shunt with prognosis. His data were drawn retrospectively from studies of hepatic blood flow after portacaval shunt (51, 52) and, therefore, excluded patients who died early or had poor liver function that precluded blood flow measurement. Furthermore, the additional variable of inferior vena caval pressure was introduced by subtracting inferior vena caval pressure from the wedged hepatic venous pressure. Subsequently, Burchell et al. (53) retrospectively correlated a limited increment in hepatic arterial flow occurring after portacaval shunt with early death and encephalopathy. Patients with less than a 200 ml/min increase in hepatic arterial flow after diversion of portal flow by portacaval shunt accounted for 90% of the patients with encephalopathy or early mortality. Unfortunately, their hemodynamic data did not include residual intrahepatic venous pressure. Nevertheless, their retrospective analysis of intraoperative data and correlation of hemodynamic response to long-term prognosis confirms the data presented here.

The prolonged survival and absence of hepatic encephalopathy in patients with residual intrahepatic pressures >25 cm suggests that this is the minimum pressure required to sustain hepatic function. The elevated portal pressure set point of 40 cm, maintained in these patients before portacaval shunt when they were at risk for variceal hemorrhage, is on the average 15 cm greater. This 15-cm excess of portal pressure appears to increase the risk of variceal hemorrhage without serving an essential role in maintaining hepatic perfusion.

There is general agreement that prior hemodynamic measurements have been of "inconsistent value in selecting the proper shunt to be done or in predicting its physiologic outcome" (54). The preoperative hemodynamic classification presented here allows a prospective quantitative stratification of cirrhotic patients that identifies the type B patients who require portal blood flow to maintain hepatic perfusion and the type A patients who tolerate the loss of portal flow produced by portacaval anastomosis relatively well.

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KUR-MAG-DE004224

Page 2560 of 5977 Magnolia, Ex. 1004, Part 3 of 4

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KUR-MAG-DE004225

Page 2561 of 5977

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MINIREVIEW

Blood Culture Contamination: Persisting Problems and Partial Progress

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Although it has been widely appreciated for many years among physicians and microbiologists that blood cultures are among the most important laboratory tests performed in the diagnosis of serious infections (35), it has become equally apparent in more recent years that contaminated blood cultures are common (25, 42), enormously costly (3, 29), and frequently confusing for clinicians (1, 12, 14, 26). Clinical studies of bloodstream infections over 3 decades have provided guidelines for differentiating true pathogens from contaminants or organisms of unknown significance (14, 18, 41, 42); however, a true "gold standard" for differentiating pathogens from contaminants does not exist (4, 25). Moreover, the most common blood culture contaminants, coagulase-negative staphylococci (CoNS), which were almost always such several decades ago (18, 41), now are pathogens more frequently (19, 25, 26, 42), and judging the clinical significance of this group of microorganisms in blood has proven to be especially problematic (1, 11, 22, 24, 26, 42; S. J. Peacock, I. C. Bowler, and D. W. Crook., Letter, Lancet **346:**191-192, 1995). This review focuses on how pathogen-contaminant decisions are made, the phenomenon of increasing contamination of blood cultures, potential methods for addressing high contamination rates, and practical laboratory approaches to the workup of likely contaminants.

TOOLS FOR INTERPRETING THE CLINICAL SIGNIFICANCE OF POSITIVE BLOOD CULTURES

A number of clinical and laboratory tools have been proposed to aid microbiologists and physicians in deciding whether a blood isolate is a pathogen or a contaminant. These include the identity of the microorganism itself; clinical features such as fever, leukocytosis, and results of imaging studies (available to the clinician but usually not to the microbiologist); the proportion of blood culture sets positive as a function of the number of sets obtained; the time it takes for growth to be detected once a blood culture is received in the laboratory; and the number of culture vials within a culture set that show growth. Some of these tools have proven to be quite useful, whereas others have not.

The identity of the microorganism that grows from a positive blood culture provides important interpretative information. MacGregor and Beaty (18) documented this observation in the early 1970s, and studies by my colleagues and I confirmed and updated the earlier findings (41, 42). A predictive model that assessed multiple variables also documented microorganism identity as an independent predictor (4). Microorganisms that always or nearly always (>90%) represent true bacteremia or fungemia include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and other members of the *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Candida albicans* (42). Although published data from large studies with multiple isolates of the following organisms are lacking, it is my observation that *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, members of the *Bacteroides fragilis* group, *Candida* species other than *C. albicans*, and *Cryptococcus neoformans* always or virtually always represent true infection. In contrast, microorganisms such as *Corynebacterium* species, *Bacillus* species other than *B. anthracis*, and *Propionibacterium acnes* represent true bacteremia only rarely (42). Detection of CoNS, the most frequent of all blood culture isolates, can be especially vexing. These bacteria are most often contaminants, but they have taken on increased clinical importance as the etiologic agents of catheter-associated bacteremia and bacteremia in patients with vascular and other prostheses (19, 26, 42). Accordingly, one can no longer judge the clinical significance of a CoNS isolate solely on the basis of its identity. Similarly, the clinical significance of other microorganisms also cannot be judged based only their identity. For example, in a recent study, enterococci and viridans group streptococci were pathogens 78 and 38% of the time, respectively, and *Clostridium perfringens* most often (77%) was a contaminant, whereas other *Clostridium* species most often (80%) were pathogens (42).

The number of blood culture sets that grow microorganisms, especially when measured as a function of the total number obtained, has proved to be a useful aid in interpreting the clinical significance of positive blood cultures (18, 41, 42). In contrast to patients with endocarditis or other bloodstream infections, in whom all blood cultures or the majority thereof are positive, patients whose blood cultures grow contaminants usually have only a single blood culture (when two or more are obtained) that is positive (42). Although obvious, it bears emphasis that if only a single blood culture is obtained, the value

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KUR-MAG-DE005271

Page 2562 of 5977

of this tool ceases to exist; and this is but one reason (another being increased blood volume) that at least two blood culture specimens are recommended as standard practice (2, 23, 37). The value of obtaining more than a single blood culture is that it also assists in interpreting the clinical significance of positive results by virtue of the following calculation. If an institution has a baseline blood culture contamination rate of 3%, the probability of recovering the same organism in two culture sets from a patient, and of that organism being a contaminant, is less than 1 in 1,000 ($0.03 \times 0.03 = 0.0009$)!

A laboratory tool that has been used as an aid to differentiating clinically significant isolates from contaminants is assessment of the time necessary for microbial growth to occur (4). The underlying premise is that growth of pathogens, which are likely to be present in larger inocula, will be detected earlier than that of contaminants, which are likely to be present in much smaller quantities (18). Whereas this concept likely has validity, the degree of overlap in the detection times of true pathogens versus contaminants is such that this variable cannot be relied upon as a predictor of a true-positive culture (8). Moreover, with the wide use of continuously monitoring blood culture systems and the concomitant decrease in the time to detection of growth, the time difference between the detection of true pathogens and contaminants has been narrowed even further.

Some microbiologists and clinicians have used the number of culture bottles positive within a blood culture set as a guide to determine whether isolates represent true pathogens or contaminants. However, there now are published data, at least for CoNS, that show that this technique is not clinically useful (22; Peacock et al., letter). Although clinically significant CoNS may grow more often in multiple bottles within a set as opposed to a single bottle, and contaminants may more often grow in only one bottle of a set, the degree of overlap is such that for a given culture this information cannot predict clinical significance reliably (22; Peacock et al., letter). Accordingly, this criterion should not be used.

THE PARADOX OF INCREASING NUMBERS OF CONTAMINANTS

Despite numerous advances in blood culture methodology and systems in recent decades, some hospitals and laboratories have noted that an increasing proportion of blood culture isolates represent contamination compared with those in years past (42). There are several possible explanations for this unexpected observation. The newer continuously monitoring blood culture systems have improved algorithms for detecting microbial growth and may be detecting microorganisms present in low numbers that previously were missed. Moreover, several broth medium formulations such as the BACTEC Plus Resin media (Becton Dickinson, Sparks, Md.) and BacT/ALERT FN media (bioMerieux, Durham, N.C.) have been shown to have improved detection of staphylococci, including CoNS which most often are contaminants (10, 20, 28, 38, 40, 43, 45). Thus, the ability of new systems and media to detect these organisms, even when present in small numbers, may be responsible in part for the observed increase in the proportion of blood cultures with contaminants.

The increased use of central venous access catheters and utilization of these devices for the purpose of obtaining blood specimens for culture may also be contributing to the increased numbers of contaminated blood cultures. Several studies have documented increased contamination when blood cultures are obtained in this fashion (5, 6, 7; R. B. Sivadas, B. Vazirani, S. Mirrett, and M. P. Weinstein, Abstr. 101st Gen. Meet. Am. Soc. Microbiol., abstr. C10, 2001), perhaps because it is more difficult to sterilize these devices than it is the skin before blood is obtained. Although physicians and nurses may believe they are saving patients the pain of an extra needle stick when blood cultures are obtained from catheters rather than by venipuncture, they may actually be doing their patients and the health care system a disservice if contaminants are grown from the culture resulting in the need for even more cultures, other diagnostic studies, unnecessary antibiotic therapy, and the associated incremental costs of care.

Prior to the human immunodeficiency virus (HIV) era, blood cultures traditionally were obtained by a two-needle technique, using a sterile needle and syringe to perform the venipuncture, then changing to a second sterile needle before inoculating the blood culture vial. The purpose of the two-needle technique was to reduce the chance that skin microorganisms that might be present on the needle used for the venipuncture would be inoculated into the blood culture vial, thereby resulting in a contaminated blood culture. As the knowledge of HIV as a bloodborne pathogen and the risks of needle stick transmission of HIV became evident, several studies were undertaken to determine whether contamination rates would be affected if only one needle was used for both venipuncture and inoculation of blood culture vials (9, 15, 16). The results of each of these studies showed no significant increase in contamination rates when the single-needle technique was used. Subsequently, however, a meta-analysis suggested that single-needle blood cultures were associated with contamination rates of 3.7% compared with 2.0% when a two-needle technique was used (30). Since the current standard of care continues to be the single-needle technique in order to reduce the risk of occupational needle stick injuries, slightly higher contamination rates may have to be tolerated.

REDUCING THE NUMBER OF CONTAMINATED BLOOD CULTURES

Although it is not possible to achieve contamination rates of zero or even close to zero (31), there are potential means by which contamination can be reduced. These include the use of collection methods that increase the chances for sterility, for example, obtaining blood via venipuncture rather than from an intravascular catheter or using a two-needle rather than a single-needle technique, as has already been mentioned. For the reasons already stated, the two-needle method is unlikely to return to widespread use; however, laboratories and institutions can and should actively promote blood cultures obtained from venipuncture rather than intravascular devices as a means of practicing evidence-based medicine.

There is also evidence that some antiseptic preparations may be more efficacious than others in reducing contamination rates. Povidone iodine preparations require 1.5 to 2 min of contact time to produce their maximum antiseptic effect, whereas iodine tincture requires approximately 30 s (13). Health care

workers who obtain blood cultures are often in a hurry, do not understand the importance of antiseptic preparation contact time, and are less likely to wait 1.5 to 2 min as opposed to half a minute before obtaining blood. At least two studies have documented a significantly lower contamination rate using iodine tincture compared with an iodophor (17, 31). Another report compared the use of 0.2% chlorine peroxide and 10% povidone iodine and demonstrated lower contamination rates when chlorine peroxide was used (29). Lastly, an alcoholic solution of 0.5% chlorhexidine gluconate used as an antiseptic prior to blood culture was associated with significantly lower contamination rates compared with a standard povidone-iodine preparation (21).

Several published studies have shown that trained phlebotomists or blood culture teams can reduce contamination rates in individual institutions (27, 32, 36), and this has been confirmed in my own institution (Sivadas et al., 101st Gen. Meet. Am. Soc. Microbiol.). At a New York City, N.Y., community teaching hospital, the contamination rate for blood cultures drawn by a blood culture team using a commercially available blood culture prep kit was approximately 1% compared with rates of 4.8% for blood cultures drawn by resident physicians using the same method (36). The contamination rate when residents did not use the commercial prep kit was even higher (8.4%) (36). In a large survey of over 600 hospitals sponsored by the College of American Pathologists, median contamination rates for institutions in which more than half of all blood cultures were collected by resident physicians was 3.9%, compared with 2.2% in the remaining institutions (27). In a pilot study at my institution, contamination of blood cultures obtained by phlebotomists trained and monitored monthly by microbiology laboratory staff was 3%, compared with nearly 11% for blood cultures obtained by resident physicians, nondegree nursing assistants, and nurses (M. P. Weinstein, unpublished observation). Subsequently, my colleagues and I assessed contamination in a larger study and again found that samples collected by phlebotomists had lower contamination rates than those collected by nondegree nursing assistants, nurses, and resident physicians (the last of whose samples had the highest contamination rates) (Sivadas et al., 101st Gen. Meet. Am. Soc. Microbiol.).

Whether or not commercially marketed blood culture prep kits are associated with reduced blood culture contamination rates remains controversial. Some studies have shown reduced contamination (27, 36) with commercial prep kits, whereas others have shown no difference (44). The manufacturer of at least one commercial prep kit has offered ongoing in-service education for personnel obtaining blood cultures (M. P. Weinstein, personal observation), which itself may be associated with reduced contamination rates.

LABORATORY WORKUP OF LIKELY BLOOD CULTURE CONTAMINANTS

In the real world of clinical microbiology laboratories, nearly half of all positive blood cultures represent contamination (42). Complete laboratory workup of contaminant isolates is associated with increased technologist workload and institutional cost. Therefore, some laboratories have developed algorithms for dealing with this problem based, at least in part, on many of the studies reviewed in this article.

At the University of Iowa, for example, Richter et al. (25) tested, validated, and implemented an algorithm to minimize the workup of blood culture contaminants. CoNS, aerobic and anaerobic diphtheroids, *Micrococcus* spp., *Bacillus* spp., and viridans group streptococci are considered contaminants if certain criteria are met. If two or more blood cultures are obtained and only one is positive, the isolate is reported as a probable contaminant and susceptibility testing is not done unless the physician calls the laboratory. If only a single blood culture is obtained and grows one of the likely contaminants, a pathology resident reviews the patient's chart and judges the clinical significance of the isolate based on published data (42). Susceptibility testing is not done if the isolate is judged to be a contaminant. If two or more blood cultures are obtained and two cultures are positive within a 48-h period, one of two actions is taken. If the isolates are viridans group streptococci, they are presumed to be clinically significant and a full workup is done. If one of the other likely contaminants is present, the pathology resident reviews the patient's chart, and the laboratory workup proceeds according to the resident's judgment regarding clinical significance.

In my laboratory, a similar protocol is followed, but it is modified somewhat based on the fact that pathology residents are not always assigned to microbiology. The same microorganisms are considered likely contaminants. If two or more blood cultures are submitted and only one is positive, neither species identification nor susceptibility testing is done; the isolate is reported as a probable contaminant. If only one blood culture is submitted and it grows a likely contaminant, the workup is the same; the isolate is reported to be of indeterminate significance and the physician is advised to call the laboratory director if additional workup is needed. If two or more blood cultures grow a likely contaminant other than CoNS (see below) within a 48-h period, a full workup is done. If the isolates are the same, the identification and susceptibility results are reported. If the isolates are different, they are reported as probable contaminants without susceptibility results.

When two or more blood cultures grow CoNS, my laboratory undertakes species identification and reports susceptibility results. I find that the additional information assists in determining whether the isolates are clinically significant (12, 39). If the strains isolated have the same biochemical profile and antibiogram, it is probable that they are identical (although only molecular typing provides proof). This information increases the likelihood that the isolates represent clinically significant bacteremia, and identification and susceptibility results are reported to the clinician. However, if the biochemical profiles and antibiograms are not the same (i.e., two or more differences in biochemical results and susceptibilities [susceptible versus resistant]), the isolates are much more likely to represent contamination. In this instance, the laboratory reports that two different CoNS strains were identified, and susceptibility results are not provided. Although this technique has proven clinically useful in most circumstances, the algorithm is not foolproof. Two studies from the same center in Belgium have described polyclonal CoNS bacteremia (33, 34). Thus, in patients who have multiple positive blood cultures growing CoNS that appear to be different strains, the labora-

tory may need to perform additional testing if clinicians believe clinically significant infection is present.

As is apparent from the foregoing discussion, the current state of the art remains suboptimal. Although progress has been made, the interpretation of the clinical significance of microorganisms that are common blood culture contaminants and the technical effort and institutional costs associated with working up probable contaminants remain problematic. Gold standards for solving these problems still are elusive.

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	First Named Inventor	Bobby E. ROGERS
	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	4	6187347		2001-02-13	PATTERSON JAMES A	
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	10	4412548		1983-11-01	HOCH LOUIS	
	11	5222502		1993-06-29	KUROSE KATSUTOSHI	
	12	5520193		1996-05-28	SUZUKI ISSEI	
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	14	6569117		2003-05-27	ZIV DAVID	
	15	3741197		1973-06-26	SANZ M	
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	25	8540663		2013-09-24	DAVEY CHRISTOPHER T	
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	66	6106509		2000-08-22	LOUBSER PAUL G	
	67	3494352		1970-02-10	RUSSO RONALD D	
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	87	6860871		2005-03-01	KURACINA THOMAS C	
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	2	20030082074		2003-05-01	JURIK FRANKLIN A	
	3	20030185707		2003-10-02	IWAKI YOSHIHIDE	
	4	20040116830		2004-06-17	TRUDEAU WILLIAM M	
	5	20090299253		2009-12-03	HURSEY FRANCIS X	
	6	20130158506		2013-06-20	HARRIS ADRIENNE ROSE	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	069366-0580418_KUR2C06US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Application Number	18783088
	Filing Date	2024-07-24
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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Application Number	18783088
	Filing Date	2024-07-24
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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18783088
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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Attorney Docket Number	069366-0580418_KUR2C06US

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	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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	Attorney Docket Number	069366-0580418_KUR2C06US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Benjamin F. Hudson/	Date (YYYY-MM-DD)	2024-08-26
Name/Print	Benjamin F. Hudson	Registration Number	71,474

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE

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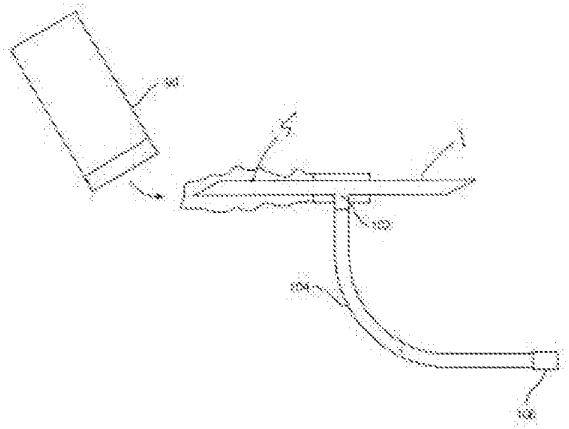
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Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

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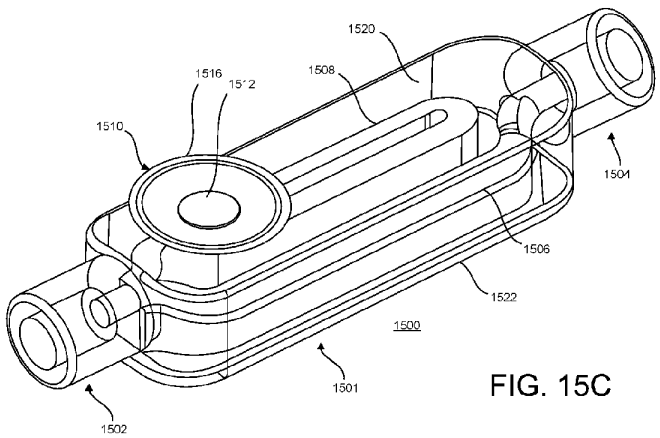


FIG. 15C

(57) Abstract: Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Non-Provisional Application Serial No. 15/140,443, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD" and U.S. Non-Provisional Application Serial No. 15/140,448, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD", both of which claim priority to U.S. Provisional Application Serial No. 62/196,797, filed on July 24, 2015 and titled "BLOOD CULTURE IMPROVEMENT SYSTEM AND METHOD"; U.S. Provisional Application Serial No. 62/238,636, filed on October 7, 2015 and titled "BLOOD SEQUESTRATION SYSTEM FOR NON-CONTAMINATED BLOOD SAMPLING"; and U.S. Provisional Application Serial No. 62/318,194, filed on April 4, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

[0002] Bacteraemia is the presence of microorganisms in the blood. Sepsis, on the other hand, is bacteraemia in the presence of clinical symptoms and signs such as fever, tachycardia, tachypnea and hypotension. Bacteraemia and sepsis are associated with a high mortality and an increased incidence and duration of hospital stay and associated costs. Many bacteraemias, sepsis, fungaemias and other pathogens actually occur within a hospital or other healthcare settings with catheters and venipunctures being a source of contamination as potential carriers of these pathogens.

[0003] Blood cultures are the standard test used to detect microbial pathogens related to bacteraemia and sepsis in a patient's blood. The term blood culture refers to a single venipuncture, either from a peripheral site or central or arterial line, with the blood inoculated into one or more blood culture bottles or containers. One bottle is considered a blood culture where two or more are considered a set. Multiple sets may be obtained from multiple venipunctures and are associated with different sites on the patient.

[0004] These methods allow for microbial identification and susceptibility testing to be performed, which is a critical component to managing sepsis, however the lack of rapid results and decreased sensitivity for fastidious pathogens has led to the development of improved systems and adjunctive molecular or proteomic testing.

[0005] Collection of blood samples for conducting blood cultures is a critical component of modern patient care and can either positively affect the patient outcome by providing an accurate diagnosis, or can adversely affect the outcome by prolonging unnecessary antimicrobial therapy, the length of hospital stays, and increasing costs.

[0006] One outcome of collection of blood cultures is contamination. Blood culture contamination can lead to a false positive culture result and/or significant increase in healthcare related costs. Sources of blood culture contamination include improper skin antisepsis, improper collection tube disinfection, and contamination of the initial blood draw which may then skew results.

[0007] Blood culture collection kits generally consist of a "butterfly" set, infusion set, or other type of venipuncture device as offered by companies like BD, Smiths, B. Braun and others, and aerobic and anaerobic blood culture bottles. Various different bottles are also available depending on the test requirements. These bottles are specifically designed to optimize recovery of both aerobic and anaerobic organisms. In conventional kits, a bottle used is known generally as a "Vacutainer," which is a blood collection tube formed of a sterile glass or plastic tube with a closure that is evacuated to create a vacuum inside the tube to facilitate the draw of a predetermined volume of liquid such as blood.

[0008] False positive blood cultures are typically a result of poor sampling techniques. They cause the use of antibiotics when not needed, increasing hospital costs and patient anxiety. Blood cultures are drawn from a needlestick into the skin, and then a Vacutainer is attached to capture a sample of blood. Contamination may occur from improper or incomplete disinfection of the skin area in and around the puncture site. It may also occur from the coring of the skin by the needle during insertion, with the cored skin cells and any associated contamination being pulled into the sample.

[0009] Blood flow through a hypodermic needle is laminar, and as such, a velocity gradient can be developed over the flow tube as a pressure drop is applied to the hypodermic needle. Either forceful aspiration of blood, or using a very small hypodermic needle, can cause lysis and a release of potassium from the red blood cells, thereby rendering the blood samples abnormal.

[0010] In other instances, some patients have delicate veins that can collapse under a pressure drop or vacuum, particularly as applied by a syringe's plunger that is drawn too quickly for the patient's condition. Since such condition is impossible to know beforehand, such vein collapses are a risk and very difficult to control.

[0011] Various strategies have been implemented to decrease blood culture contamination rates, e.g. training staff with regard to aseptic collection technique, feedback with regard to contamination rates and implementation of blood culture collection kits. Although skin antisepsis can reduce the burden of contamination, 20% or more of skin organisms are located deep within the dermis and are unaffected by antisepsis. Changing needles before bottle inoculation is not advisable as it increases the risk to acquire needle stick injuries without decreasing contamination rates.

[0012] Some conventional systems and techniques for reducing blood culture contamination include discarding the initial aliquot of blood taken from central venous catheters, venipunctures, and other vascular access systems. However, these systems require the user to mechanically manipulate an intravascular device, or require a complex series of steps that are difficult to ensure being followed.

SUMMARY

[0013] This document presents systems and methods for reducing blood culture contamination, lysing of cells, and vein collapse. In some implementations, a system and method can eliminate user variability in disinfection, and also eliminate the risk of skin cells getting into the blood culture sample. The systems and methods disclosed herein do not require a change in existing clinical processes, other than to potentially indicate when a vacutainer or other blood collection device (i.e., syringe) should be attached for drawing contaminant-free blood samples.

[0014] In some implementations of the systems and methods disclosed herein the withdrawal of blood is accomplished passively by use of the patient's own blood pressure, thereby reducing the risk of vein collapse and eliminating any additional user steps over current practice. The systems and methods can be applied to accommodate short-path direct stick or butterfly venipuncture systems. They can also be used with samples drawn through a catheter.

[0015] In one aspect, a blood sequestration device is presented. The blood sequestration device includes an inlet port and an outlet port. The blood sequestration device further includes a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port.

[0016] In another aspect, a blood sequestration device connected with a blood sampling pathway is described. The blood sampling pathway has a patient needle and a sample collection device. The blood sequestration device includes an inlet port connected with the patient needle, and a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, and an outlet port connected with a distal end of the sampling channel and with the sample collection device.

[0017] In yet another aspect, a blood sequestration device connected with a blood sampling system is described. The blood sampling system includes a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed and adapted for receiving an evacuated blood collection tube. The blood sequestration device includes an inlet port connected with the patient needle to receive the blood sample from the patient. The blood sequestration device further includes a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed by the evacuated blood collection tube. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a subsequent portion of the blood sample once the sample needle is unsealed by the evacuated blood collection tube. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel for conveying the subsequent portion of the blood sample to the sample needle.

[0018] In yet another aspect, a blood sample optimization system is disclosed and described. The blood sample optimization system includes a blood sampling system for accessing and acquiring one or more samples of a patient's blood, and a blood sequestration device for receiving and sequestering a first portion of the one or more samples of the patient's blood which might be contaminated by a venipuncture process and which could result in a false positive identification of a pathogen in the patient's blood.

[0019] The blood sampling system includes a patient needle configured for a venipuncture of a patient to access a sample of blood of a patient, a blood sampling pathway connected with the patient needle for conveying the sample of blood, and a sample needle configured for receiving an evacuated blood collection container to collect and contain a subsequent portion of the sample of blood.

[0020] In yet another aspect, a blood sequestration device is disclosed and described. In some implementations, the blood sequestration device can include an inlet port, an outlet port connected with the inlet port, and a sequestration chamber connected with the inlet port. The sequestration chamber can have a vent comprising an air permeable blood barrier.

[0021] The blood sequestration device is connected along the blood sampling pathway between the patient needle and the sample needle, and includes an inlet port for receiving the sample of blood. The blood sequestration device further includes a sequestration chamber connected with the inlet port for receiving a first amount of the sample of blood, the sequestration chamber having a vent comprising an air permeable blood barrier for sequestering at least a first portion of the first amount of the sample of blood. The blood sequestration device may further include a sampling channel having a proximal end connected with the inlet port, the sampling channel conveying a subsequent amount of the sample of blood to the evacuated blood collection container upon the sequestration chamber sequestering at least the first portion of the first amount of the sample of blood. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel, the outlet port for outputting the subsequent amount of the sample of blood.

[0022] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features and advantages will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other aspects will now be described in detail with reference to the following drawings.

[0024] FIG. 1 illustrates a blood sample optimization system.

[0025] FIG. 2 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0026] FIG. 3 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0027] FIG. 4 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0028] FIG. 5 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0029] FIG. 6 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0030] FIG. 7 is a flowchart of a method for optimizing a quality of a blood culture.

[0031] FIGS. 8A – 8E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with some implementations.

[0032] FIG. 9 illustrates a pathway splitter for use in a blood sequestrations system.

[0033] FIGS. 10A – 10D illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with alternative implementations.

[0034] FIGS. 11A – 11E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with other alternative implementations.

[0035] FIGS. 12A-12D illustrate a blood sample optimization system including a blood sequestration device in accordance with yet other alternative implementations.

[0036] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet another alternative implementations.

[0037] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample.

[0038] FIGS. 15A-15G illustrate a blood sequestration device and method of using the same, in accordance with yet another implementation.

[0039] FIGS. 16A-16D illustrate a blood sequestration device in accordance with yet another implementation.

[0040] FIGS. 17A – 17E illustrate a bottom member of a housing for a blood sequestration device.

[0041] FIGS. 18A – 18F illustrate a top member of a housing for a blood sequestration device.

[0042] FIGS. 19A and 19B illustrate a blood sequestration device having a top member mated with a bottom member.

[0043] FIG. 20 shows a blood sample optimization system including a blood sequestration device.

[0044] FIG. 21 illustrates a non-vented blood sequestration device using a wicking material chamber.

[0045] FIGS. 22A and 22B illustrate a material makeup of a filter for sequestering blood in a sequestration chamber of a blood sequestration device.

[0046] FIGS. 23A and 23B illustrate another implementation of a blood sequestration device that uses a vacuum force from a blood collection device.

[0047] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0048] This document describes blood sample optimization systems and methods for reducing or eliminating contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. In some implementations, a blood sample optimization system includes a patient needle for vascular access to a patient's bloodstream, a sample needle for providing a blood sample to a blood collection container, such as an evacuated blood collection container or tube like a Vacutainer™ or the like, or other sampling device, and a blood sequestration device located between the patient needle and the sample needle. The blood sequestration device includes a sequestration chamber for sequestering an initial, potentially contaminated

aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

[0049] FIG. 1 illustrates a blood sample optimization system in accordance with some implementations. The system includes a patient needle 1 to puncture the skin of a patient to access the patient's vein and blood therein. The system further includes a sample needle (i.e., a resealably closed needle for use with Vacutainers™ or the like) 5, which may be contained within and initially sealed by a resealable boot 10, a Luer activated valve, or another collection interface or device. The resealable boot 10 can be pushed aside or around the sample needle 5 by application of a Vacutainer™ bottle (not shown) for drawing the patient's blood. The system can further include a low volume chamber 30 that leads to the sample needle 5, but also includes an orifice or one or more channels 45 that lead to a sequestration chamber 55 formed by a housing 50.

[0050] The sequestration chamber 55 is a chamber, channel, pathway, lock, or other structure for receiving and holding a first aliquot of the patient's blood, which may be in a predetermined or measured amount, depending on a volume of the sequestration chamber 55. The first draw of blood typically contains or is more susceptible to containing organisms that cause bacteraemia and sepsis or other pathogens than subsequent blood draws. The sequestration chamber 55 can be a vessel encased in a solid housing, formed in or defined by the housing itself, or can be implemented as tubing or a lumen. The sequestration chamber 55, regardless how formed and implemented, may have a predetermined volume. In some implementations, the predetermined volume may be based on a volume of the patient needle, i.e. ranging from less than the volume of the patient needle to any volume up to or greater than 20 times or more of the volume of the patient needle. The predetermined volume of the sequestration chamber 55 may also be established to economize or minimize an amount of blood to be sequestered and disposed of.

[0051] The sequestration chamber 55 can be formed, contained or housed in a chamber housing 50, and can be made of plastic, rubber, steel, aluminum or other suitable material. For example, the sequestration chamber 55 could be formed of flexible tubing or

other elastomeric materials. The sequestration chamber 55 further includes an air permeable blood barrier 20 that allows air to exit the sequestration chamber 55. As used herein the term "air permeable blood barrier" means an air permeable but substantially blood impermeable substance, material, or structure. Examples may include hydrophobic membranes and coatings, a hydrophilic membrane or coating combined with a hydrophobic membrane or coating, mesh, a filter, a mechanical valve, antimicrobial material, or any other means of allowing air to be displaced from the sequestration chamber 55 as it is filled with blood. In various exemplary embodiments, an air permeable blood barrier may be formed by one or more materials that allow air to pass through until contacted by a liquid, such material then becomes completely or partially sealed to prevent or inhibit the passage of air and/or liquid. In other words, prior to contact with liquid, the material forms a barrier that is air permeable. After contact with a liquid, the material substantially or completely prevents the further passage of air and/or liquid.

[0052] The orifice or channel 45 can be any desired length, cross-sectional shape or size, and/or can be formed to depart from the low volume chamber 30 at any desired angle or orientation. The orifice or channel 45 may also include a one-way flap or valve 60 that maintains an initial aliquot of blood sample within the sequestration chamber 55. In some specific implementations, the orifice or channel 45 can include a "duck bill" or flapper valve 60, or the like, for one-way flow of blood from low volume chamber 30 to the sequestration chamber 55. The air permeable blood barrier 20 can also be constructed of a material that allows air to exit but then seals upon contact with blood, thereby not allowing external air to enter sequestration chamber 55. This sealing would eliminate the need for a valve.

[0053] Valve 60 can be any type of valve or closing mechanism. Chamber 30 is designed to hold virtually no residual blood, and can be designed to be adapted to hold or allow pass-through of a particular volume or rate of blood into sequestration chamber 55. Likewise, sequestration chamber 55 may also include any type of coating, such as an anti-microbial coating, or a coating that aids identification and/or diagnosis of components of the first, sequestered blood draw.

[0054] Housing 50 and 40 can be formed of any suitable material, including plastic, such as acrylonitrile butadiene styrene (ABS) or other thermoplastic or polymeric material, rubber, steel, or aluminum. The air permeable blood barrier 20 can include a color-providing substance, or other signaling mechanism, that is activated upon contact with blood from the initial blood draw, or when air displacement is stopped, or any combination of events with blood in the sequestration chamber 55. The air permeable barrier may also include an outer layer such as a hydrophobic membrane or cover that inhibits or prevents the inadvertent or premature sealing of the filter by an external fluid source, splash etc. Sequestration chamber 55 can also be translucent or clear to enable a user to visually confirm the chamber is filled.

[0055] FIG. 2 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown in FIG. 2, a sequestration chamber 55, or waste chamber, surrounds the patient needle 1, with an open-ended cuff or housing connected with the waste chamber and encircling the sample needle housing base and housing. The patient needle 1 and sample needle 5 are connected together by a boot 56, which forms a continuous blood draw channel therethrough. The boot 56 includes a single orifice or channel leading from the blood draw channel into sequestration chamber 55. The device can include more than one single orifice or channel, in other implementations. Each orifice or channel can include a one-way valve, and can be sized and adapted for predetermined amount of blood flow.

[0056] The sequestration chamber 55 includes an air permeable blood barrier. The filter can further include a sensor or indicator to sense and/or indicate, respectively, when a predetermined volume of blood has been collected in the sequestration chamber 55. That indication will alert a user to attach an evacuated blood collection tube or bottle, such as a Vacutainer™ to the sample needle 5. The housing for the sequestration chamber 55 can be any size or shape, and can include any type of material to define an interior space or volume therein. The interior space is initially filled only with air, but can also be coated with an agent or substance, such as a decontaminate, solidifying agent, or the like. Once evacuated blood collection tube is attached to the sample needle 5, blood will flow automatically into the patient needle 1, through the blood draw channel and sample needle 5, and into the bottle.

The sample needle 5 is covered by a resealable boot, coating or membrane that seals the sample needle when a blood collection bottle is not attached thereon or thereto.

[0057] FIG. 3 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is surrounded by a resealable boot or membrane, and is further connected with a patient needle 1. A blood flow channel is formed through the sample needle and the patient needle. The connection between the sample needle and patient needle includes a "T" or "Y" connector 102, which includes a channel, port or aperture leading out from the main blood flow channel to a sequestration chamber 104.

[0058] The T or Y connector 102 may include a flap or one-way valve, and have an opening that is sized and adapted for a predetermined rate of flow of blood. The sequestration chamber 104 can be formed from tubing, or be formed by a solid housing, and is initially filled with air. The sequestration chamber 104 will receive blood that flows out of a patient automatically, i.e. under pressure from the patient's own blood pressure. The sequestration chamber 104 includes an air permeable blood barrier 106, preferably at the distal end of tubing that forms the sequestration chamber 104, and which is connected at the proximal end to the T or Y connector 102. The T or Y connector 102 can branch off at any desired angle for most efficient blood flow, and can be formed so as to minimize an interface between the aperture and channel and the main blood flow channel, so as to minimize or eliminate mixing of the initial aliquot of blood with main blood draw samples.

[0059] In some alternative implementations, the sample needle may be affixed to a tubing of any length, as shown in FIG. 4, connecting at its opposite end to the T or Y connector 102. The sequestration chamber 104 can be any shape or volume so long as it will contain a predetermined amount of blood sample in the initial aliquot. The T or Y connector 102 may also include an opening or channel that is parallel to the main blood flow channel. The air permeable blood barrier may further include an indicator 107 or other mechanism to indicate when a predetermined amount of blood has been collected in the sequestration chamber, or when air being expelled reaches a certain threshold, i.e. to zero. The tubing can also include a clip 109 that can be used to pinch off and prevent fluid flow therethrough.

[0060] Once the air permeable blood barrier and primary chamber are sealed the initial aliquot of blood is trapped in the sequestration chamber 104, an evacuated blood collection tube, such as a Vacutainer™ bottle may be attached to the sample needle 5 to obtain the sample. The blood collection tube can be removed, and the sample needle 5 will be resealed. Any number of follow-on blood collection tubes can then be attached for further blood draws or samples. Upon completion of all blood draws, the system can be discarded, with the initial aliquot of blood remaining trapped in the sequestration chamber 104.

[0061] FIG. 5 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is connected with a patient needle by tubing. A "T" or "Y" connector 120 is added along the tubing at any desired location, and includes an aperture, port or channel leading to a sequestration chamber 204, substantially as described above.

[0062] FIG. 6 illustrates a blood sample optimization system in accordance with some alternative implementations, in which a sequestration chamber 304, formed as a primary collection channel, receives an initial aliquot of blood, and is provided adjacent to the blood sampling channel. The sequestration chamber 304 can encircle the blood sampling channel, the patient needle 1, and/or the sample needle 5. The primary collection channel can include a T or Y connector 120, or other type of aperture or channel. The sequestration chamber 304 includes an air permeable blood barrier, which can also include an indicator of being contacted by a fluid such as blood, as described above.

[0063] In some implementations, either the patient needle 1 or the sample needle 5, or both, can be replaced by a Luer lock male or female connector. However, in various implementations, the connector at a sample needle end of the blood sample optimization system is initially sealed to permit the diversion of the initial aliquot of blood to the sequestration chamber, which is pressured at ambient air pressure and includes the air outlet of the air permeable blood barrier. In this way, the system passively and automatically uses a patient's own blood pressure to overcome the ambient air pressure of the sequestration chamber to push out air through the air permeable blood barrier and displace air in the sequestration chamber with blood.

[0064] FIG. 7 is a flowchart of an exemplary method for optimizing the quality of a blood culture. At 702, a clinician places a needle into a patient's vein. At 704, blood then flows into a sequestration chamber, pushing the air in the sequestration chamber out of the sequestration chamber through an air permeable blood barrier. In some implementations, the volume of the sequestration chamber is less than 0.1 to more than 5 cubic centimeters (cc's), or more. The sequestration chamber is sized and adapted to collect a first portion of a blood sample, which is more prone to contamination than secondary and other subsequent portion of the blood sample or subsequent draws. Since the sequestration chamber has an air-permeable blood barrier through which air can be displaced by blood pushed from the patient's vein, such blood will naturally and automatically flow into the sequestration chamber before it is drawn into or otherwise enters into a Vacutainer or other bottle for receiving and storing a blood sample.

[0065] When the sequestration chamber fills, the blood will gather at or otherwise make contact with the air permeable blood barrier, which will inhibit or prevent blood from passing therethrough. At 706, when the blood comes into contact with the entire internal surface area of the air permeable blood barrier, the air permeable blood barrier is then closed and air no longer flows out or in. At 708, the clinician may be provided an indictor or can see the full chamber, to indicate the evacuated blood collection tube, such as a Vacutainer™ can be attached. The indicator can include visibility into the primary chamber to see whether it is full, the blood barrier changing color, for example, or other indicator. The fill time of the sequestration chamber may be substantially instantaneous, so such indicator, if present, may be only that the sequestration chamber is filled.

[0066] Prior to an evacuated blood collection tube being attached, communication between the needle, sampling channel, and the sequestration chamber is restricted by the sealing of the sequestration chamber blood barrier thereby not permitting air to reenter the system through the sequestration. Sealing the communication path could also be accomplished with a mechanical twist or other movement, a small orifice or tortuous pathway, eliminating the need for a separate valve or mechanical movement or operation by the clinician. At 710, once the evacuated blood collection tube is removed, the self-sealing membrane closes the sample needle, and at 712, additional subsequent evacuated blood

collection tubes may be attached. Once samples have been taken, at 714 the device is removed from the patient and discarded.

[0067] FIGS. 8A – 8E illustrate an exemplary blood sample optimization system 800 for non-contaminated blood sampling, in accordance with some implementations. The blood sample optimization system 800 includes an inlet port 802 that can be connected to tubing, a patient needle (or both), or other vascular or venous access device, and a pathway splitter 804 having a first outlet to a sequestration chamber tubing 806 and a second outlet to sample collection tubing 808. One or both of the sequestration chamber tubing 806 and the sample collection tubing 808 can be formed of tubing. In some implementations, the sequestration chamber tubing 806 is sized so as to contain a particular volume of initial blood sample. The sample collection tubing 808 will receive a blood sample once the sequestration chamber tubing 806 is filled. The sample collection tubing 808 can be connected to a Vacutainer™ base or housing 810, or other blood sample collection device.

[0068] The blood sequestration system 800 further includes a blood sequestration device 812 which, as shown in more detail in FIGS. 8B – 8D, includes a housing 818 that includes a sampling channel 820 defining a pathway for the non-contaminated sample collection tubing 808 or connected at either end to the non-contaminated sample collection tubing 808. The sampling channel 820 can be curved through the housing 818 so as to better affix and stabilize the housing 818 at a location along the non-contaminated sample collection tubing 808.

[0069] The blood sequestration device 812 further includes a sequestration chamber 822 connected with the sequestration chamber tubing 806 or other chamber. The sequestration chamber 822 terminates at an air permeable blood barrier 824. The air permeable blood barrier 824 can also include a coloring agent that turns a different color upon full contact with blood, as an indicator that the regular collection of blood samples (i.e. the non-contaminated blood samples) can be initiated. Other indicators may be used, such as a small light, a sound generation mechanism, or the like. In some implementations, the air permeable blood barrier is positioned at a right angle from the direction of sequestration chamber 822, but can be positioned at any distance or orientation in order to conserve space

and materials used for the housing 818. The housing 818 and its contents can be formed of any rigid or semi-rigid material or set of materials.

[0070] FIG. 9 illustrates a pathway splitter 900 for use in a blood sequestrations system, such as those shown in FIGS. 8A – 8E, for example. The pathway splitter 900 includes an inlet port 902, a main line outlet port 904, and a sequestration channel outlet port 906. The inlet port 902 can be connected to main tubing that is in turn connected to a patient needle system, or directly to a patient needle. The main line outlet port 904 can be connected to main line tubing to a blood sampling system, such as a vacutainer base or housing, or directly to such blood sampling system. The sequestration channel outlet port 906 can be connected to sequestration tubing for receiving and sequestering a first sample of blood, up to a measured amount or predetermined threshold. Alternatively, the sequestration channel outlet port 906 can be connected to a sequestration chamber. The sequestration channel outlet port 906 is preferably 20-70 degrees angled from the main line outlet port 904, which in turn is preferably in-line with the inlet port 902. Once the predetermined amount of initial blood sample is sequestered in the sequestration tubing or chamber, in accordance with mechanisms and techniques described herein, follow-on blood samples will flow into the inlet port 902 and directly out the main line outlet port 904, without impedance.

[0071] FIGS. 10A – 10D illustrate a blood sequestration device 1000 in accordance with alternative implementations. The blood sequestration device 1000 includes an inlet port 1002, a main outlet port 1004, and a sequestration channel port 1006. The inlet port 1002 can be connected to a patient needle or related tubing. The main outlet port 1004 can be connected to a blood sample collection device such as a Vacutainer, associated tubing, or a Luer activated valve, or the like. The sequestration channel port 1006 splits off from the main outlet port 1004 to a sequestration chamber 1008. In some implementations, the sequestration chamber 1008 is formed as a helical channel within a housing or other container 1001.

[0072] The sequestration chamber 1008 is connected at the distal end to an air permeable blood barrier 1010, substantially as described above. Air in the sequestration chamber 1008 is displaced through the air permeable blood barrier 1010 by an initial aliquot

of blood that is guided into the sequestration channel port 1006. Once the sequestration chamber 1008 is filled, further blood draws through the main outlet port 1004 can be accomplished, where these samples will be non-contaminated.

[0073] FIGS. 11A – 11E illustrate a blood sequestration device 1100 in accordance with other alternative implementations. The blood sequestration device 1100 includes an inlet port 1102, similar to the inlet ports described above, a main outlet port 1104, and a sequestration channel port 1106 that splits off from the main outlet port 1104 and inlet port 1102. The sequestration channel port is connected to a sequestration chamber 1108. In the implementation shown in FIGS. 11A – 11E, the blood sequestration device includes a base member 1101 having a channel therein, which functions as the sequestration chamber 1108. The channel can be formed as a tortuous path through the base member 1101, which is in turn shaped and formed to rest on a limb of a patient.

[0074] A portion of the sequestration chamber 1108 can protrude from the base member or near a top surface of the base member, just before exiting to an air permeable blood barrier 1110, to serve as a blood sequestration indicator 1109. The indicator 1109 can be formed of a clear material, or a material that changes color when in contact with blood.

[0075] In some implementations, the blood sequestration device 1100 can include a blood sampling device 1120 such as a normally closed needle, Vacutainer™ shield or other collection device. The blood sampling device 1120 can be manufactured and sold with the blood sequestration device 1100 for efficiency and convenience, so that a first aliquot of blood that may be contaminated by a patient needle insertion process can be sequestered. Thereafter, the blood sampling device 1120 can draw non-contaminated blood samples to reduce the risk of false positive testing and ensure a non-contaminated sample.

[0076] FIGS. 12A-12D illustrate a blood sample optimization system 1200 in accordance with yet other alternative implementations. The system 1200 includes a blood sequestration device 1202 for attaching to a blood sampling device 1204, such as a Vacutainer™ or other collection and sampling device. The blood sequestration device 1202 is configured and arranged to receive, prior to a Vacutainer™ container or vial being attached to a collection needle of the blood sampling device 1204, a first aliquot or amount of blood,

and sequester that first aliquot or amount in a sequestration channel of the blood sequestration device 1202.

[0077] In some implementations, the blood sequestration device 1202 can include an inlet port 1212, a main outlet port, and a sequestration channel port. The inlet port 1212 can be connected to a patient needle or related tubing. The main outlet port 1214 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port splits off from the main outlet port to a sequestration chamber 1218.

[0078] In some implementations, the sequestration chamber 1218 is formed as a channel within the body of a sequestration device 1202. The sequestration chamber 1218 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel. The sequestration device 1202 can include a housing or other containing body, and one or more channels formed therein. As shown in FIGS. 12A and 12B, the sequestration device 1202 includes a main body 1206 and a cap 1208. The main body 1206 is formed with one or more cavities or channels, which are further formed with one or more arms 1210 that extend from the cap 1208, and which abut the cavities or channels in the main body 1206 to form the primary collection port and main outlet port.

[0079] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet other alternative implementations. The system 1300 includes a blood sequestration device 1302 for attaching to a blood sampling device 1304, such as a Vacutainer or other bodily fluid collection and sampling device. The blood sequestration device 1302 is configured and arranged to receive, prior to a Vacutainer container or vial being attached to a collection needle of the blood sampling device 1304, a first aliquot or amount of blood, and to sequester that first aliquot or amount of blood or other bodily fluid in a sequestration channel of the blood sequestration device 1302.

[0080] The blood sequestration device 1302 includes a housing 1301 having an inlet port 1314, a main outlet port 1312, and a sequestration channel port 1316. The inlet port 1314 can be connected to a patient needle or associated tubing. The main outlet port 1312

can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port 1316 splits off from the main inlet port 1314 to a sequestration chamber 1318.

[0081] In the implementation shown in FIGS. 13A-D, the sequestration chamber 1318 is formed as a cavity or chamber within housing 1301 or formed by walls that define housing 1301. The sequestration chamber 1318 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel, that is defined by the cooperation and connection of housing 1301 with cap 1307 which cap 1307 can include a protrusion 1305 that provides one or more walls or directors for the winding channel in the sequestration chamber 1318. The protrusion 1305 from the cap 1307 can be straight or curved, and may have various channels, apertures or grooves embedded therein, and can extend from the cap 1307 any angle or orientation. When the cap 1307 is connected with the housing 1301 to complete the formation of the sequestration chamber 1318, the protrusion 1305 forms at least part of the winding channel to sequester a first aliquot or amount of blood or other bodily fluid in a sequestration channel formed in the sequestration chamber 1318 and by the winding channel.

[0082] The sequestration chamber 1318 includes an air permeable blood barrier 1310, substantially as described above. Air in the sequestration chamber 1318 is displaced through the air permeable blood barrier 1310 by an initial aliquot of blood that is provided into the sequestration chamber 1318 by the blood pressure of the patient. Once the sequestration chamber 1318 is filled and the air in the sequestration chamber 1318 displaced, the blood pressure of the patient will be insufficient to drive or provide further blood into the blood sequestration device 1302, and in particular the outlet port 1312, until a force such as a vacuum or other pressure, such as provided by the blood sample collection device like Vacutainer is provided to draw out a next aliquot or amount of blood or bodily fluid. Further blood draws through the main outlet port 1312 can be accomplished, where these samples will be non-contaminated since any contaminants would be sequestered in the sequestration chamber 1318 with the first aliquot of blood.

[0083] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system 1400 to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample. The blood sampling system 1400 includes a blood sequestration device 1401 that can be connected between a blood sample collection device 1403 and a patient needle (not shown). The blood sample collection device 1403 can be a Vacutainer or the like. The blood sequestration device 1401 includes an inlet port 1402 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1402 may also be connected with tubing or other conduit that is in turn connected with the patient needle.

[0084] The inlet port 1402 defines an opening into the blood sequestration device 1401, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more. The blood sequestration device 1401 further includes an outlet port 1404, which defines an opening out of the blood sequestration device 1401 and to the blood sample collection device 1403. The outlet port 1404 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device 1403. The outlet port 1404 can further include a connector device such as a threaded cap, a Luer connector (male or female), a non threaded interference or glue joint fitting for attachment of various devices including but not limited to tubing, or the like.

[0085] The blood sequestration device 1401 further includes a sampling channel 1406 between the inlet port 1402 and the outlet port 1404, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1406 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1406 has a substantially similar cross sectional area as the opening of the inlet port 1402. In other implementations, the sampling channel 1406 can gradually widen from the inlet port 1402 to the outlet port 1404.

[0086] The blood sequestration device 1401 further includes a sequestration chamber 1408 that is connected to and split off or diverted from the sampling channel 1406 at any point between the inlet port 1402 and the outlet port 1404, but preferably from a proximal end of the sampling channel 1406 near the inlet port 1402. The sequestration chamber 1408 is at first maintained at atmospheric pressure, and includes an air outlet 1412 at or near a distal end of the sequestration chamber 1408 opposite the diversion point from the sampling channel 1406. The air outlet 1412 includes an air permeable blood barrier 1412. As shown in FIG. 14B, the air permeable blood barrier 1412 can be overlaid with a protective cover 1416. The protective cover 1416 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1412 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1412 as the air is displaced from the sequestration chamber 1408 by blood being forced into the sequestration chamber 1408 by a patient's own blood pressure. In addition the protective cover 1416 can be constructed to inhibit or prevent accidental exposure of the air permeable blood barrier to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0087] As shown in FIGS. 14C and 14D, the sampling channel 1406 can be cylindrical or frusto-conical in shape, going from a smaller diameter to a larger diameter, to minimize a potential to lyse red blood cells. Likewise, the sampling channel 1406 is formed with a minimal amount of or no sharp turns or edges, which can also lyse red blood cells. The sampling channel 1406 splits off to the sequestration chamber 1408 near the inlet port 1402 via a diversion pathway 1409. The diversion pathway 1409 can have any cross-sectional shape or size, but is preferably similar to the cross-sectional shape of at least part of the inlet port 1402.

[0088] In some implementations, the sampling channel 1406 and the sequestration chamber 1408 are formed by grooves, channels, locks or other pathways formed in housing 1414. The housing 1414 can be made of plastic, metal or other rigid or semi-rigid material. The housing 1414 can have a bottom member that sealably mates with a top member. One or both of the bottom member and the top member can include the sampling channel 1406 and the sequestration chamber 1408, as well as the diversion pathway 1409, the inlet port 1402,

and the outlet port 1404. In some other implementations, one or more of the diversion pathway 1409, the inlet port 1402, and/or the outlet port 1404 can be at least partially formed by a cap member that is connected to either end of the housing 1414. In some implementations, the top member and the bottom member, as well as the cap member(s), can be coupled together by laser welding, heat sealing, gluing, snapping, screwing, bolting, or the like. In other implementations, some or all of the interior surface of the diversion pathway 1409 and/or sequestration chamber 1408 can be coated or loaded with an agent or substance, such as a decontaminate, solidifying agent, or the like. For instance, a solidifying agent can be provided at the diversion pathway 1409 such that when the sequestration chamber 1408 is filled and the initial aliquot of blood backs up to the diversion pathway 1409, that last amount of sequestered blood could solidify, creating a barrier between the sequestration chamber 1408 and the sampling channel 1406.

[0089] FIGS. 15A-15G illustrate a blood sequestration device 1500. The blood sequestration device 1500 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like.

[0090] The blood sequestration device 1500 includes an inlet port 1502 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1502 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1502 defines an opening into the blood sequestration device 1500, which opening may be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[0091] The inlet port 1502 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1502, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner,

the blood sequestration device 1500 can be fabricated and sold with the patient needle as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1500 at the time of blood draw or sampling.

[0092] The blood sequestration device 1500 further includes an outlet port 1504, which defines an opening out of the blood sequestration device 1500 and to the blood sample collection device. The outlet port 1504 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1500 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1500 at the time of blood draw or sampling.

[0093] The blood sequestration device 1500 further includes a sampling channel 1506 between the inlet port 1502 and the outlet port 1504, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1506 can be any sized, shaped or configured channel or conduit. In some implementations, the sampling channel 1506 has a substantially similar cross sectional area as the opening of the inlet port 1502. In other implementations, the sampling channel 1506 can gradually widen from the inlet port 1502 to the outlet port 1504.

[0094] The blood sequestration device 1500 further includes a sequestration chamber 1508 that is connected to and split off or diverted from the sampling channel 1506 at any point between the inlet port 1502 and the outlet port 1504, but preferably from a proximal end of the sampling channel 1506 near the inlet port 1502. In some implementations, the diversion includes a Y-shaped junction. The sequestration chamber 1508 is preferably maintained at atmospheric pressure, and includes a vent 1510 at or near a distal end of the sequestration chamber 1508. The vent 1510 includes an air permeable blood barrier 1512. FIG. 15C illustrates the blood sequestration device 1500 with the sequestration chamber 1508 filled with a first aliquot or sample of blood from the patient.

[0095] The air permeable blood barrier 1512 can be covered with a protective cover 1516. The protective cover 1516 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1512 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1512 as the air is displaced from the sequestration chamber 1508 by blood being forced into the sequestration chamber 1508 by a patient's own blood pressure. The protective cover 1516 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0096] FIG. 15B is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating an initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before a sample collection device is activated. FIG. 15G is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and bottom side of the housing 1501 of the blood sequestration device 1500, and illustrating the initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before the sample collection device is activated. FIG. 15C is another perspective view of the blood sequestration device 1500 from the inlet port 1502 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating blood now being drawn through sampling channel 1506 while the sequestered blood remains substantially in the sequestration chamber 1508.

[0097] FIG. 15D is a cross section of the blood sequestration device 1500 in accordance with some implementations, showing the housing 1501 that defines the sampling channel 1506 and the sequestration chamber 1508. FIGS. 15E and 15F illustrate various form factors of a housing for a blood sequestration device, in accordance with one or more implementations described herein.

[0098] The sequestration chamber 1508 can have a larger cross-sectional area than the sampling channel 1506, and the cross-sectional area and length can be configured for a predetermined or specific volume of blood to be sequestered or locked. The sampling

channel 1506 can be sized to be compatible with tubing for either or both of the patient needle tubing or the blood collection device tubing.

[0099] The housing 1501 can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIG. 15D, the housing 1501 includes a top member 1520 and a bottom member 1522 that are mated together, one or both of which having grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc. The top member 1520 can be connected with the bottom member 1522 by any mating or connection mechanism, such as by laser welding, thermal bonding, ultrasonic welding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like.

[00100] In some implementations, such as shown in FIG. 15D, the top member 1520 can include the grooves, channels, locks, conduits or other pathways, while the bottom member 1522 can include a protrusion 1524 that is sized and adapted to fit into at least one of the grooves, channels, locks or other pathways of the top member 1520. The protrusion 1524 can provide a surface feature, such as a partial groove or channel, for instance, to complete the formation of either the sampling channel 1506 and/or the sequestration chamber 1508. In some implementations, the protrusion 1524 can be formed with one or more angled sides or surfaces for a tighter fit within the corresponding groove, channel, lock or other pathway. In yet other implementations, both the top member 1520 and the bottom member can include grooves, channels, locks or other pathways, as well as one or more protrusions 1524.

[00101] In some implementations, the sampling channel 1506 and the sequestration chamber 1508 are formed by grooves, channels, locks or other pathways formed in housing 1501. The housing 1501 can be made of any suitable material, including rubber, plastic, metal or other material. The housing 1501 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1501 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1506 and/or the sequestration chamber 1508 is clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 1508 is first filled to the

extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1506. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1512 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00102] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will make its way into the input port 1502 blood sequestration device 1500 and flow into the sequestration chamber 1508 by following the path of least resistance, as the patient's own blood pressure overcomes the atmospheric pressure in the sequestration chamber 1508 to displace air therein through the air permeable blood barrier 1512. The patient's blood pressure will not be sufficient to overcome the air pressure that builds up in the sealed sampling channel 1506. Eventually, the sequestration chamber 1508, which has a predetermined volume, is filled with blood that displaces air through the air permeable blood barrier 1512. Once the blood hits the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1512 material to completely or partially seal the vent 1510. A signal or indication may be provided that the practitioner can now utilize the Vacutainer capsule or other blood sample collection device to acquire a next amount of the patient's blood for sampling. The blood in the sequestration chamber 1508 is now effectively sequestered in the sequestration chamber.

[00103] Upon filling the blood sequestration pathway 1508 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1506, possibly resulting in a small amount of blood moving past the diversion point to the sequestration chamber 1508 and into the sampling channel 1506, queuing up the uncontaminated blood to be drawn through the sampling channel 1506.

[00104] FIGS. 16-19 illustrate yet another implementation of a blood sequestration device. FIGS. 16A-16D illustrate a blood sequestration device 1600 that can be connected

between a blood sample collection device, such as an evacuated blood collection container like a Vacutainer™ (not shown), and a patient needle (not shown) and/or associated tubing. FIG. 17 illustrates a bottom member of the blood sequestration device, and FIG. 18 illustrates a top member of the blood sequestration device, which top member and bottom member can be mated together to form an input port, and output port, a sequestration chamber and a sampling channel, as explained more fully below. FIGS. 19A and B show the top member and bottom member mated together. It should be understood that FIGS. 16-19 illustrate one exemplary manner of constructing a blood sequestration device as described herein, and other forms of construction are possible.

[00105] Referring to FIGS. 16A – D, the blood sequestration device 1600 includes an inlet port 1602 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1602 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1602 defines an opening into the blood sequestration device 1600, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[00106] The inlet port 1602 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1602, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1600 at the time of blood draw or sampling.

[00107] The blood sequestration device 1600 further includes an outlet port 1604, which defines an opening out of the blood sequestration device 1600 and to the blood sample collection device. The outlet port 1604 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing

or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1600 at the time of blood draw or sampling.

[00108] The blood sequestration device 1600 further includes a sampling channel 1606 between the inlet port 1602 and the outlet port 1604, and a sequestration chamber 1608 that is connected to and split off or diverted from the sampling channel 1606 at any point between the inlet port 1602 and the outlet port 1604. The sampling channel 1606 functions as a blood sampling pathway once a first aliquot of blood has been sequestered in the sequestration chamber 1608. The sampling channel 1606 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1606 has a substantially similar cross sectional area as the opening of the inlet port 1602. In other implementations, the sampling channel 1606 can gradually widen from the inlet port 1602 to the outlet port 1604. The sequestration chamber 1608 may have a larger cross section to form a big reservoir toward the sequestration channel path so that the blood will want to enter the reservoir first versus entering a smaller diameter on the sampling channel 1606, as is shown more fully in FIGS. 17 and 19.

[00109] In some exemplary implementations, the diversion between the sampling channel 1606 and the sequestration chamber 1608 is by diverter junction 1607. Diverter junction 1607 may be a substantially Y-shaped, T-shaped, or U-shaped. In some preferred exemplary implementations, and as shown in FIG. 17A – 17B, the diverter junction 1607 is configured such that the flow out of the inlet port 1602 is preferentially directed toward the sequestration chamber 1608. The sequestration chamber 1608 may also include or form a curve or ramp to direct the initial blood flow toward and into the sequestration chamber 1608.

[00110] The sequestration chamber 1608 is preferably maintained at atmospheric pressure, and includes a vent 1610 at or near a distal end of the sequestration chamber 1608. The vent 1610 may include an air permeable blood barrier 1612 as described above.

[00111] The blood sequestration device 1600 can include a housing 1601 that can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIGS. 17A – 17D and FIGS. 18A – 18F, the housing 1601 includes a top member 1620 and a bottom member 1622 that are mated together. The blood sequestration device 1600 can also include a gasket or other sealing member (not shown) so that when the top member 1620 is mechanically attached with the bottom member 1622, the interface between the two is sealed by the gasket or sealing member. The FIGS. 17A – 17D illustrate a bottom member 1622 of a housing for a blood sequestration device 1600. The bottom member 1622 can include grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc., to form the sampling channel 1606, the sequestration chamber 1608, and diverter junction 1607.

[00112] The sequestration chamber 1608 may have a larger cross section than the sampling channel 1606 so that the blood will preferentially move into the sequestration chamber first versus entering a smaller diameter on the sampling channel 1606.

[00113] FIGS. 18A – 18F illustrate the top member 1620, which can be connected with the bottom member 1622 by any mating or connection mechanism, such as by laser welding, thermal bonding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like. The top member 1620 can include some or all of the grooves, channels, locks, conduits or other pathways to form the sampling channel 1606, the sequestration chamber 1608, and the diverter junction 1607. In yet other implementations, both the top member 1620 and the bottom member 1622 can include the grooves, channels, locks or other pathways.

[00114] In some implementations, the sampling channel 1606 and the sequestration chamber 1608 are formed by grooves, channels, locks or other pathways formed in housing 1601. The housing 1601 can be made of rubber, plastic, metal or any other suitable material. The housing 1601 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1601 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1606 and/or the sequestration chamber 1608 may be clear or translucent, giving a practitioner a

visual cue or sign that the sequestration chamber 1608 is first filled to the extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1606. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1612 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00115] As shown in FIGS. 18A – 18F, the air permeable blood barrier 1612 can be covered with, or surrounded by, a protective member 1616. The protective member 1616 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1612 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1612 as the air is displaced from the sequestration chamber 1608. In some implementations, the protective member 1616 includes a protrusion that extends up from a top surface of the top member 1620 and around the air permeable blood barrier 1612. The protective cover 1616 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[00116] In use, the blood sequestration device 1600 includes a sampling channel 1606 and a sequestration chamber 1608. Both pathways are initially air-filled at atmospheric pressure, but the sampling channel 1606 is directed to an output port 1604 that will be initially sealed by a Vacutainer or other such sealed blood sampling device, and the sequestration chamber 1608 terminates at a vent 1610 to atmosphere that includes an air permeable blood barrier 1612.

[00117] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will pass through input port 1602 of blood sequestration device 1600. This initial volume of potentially contaminated blood will preferentially flow into the sequestration chamber 1608 by finding the path of least resistance. The patient's own blood

pressure overcomes the atmospheric pressure in the vented sequestration chamber 1608 to displace air therein through the air permeable blood barrier 1612, but is not sufficient to overcome the air pressure that builds up in the sealed sampling channel 1606. In various exemplary embodiments, the sequestration chamber 1608 and sampling channel 1606 can be configured such that the force generated by the patient's blood pressure is sufficient to overcome any effect of gravity, regardless of the blood sequestration device's orientation.

[00118] Eventually, the sequestration chamber 1608 fills with blood that displaces air through the air permeable blood barrier 1612. Once the blood contacts the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1612 material to completely or partially seal the vent 1610. A signal or indication may be provided that the practitioner can now utilize the Vacutainer or other blood sampling device.

[00119] Upon filling the blood sequestration pathway 1608 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1606, possibly resulting in a small amount of blood moving past the diversion point into the sampling channel 1606, queuing up the uncontaminated blood to be drawn through the sampling channel 1606.

[00120] FIG. 19A is a side view, and FIG. 19B is a cross-sectional view, of the blood sequestration device 1600, illustrating the top member 1620 mated with the bottom member 1622.

[00121] FIG. 20 shows a blood sample optimization system 2000 that includes a patient needle 2002 for vascular access to a patient's bloodstream, a blood sample collection device 2004 to facilitate the collecting of one or more blood samples, and a conduit 2006 providing a fluid connection between the patient needle 2002 and the blood sample collection device 2004. In some implementations, the blood sample collection device 2004 includes a protective shield that includes a sealed collection needle on which a sealed vacuum-loaded container is placed, which, once pierced by the collection needle, draws in a blood sample under vacuum pressure or force through the conduit 2006 from the patient needle 2002.

[00122] The blood sample optimization system 2000 further includes a blood sequestration device 2008, located at any point on the conduit 2006 between the patient needle 2002 and the blood sample collection device 2004 as described herein.

[00123] FIG. 21 illustrates a non-vented blood sequestration device 2100 using a wicking material chamber. The blood sequestration device 2100 includes a housing 2101 that has a sampling channel 2104 that is at least partially surrounded or abutted by a sequestration chamber 2102 that is filled with a wicking material. An initial aliquot of blood is drawn in from the patient needle into the sampling channel 2104 where it is immediately wicked into the wicking material of the sequestration chamber 2102. The wicking material and/or sequestration chamber 2102 is sized and adapted to receive and hold a predetermined amount of blood, such that follow-on or later blood draws pass by the wicking material and flow straight through the sampling channel 2104 to a sampling device such as a Vacutainer. The wicking material can include a substance such as a solidifier, a decontaminate, or other additive.

[00124] As described herein, an air permeable blood barrier may be created using a wide variety of different structures and materials. As shown in FIGS. 22A and B, an air permeable blood barrier 2202 of a blood sequestration device 2200 can include a polymer bead matrix 2204, in which at least some beads are treated to make them hydrophilic. The air permeable blood barrier 2202 further includes a self-sealing material 2206, such as carboxymethyl cellulose (CMC) or cellulose gum, or other sealing material. The air permeable blood barrier 2202 can further include voids 2208 that permit air flow before contact or during partial contact with a fluid such as blood. As shown in FIG. 22B, contact with a fluid causes the self-sealing material 2206 to swell and close off the voids 2208, occluding air flow through the voids 2208 and creating a complete or partial seal.

[00125] FIGS. 23A and B illustrate yet another implementation of a blood sequestration device 2300, having an inlet port 2302 to connect with a patient needle, an outlet port 2304 to connect with a blood sample collection device, a sequestration chamber 2306, and a sampling channel 2308 that bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be

sequestered. The sequestration chamber 2306 includes a hydrophobic plug 2312 at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302. A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. A small amount of blood may make its way into the sampling channel 2308, which is initially closed off by valve 2308. Upon release of the valve 2308, and under further force of the vacuum or other force, follow-on amounts of blood will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 toward the outlet port 2304 and to the collection device.

[00126] The sampling channel 2308 can have any suitable geometry and can be formed of plastic tubing or any other suitable material. Valve 2308 can be a clip or other enclosing device to pinch, shunt, bend or otherwise close off the sampling channel before the initial aliquot of blood is sequestered in the sequestration chamber 2306.

[00127] Although a variety of embodiments have been described in detail above, other modifications are possible. Other embodiments may be within the scope of the following claims.

CLAIMS

1. A blood sequestration device comprising;

an inlet port;

an outlet port;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

2. The blood sequestration device in accordance with claim 1, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

3. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber includes a sequestration channel defined in the housing.

4. The blood sequestration device in accordance with claim 3, further comprising a blood sampling pathway connected with the inlet port, and wherein the inlet port defined by the housing has a cross-sectional geometry consistent with the blood sampling pathway.

5. The blood sequestration device in accordance with claim 3, wherein the sampling channel defined by the housing has a cross-sectional geometry consistent with the inlet port.

6. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

7. The blood sequestration device in accordance with claim 3, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

8. A blood sequestration device connected with a blood sampling pathway having a patient needle and a sample collection device, the blood sequestration device comprising;

an inlet port connected with the patient needle;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port; and

an outlet port connected with a distal end of the sampling channel and with the sample collection device; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

9. The blood sequestration device in accordance with claim 8, wherein the inlet port is connected with the patient needle via a first portion of the blood sampling pathway.

10. The blood sequestration device in accordance with claim 8, wherein the outlet port is connected with the sample collection device via a second portion of the blood sampling pathway.

11. The blood sequestration device in accordance with claim 8, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

12. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber includes a sequestration channel defined in the housing.

13. The blood sequestration device in accordance with claim 12, wherein the sequestration channel has a proximal end connected with the inlet port, and a distal end having the vent comprising an air permeable blood barrier.

14. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

15. The blood sequestration device in accordance with claim 8, wherein the sampling channel has a substantially uniform cross-sectional geometry that is consistent with the blood sampling pathway.

16. The blood sequestration device in accordance with claim 15, wherein the sequestration chamber includes a sequestration chamber that has a cross-sectional area that is larger than the cross-sectional geometry of the sampling channel.

17. A blood sequestration device connected with a blood sampling system comprising a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed, the blood sequestration device comprising;

an inlet port connected with the patient needle to receive the blood sample from the patient;

a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed; and

a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a second portion of the blood sample once the sample needle is unsealed;

an outlet port connected with a distal end of the sampling channel for conveying the second portion of the blood sample to the sample needle; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

18. The blood sequestration device in accordance with claim 17, wherein the sequestration chamber is at ambient air pressure, and wherein the sequestration chamber receives the first portion of the blood sample by blood pressure of the patient overcoming the ambient air pressure in the sequestration chamber.

19. The blood sequestration device in accordance with claim 17, wherein the sampling channel causes the second portion of the blood sample to bypass the sequestered first portion of blood, and exit the outlet port for conveyance to a blood collection device.

20. The blood sequestration device in accordance with claim 17, wherein the air permeable blood barrier includes an air permeable material that seals upon contact with blood.

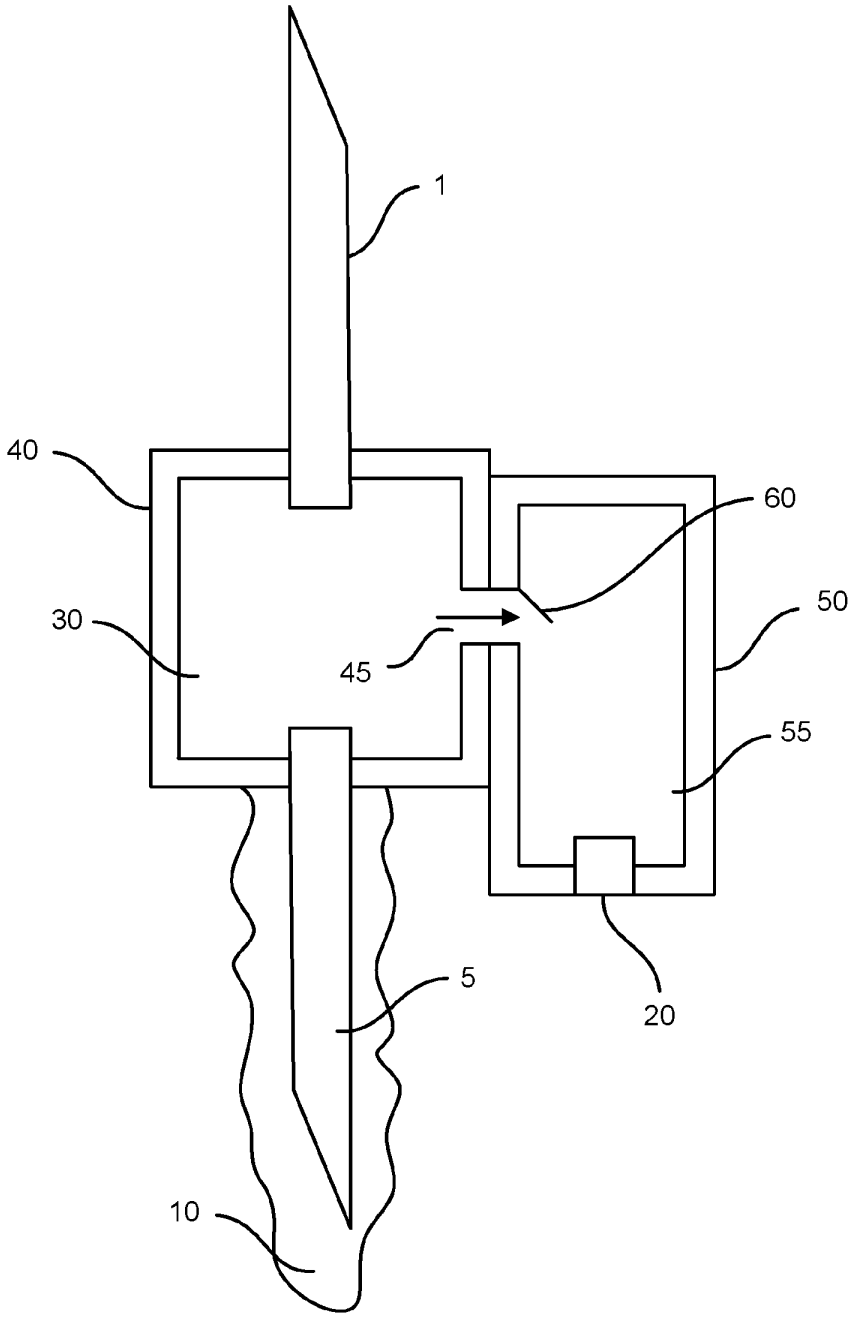


FIG. 1

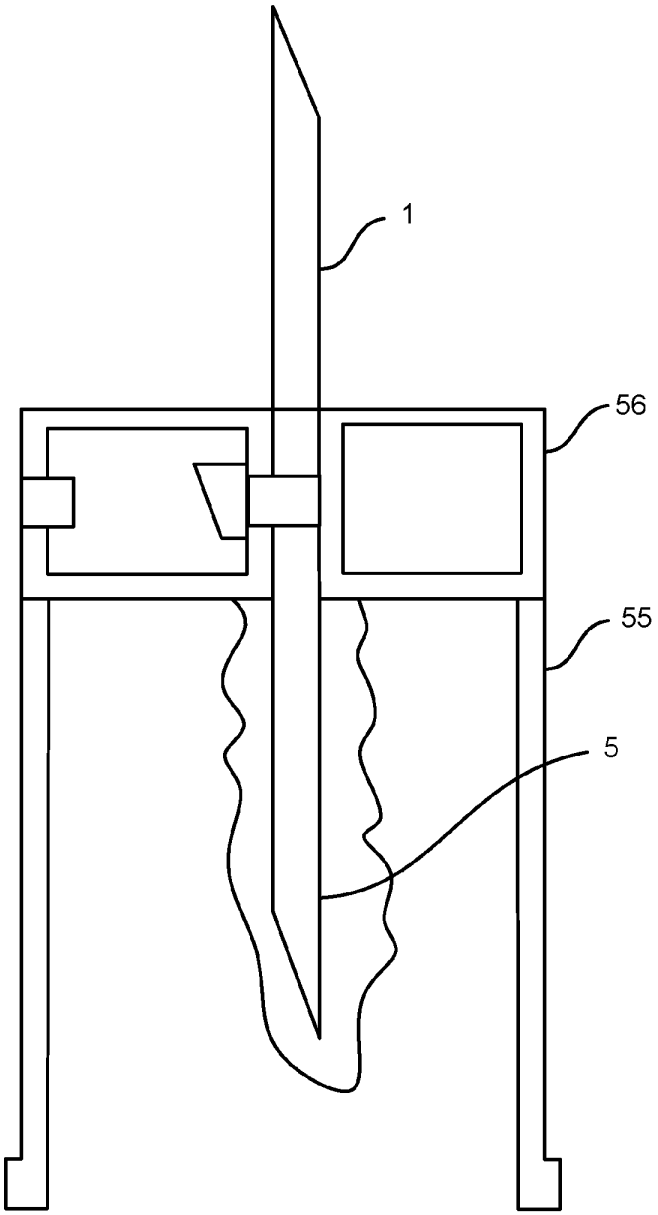


FIG. 2

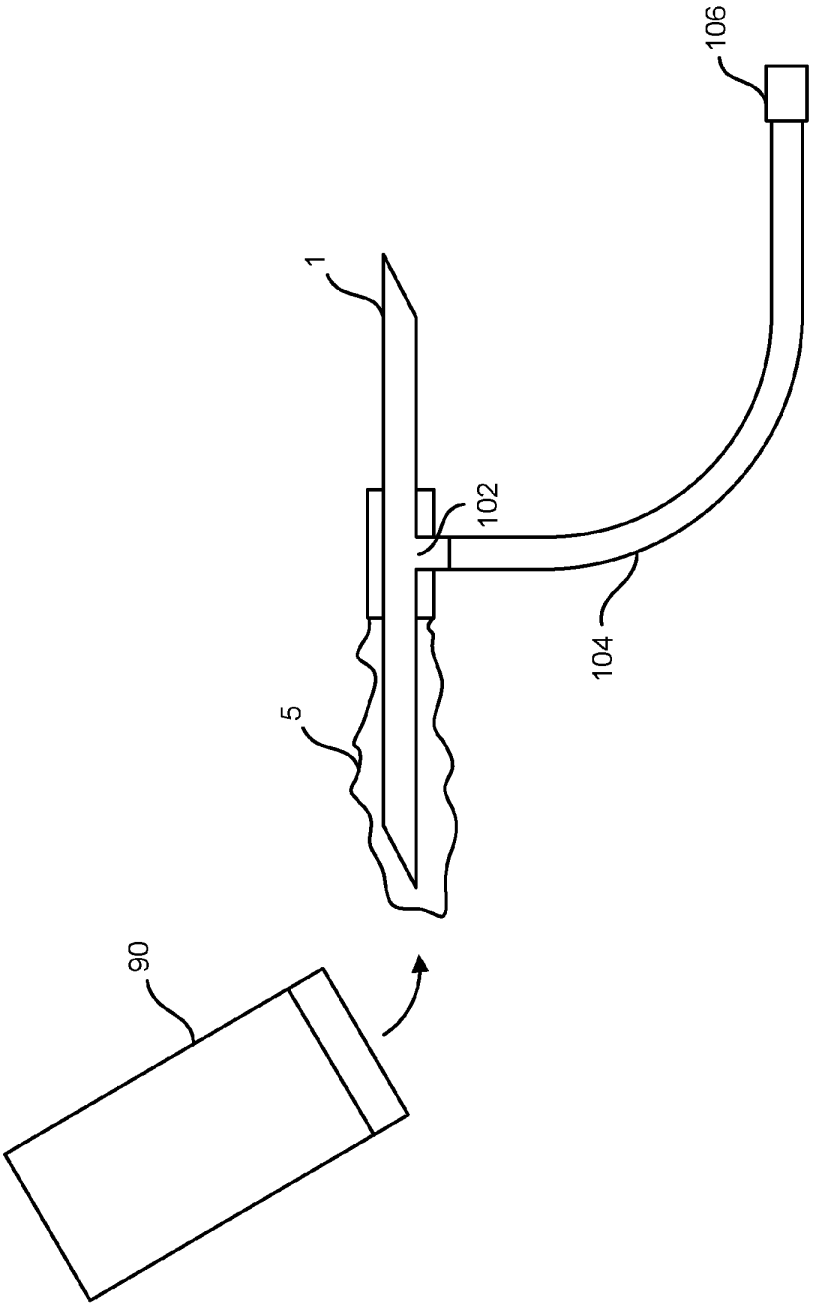


FIG. 3

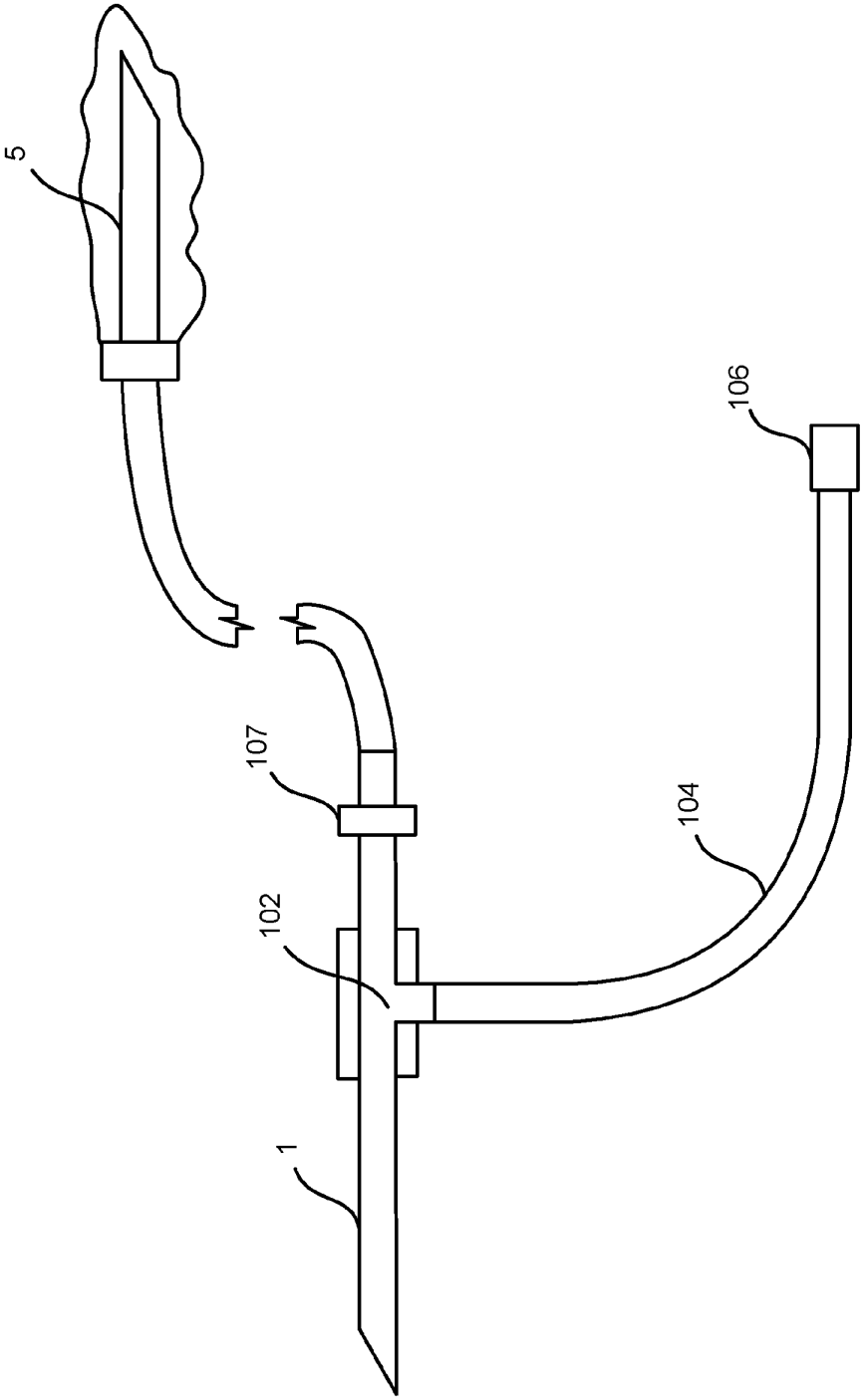


FIG. 4

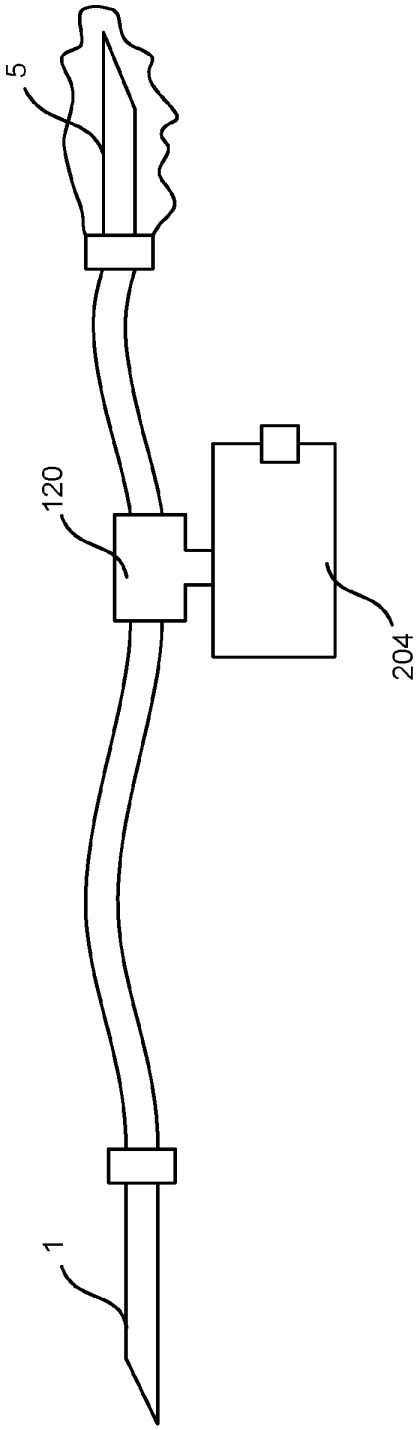


FIG. 5

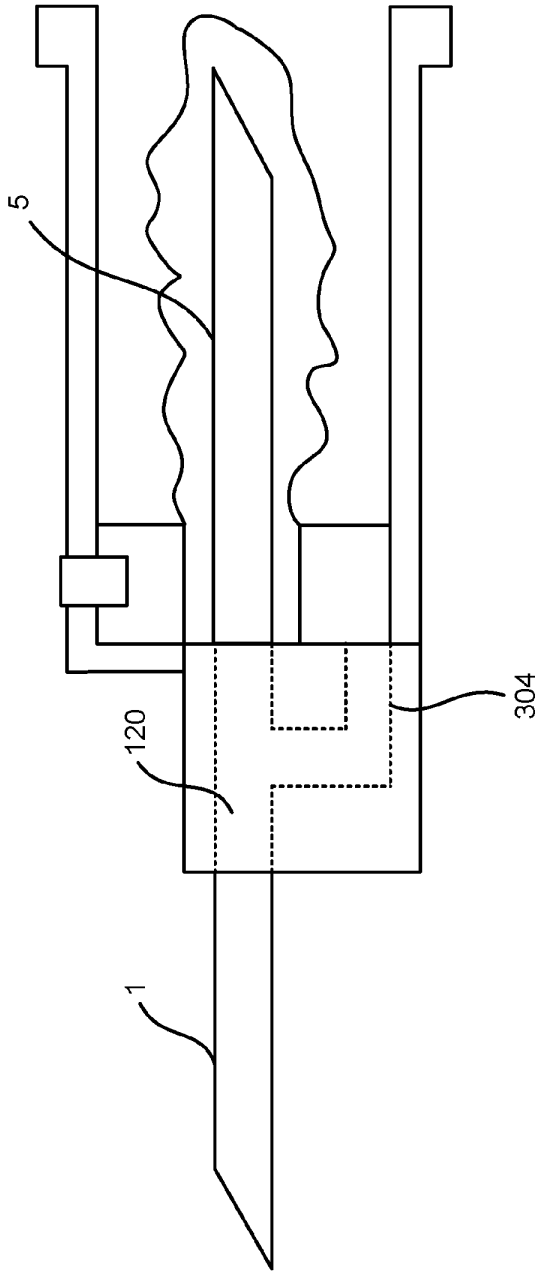


FIG. 6

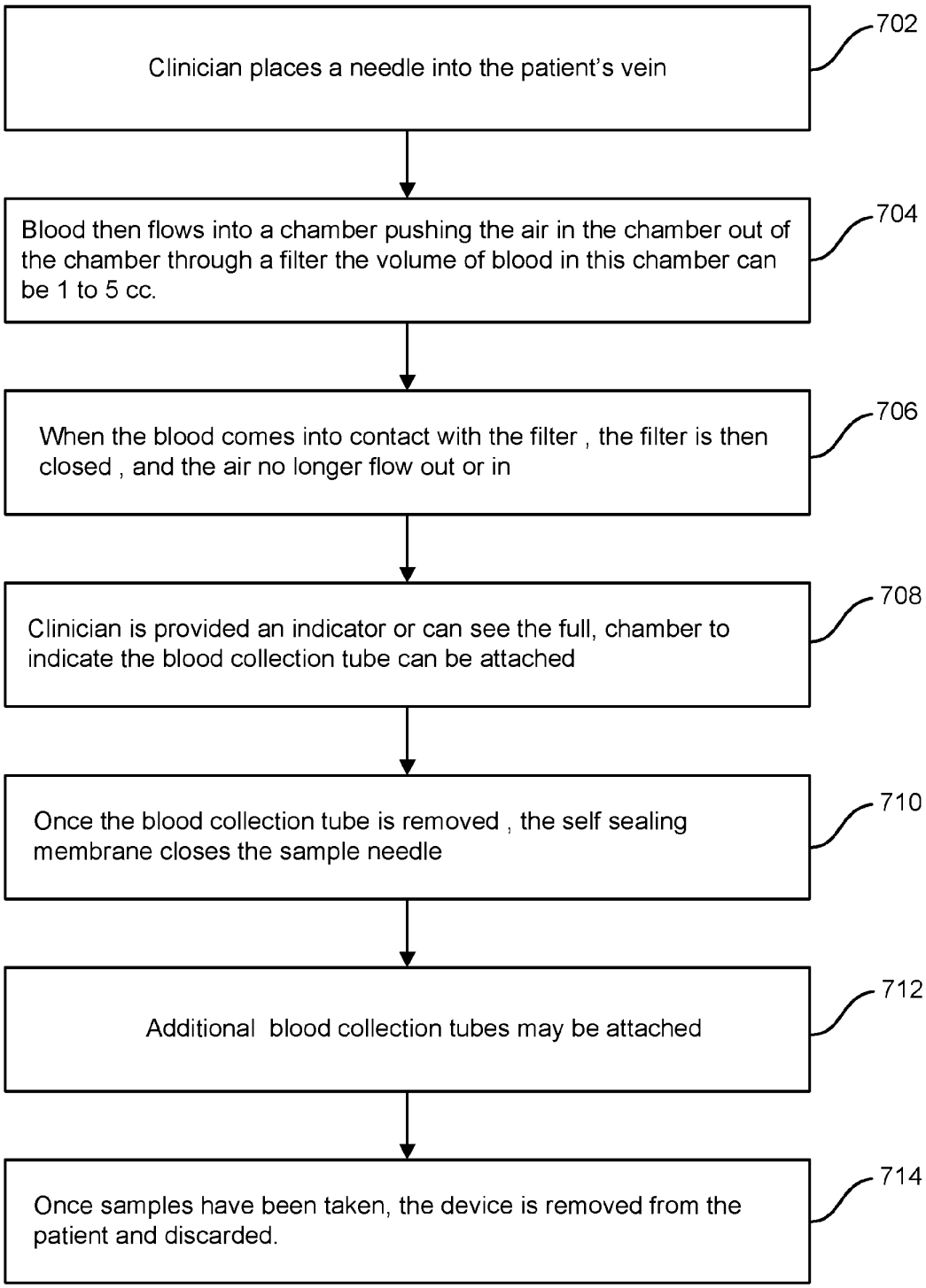

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air no longer flow out or in
706
Clinician is provided an indicator or can see the full, chamber to indicate the blood collection tube can be attached
708
Once the blood collection tube is removed , the self sealing membrane closes the sample needle
710
Additional blood collection tubes may be attached
712
Once samples have been taken, the device is removed from the patient and discarded.
714

FIG. 7

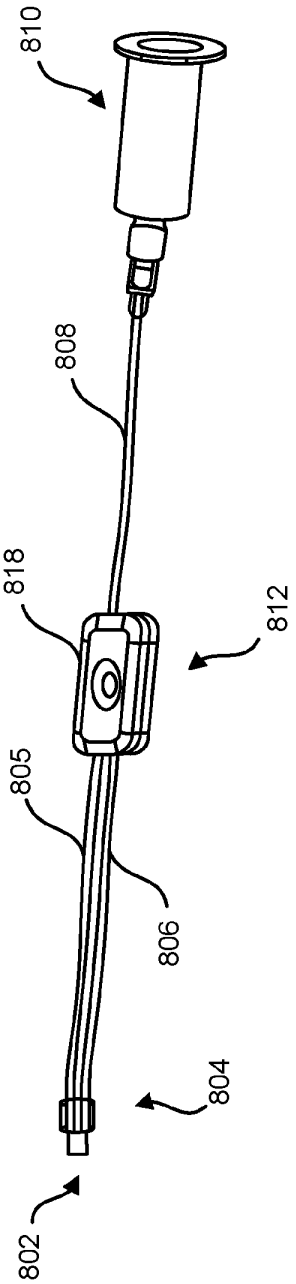


FIG. 8A

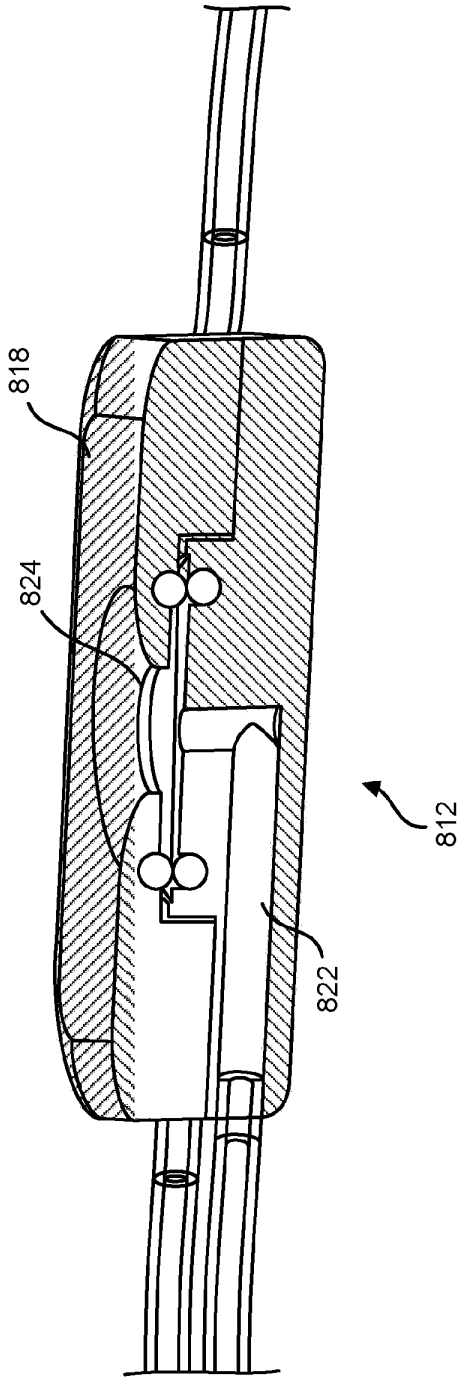


FIG. 8B

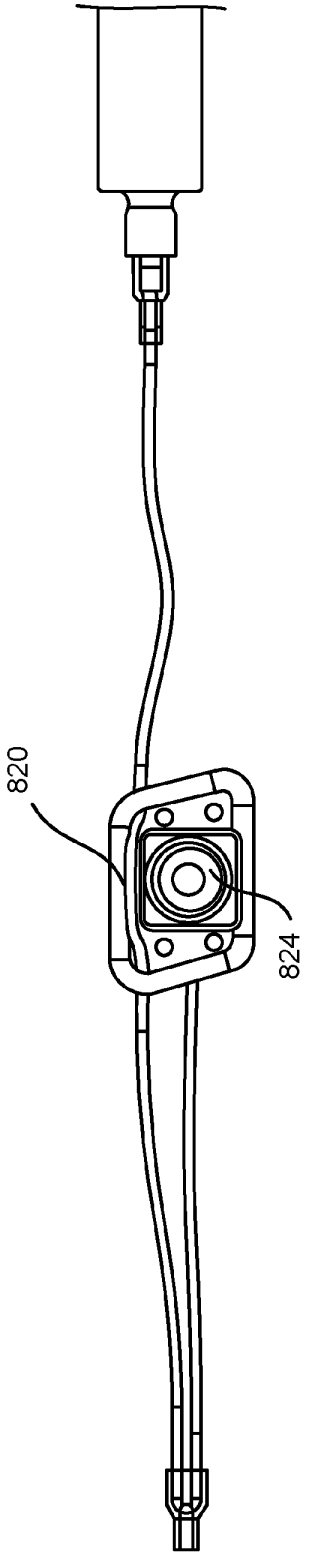


FIG. 8C

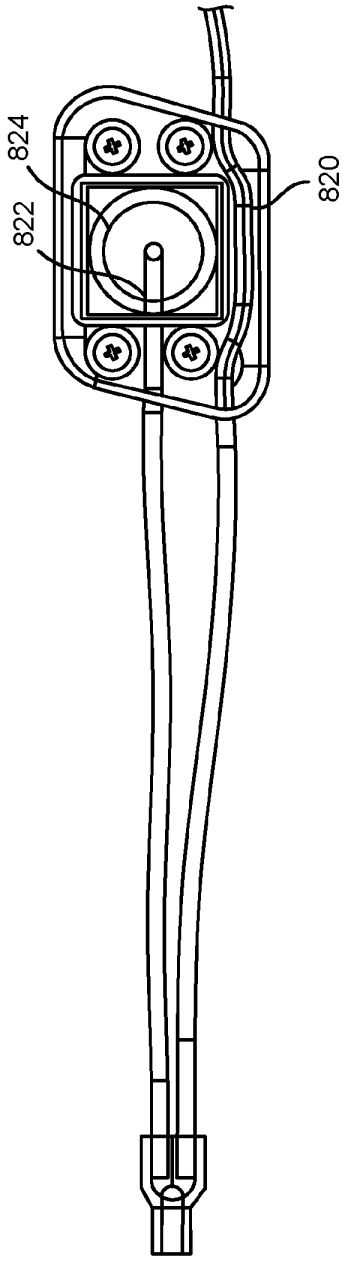


FIG. 8D

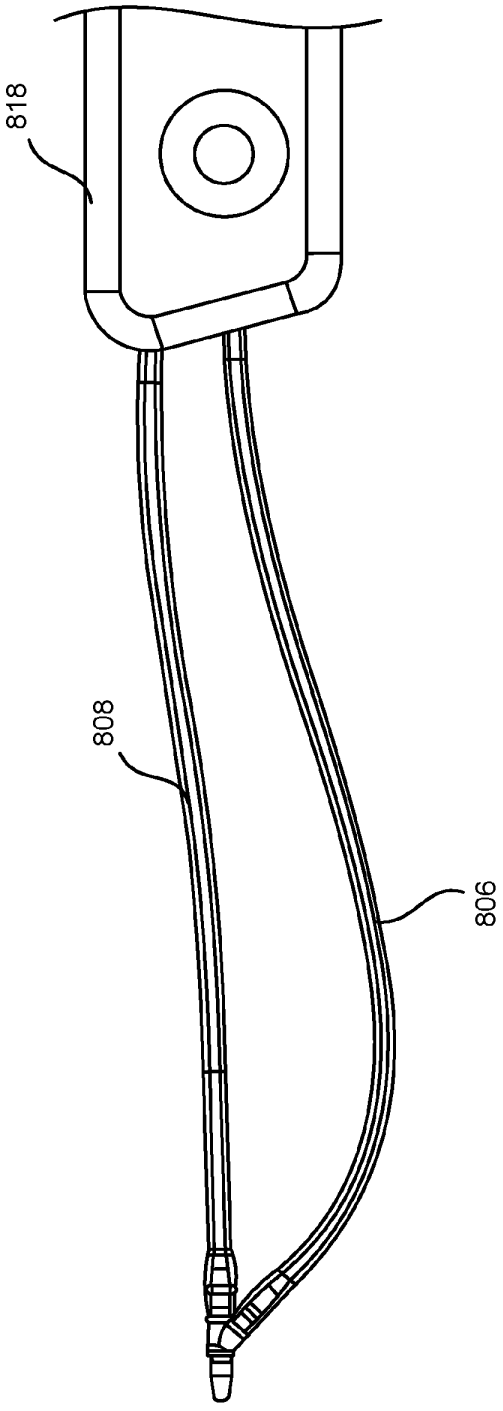


FIG. 8E

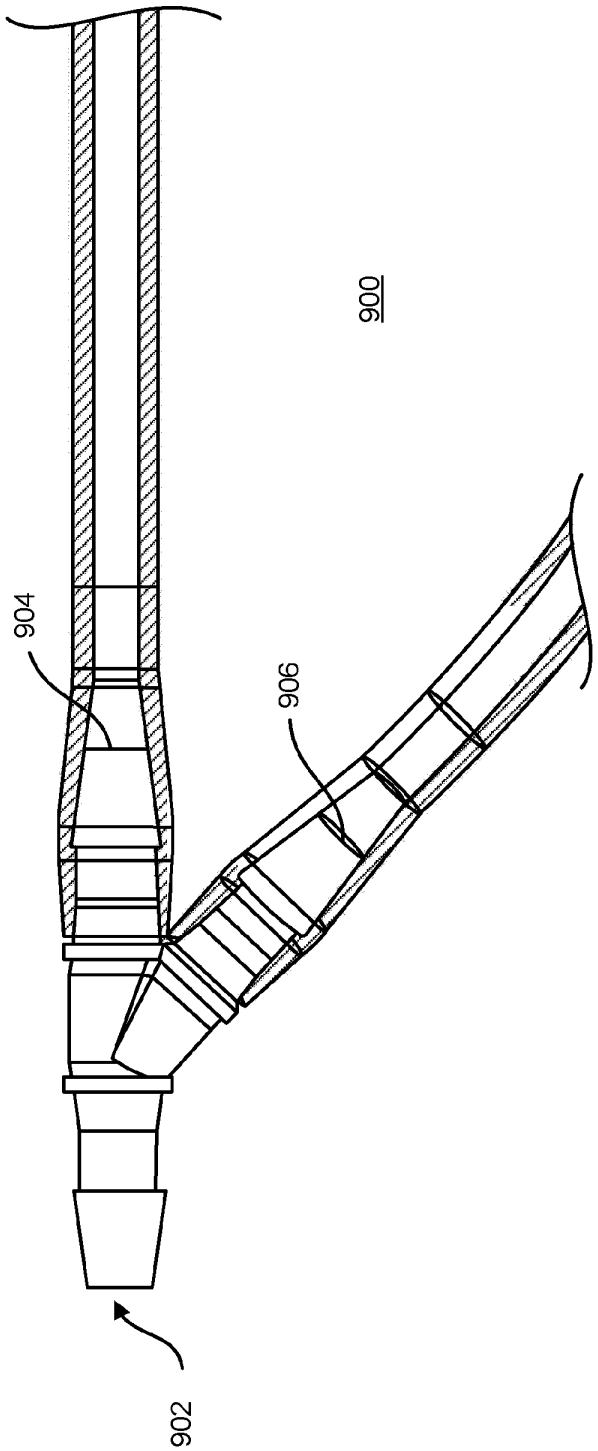


FIG. 9

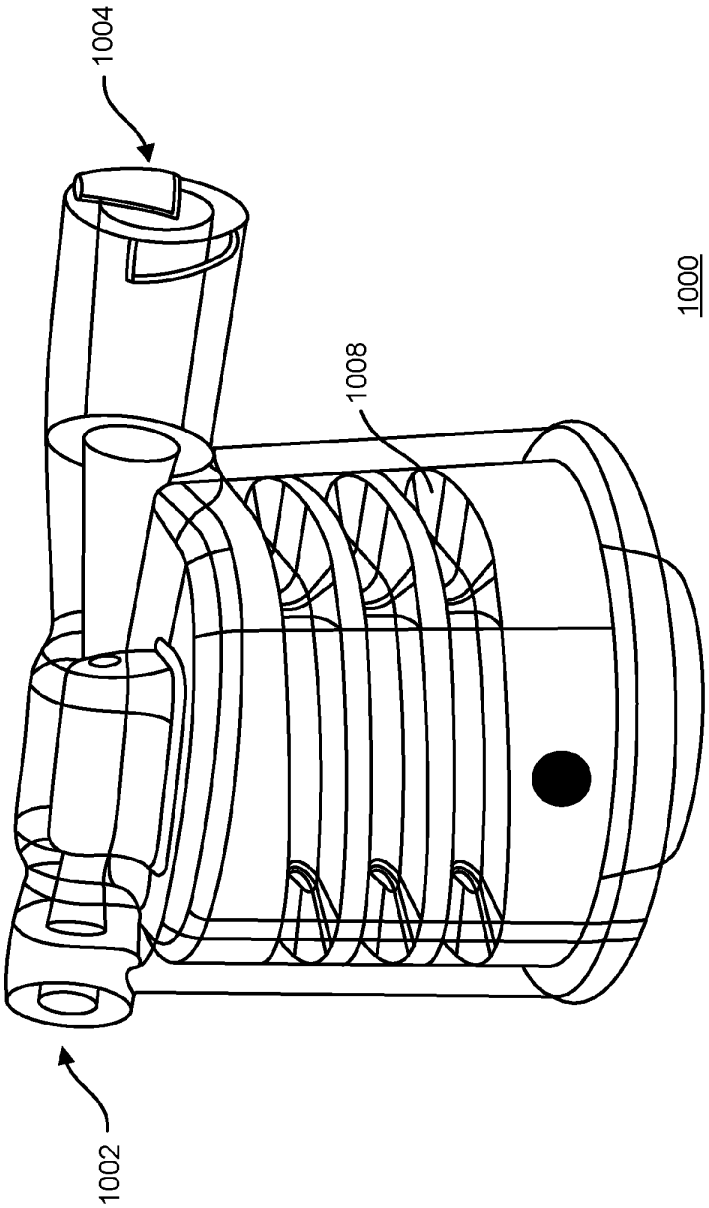


FIG. 10A

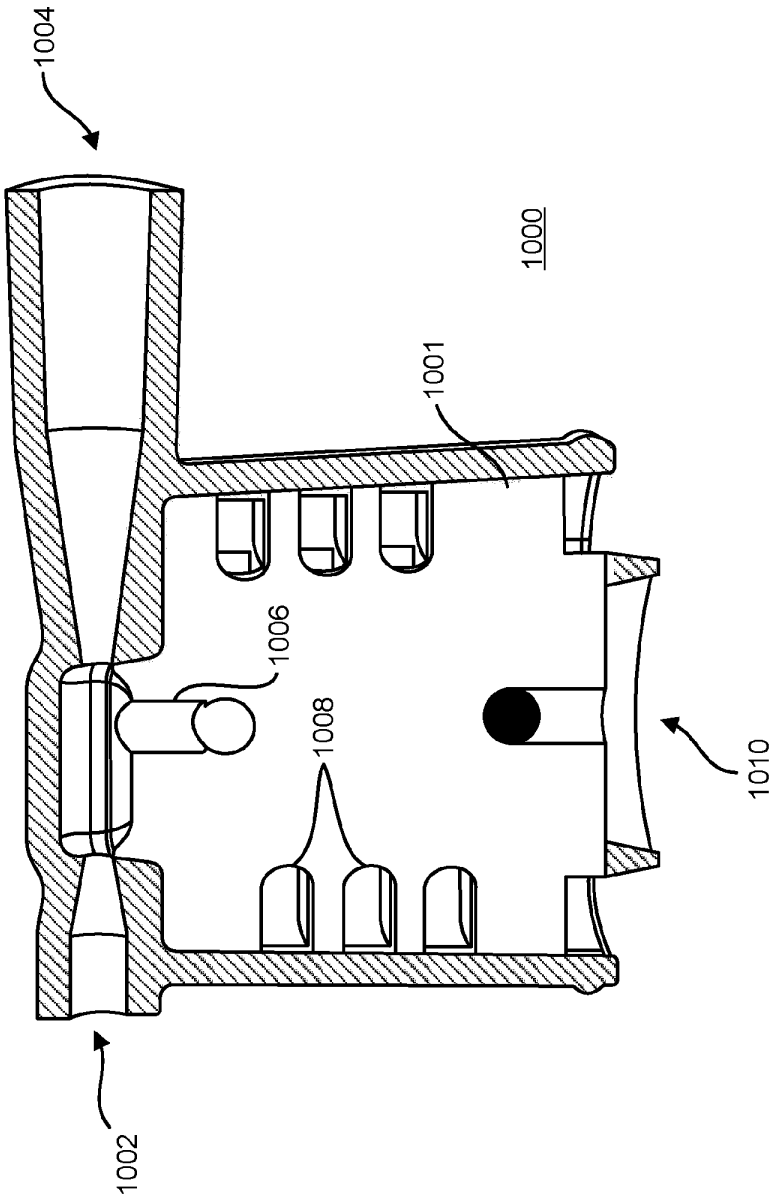


FIG. 10B

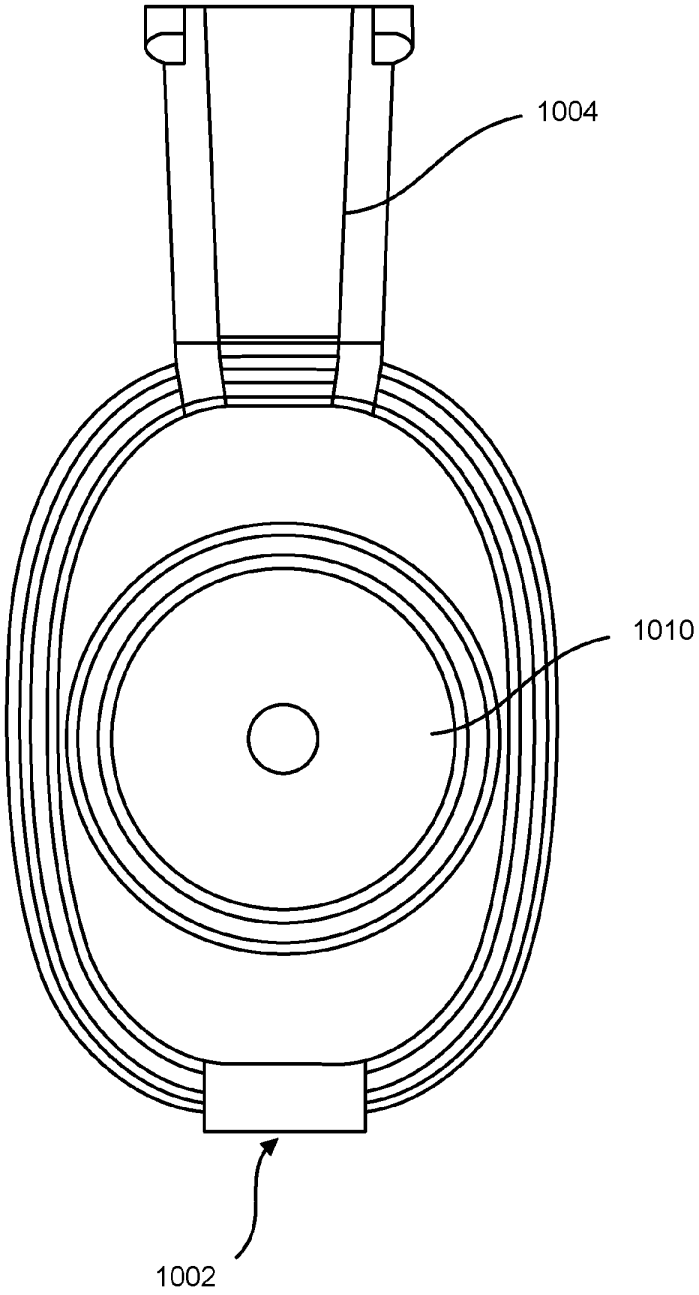


FIG. 10C

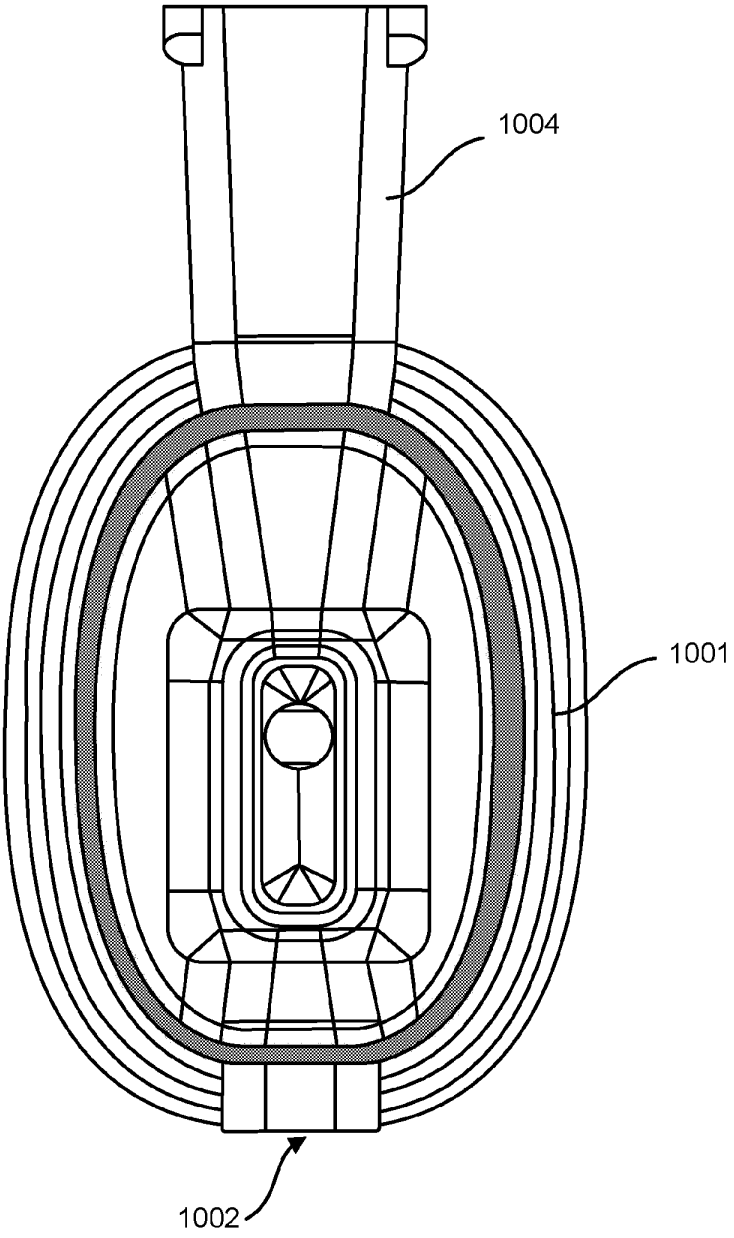


FIG. 10D

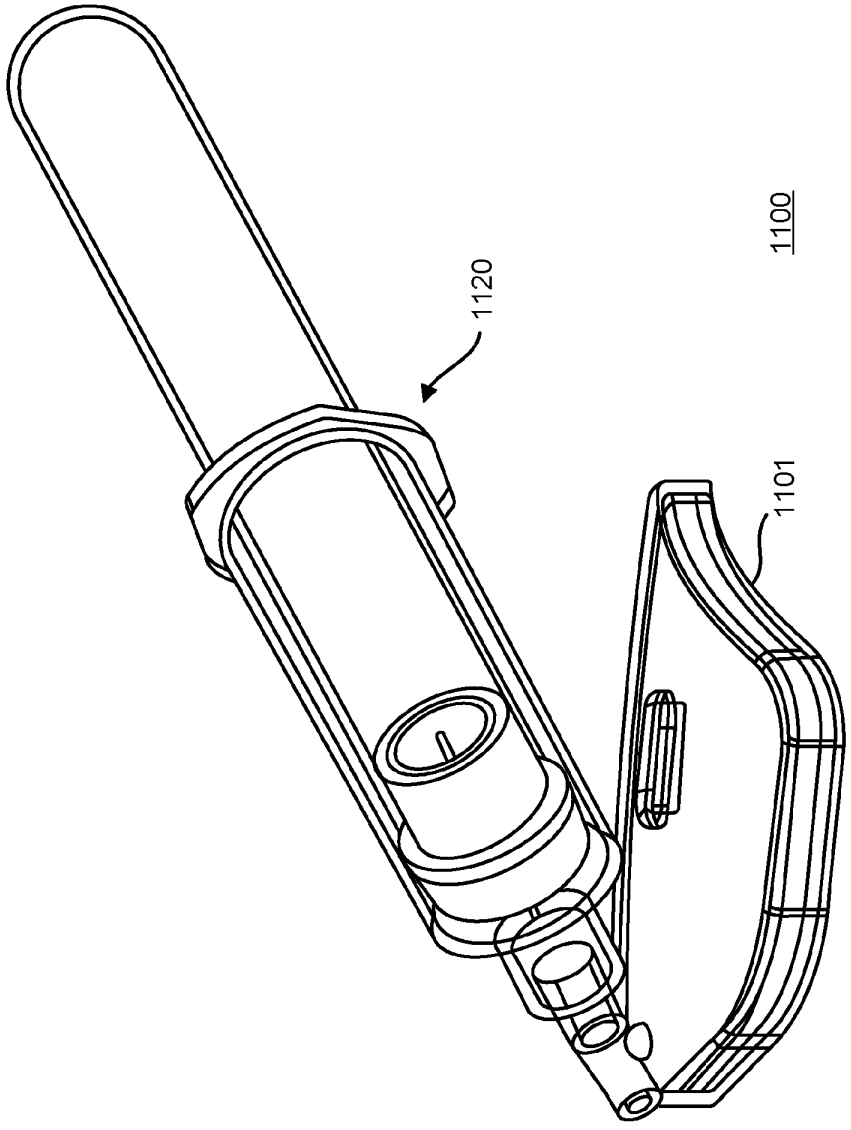


FIG. 11A

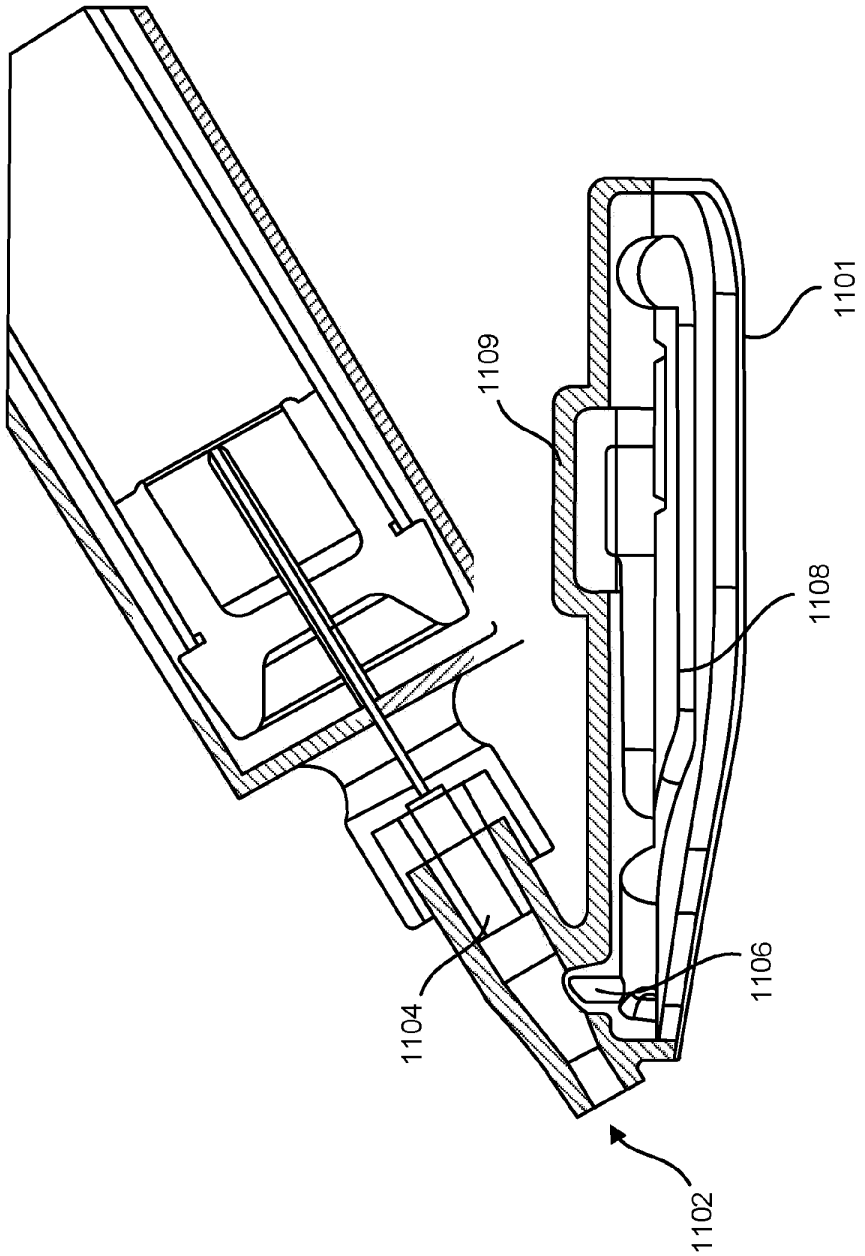


FIG. 11B

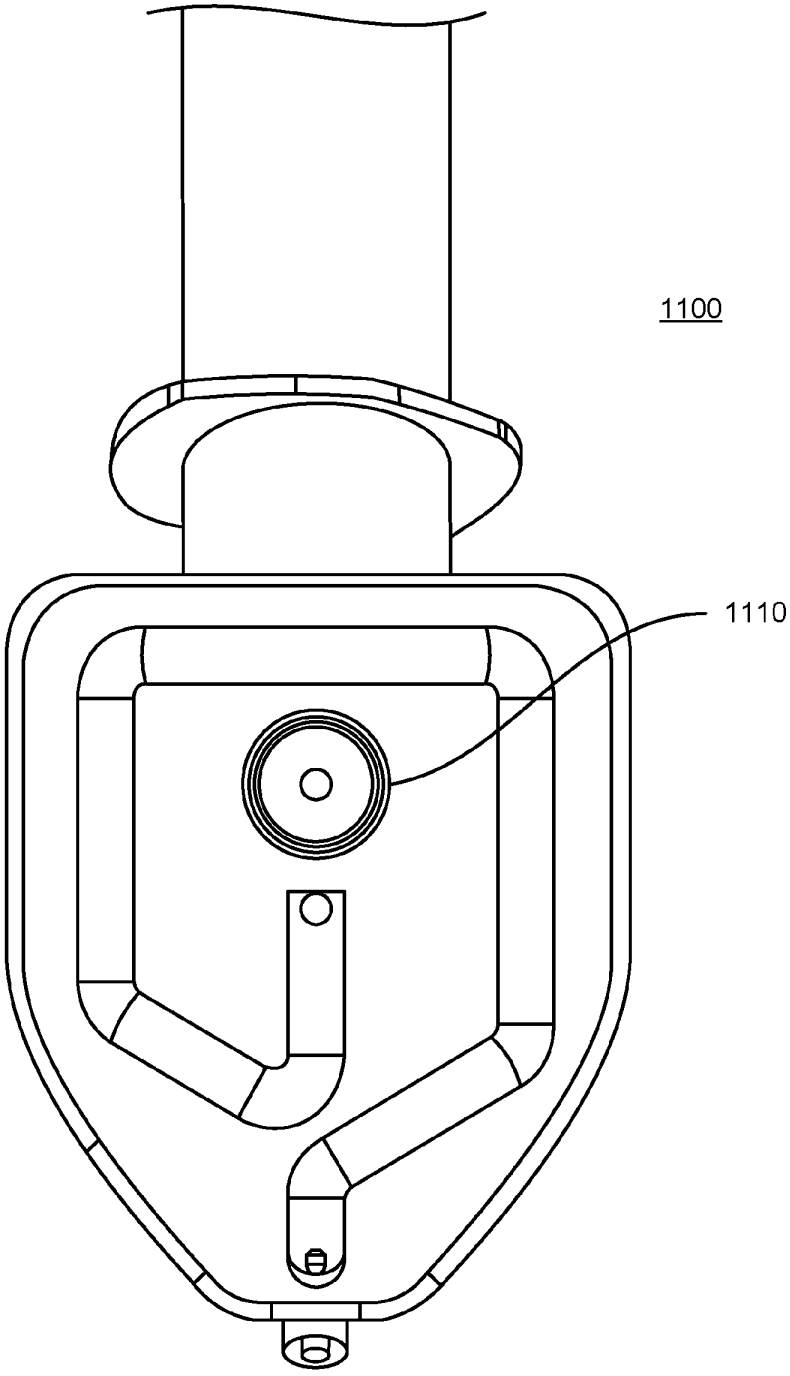


FIG. 11C

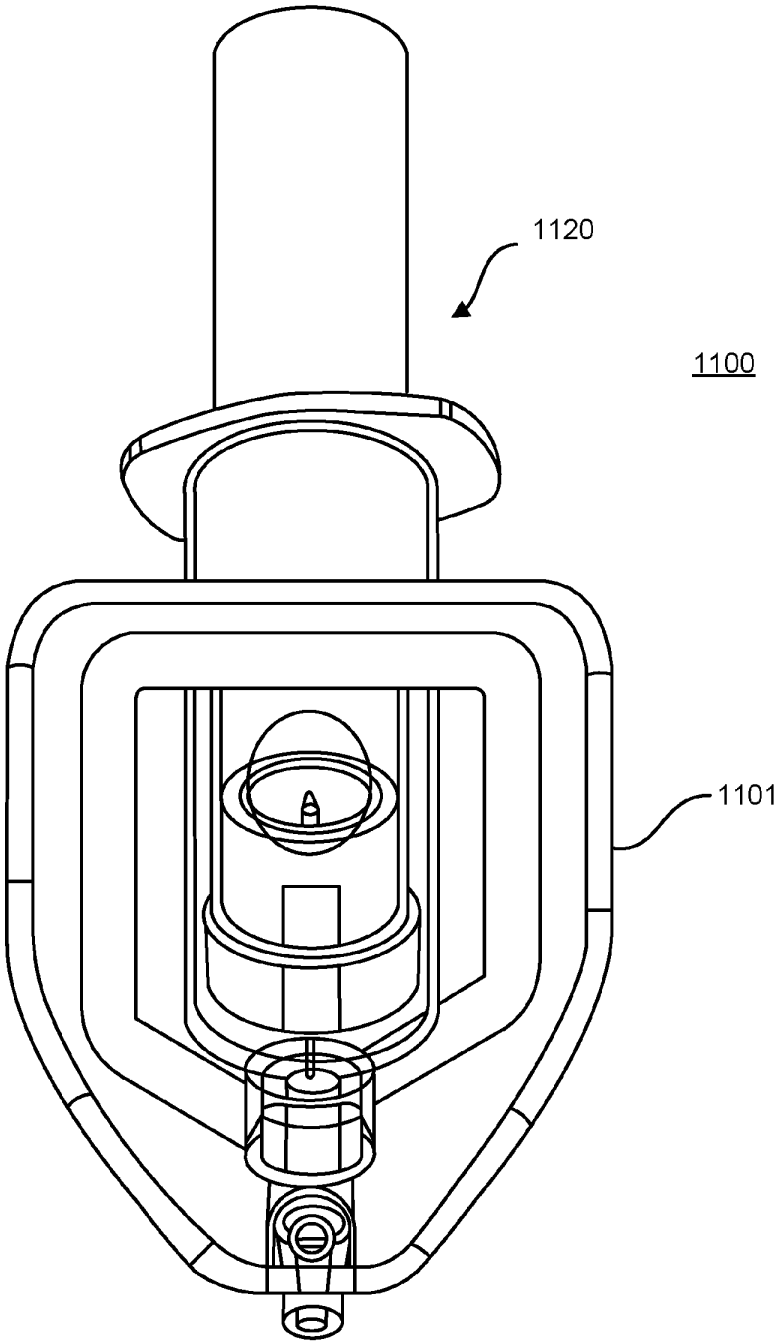


FIG. 11D

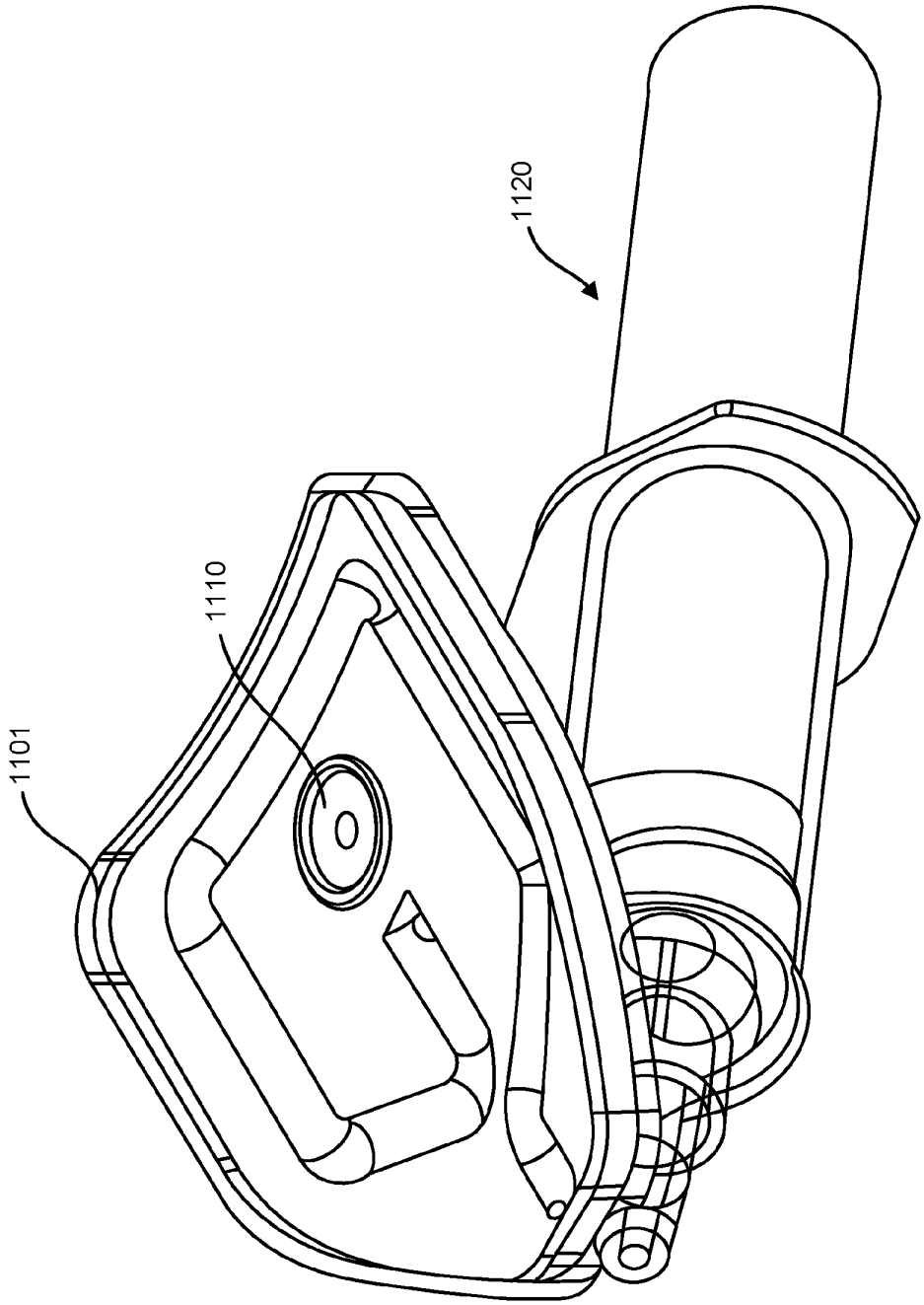


FIG. 11E

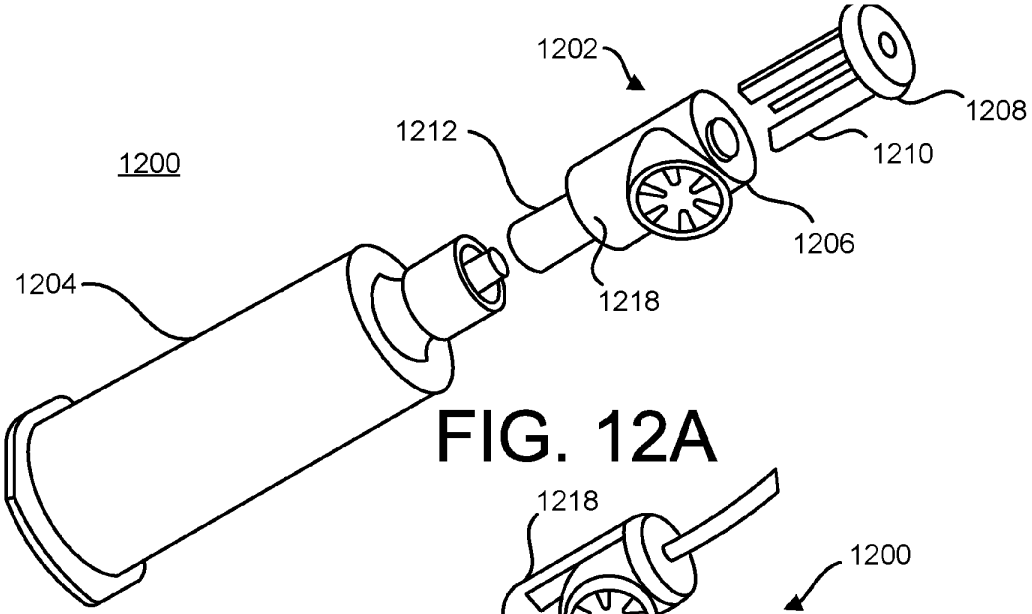


FIG. 12A

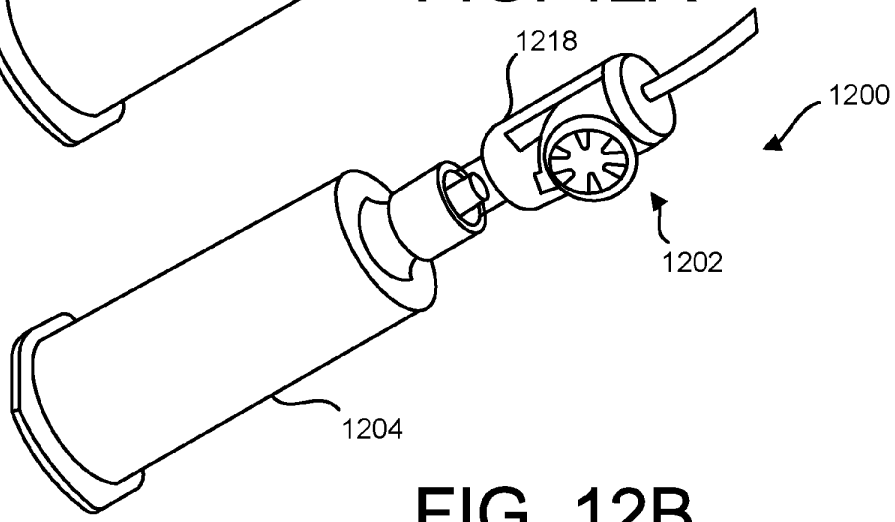


FIG. 12B

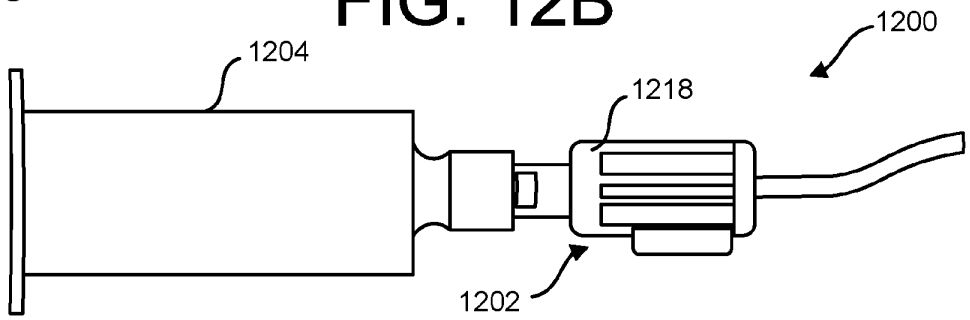


FIG. 12C

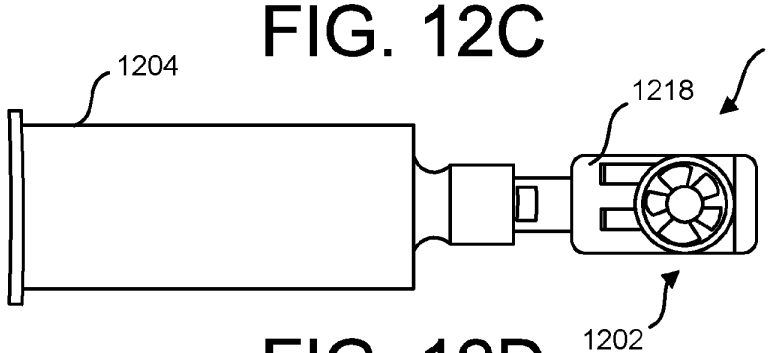


FIG. 12D

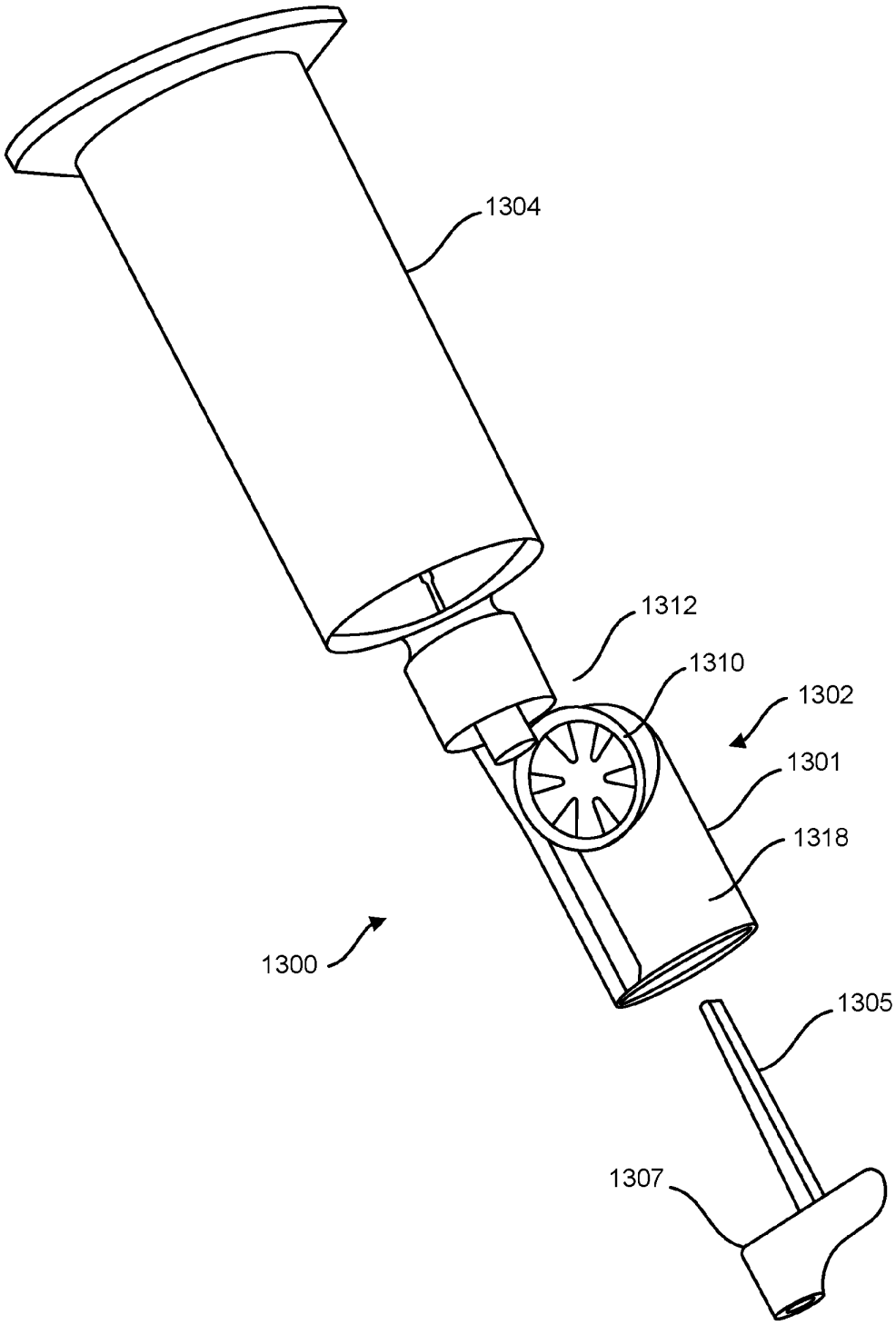


FIG. 13A

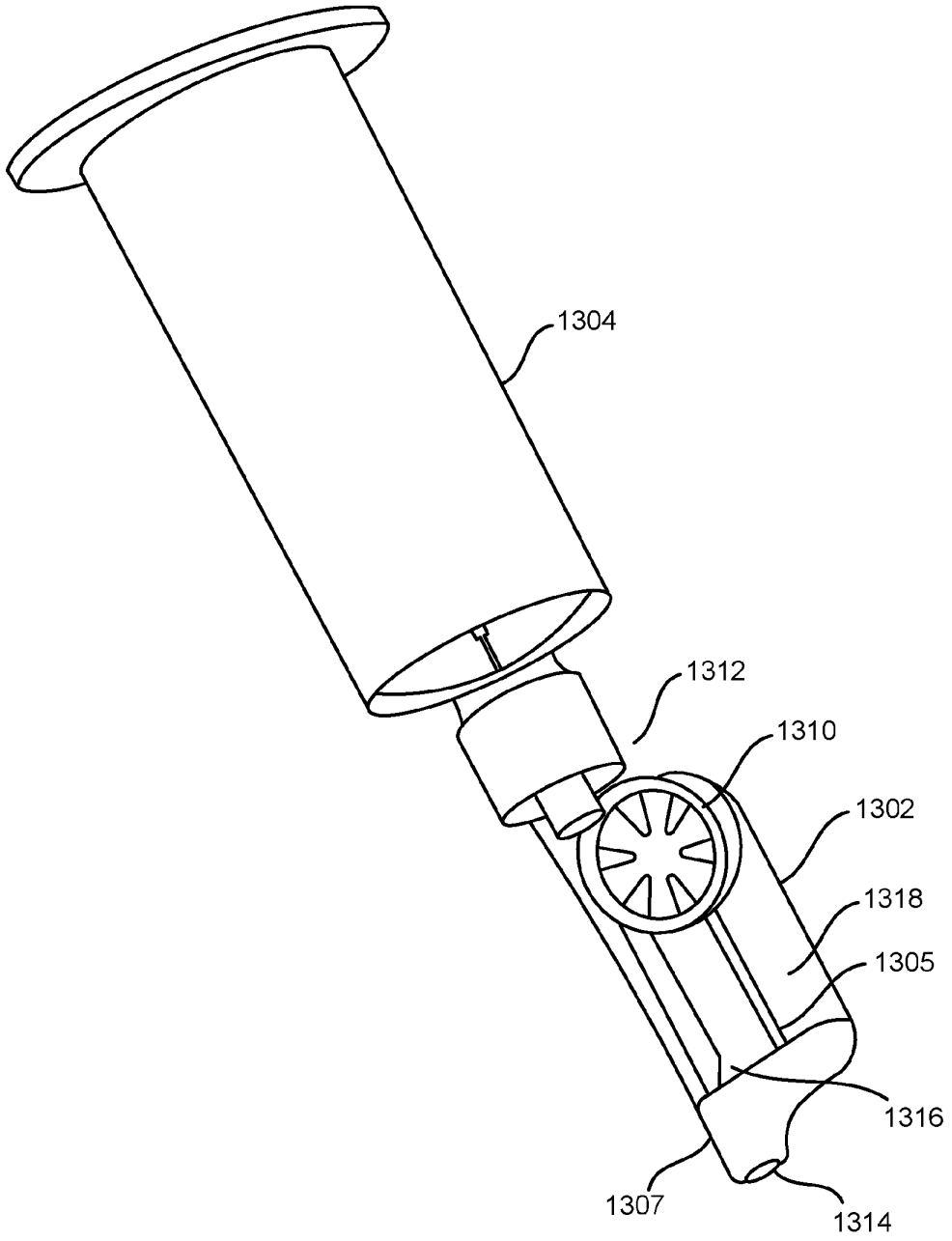


FIG. 13B

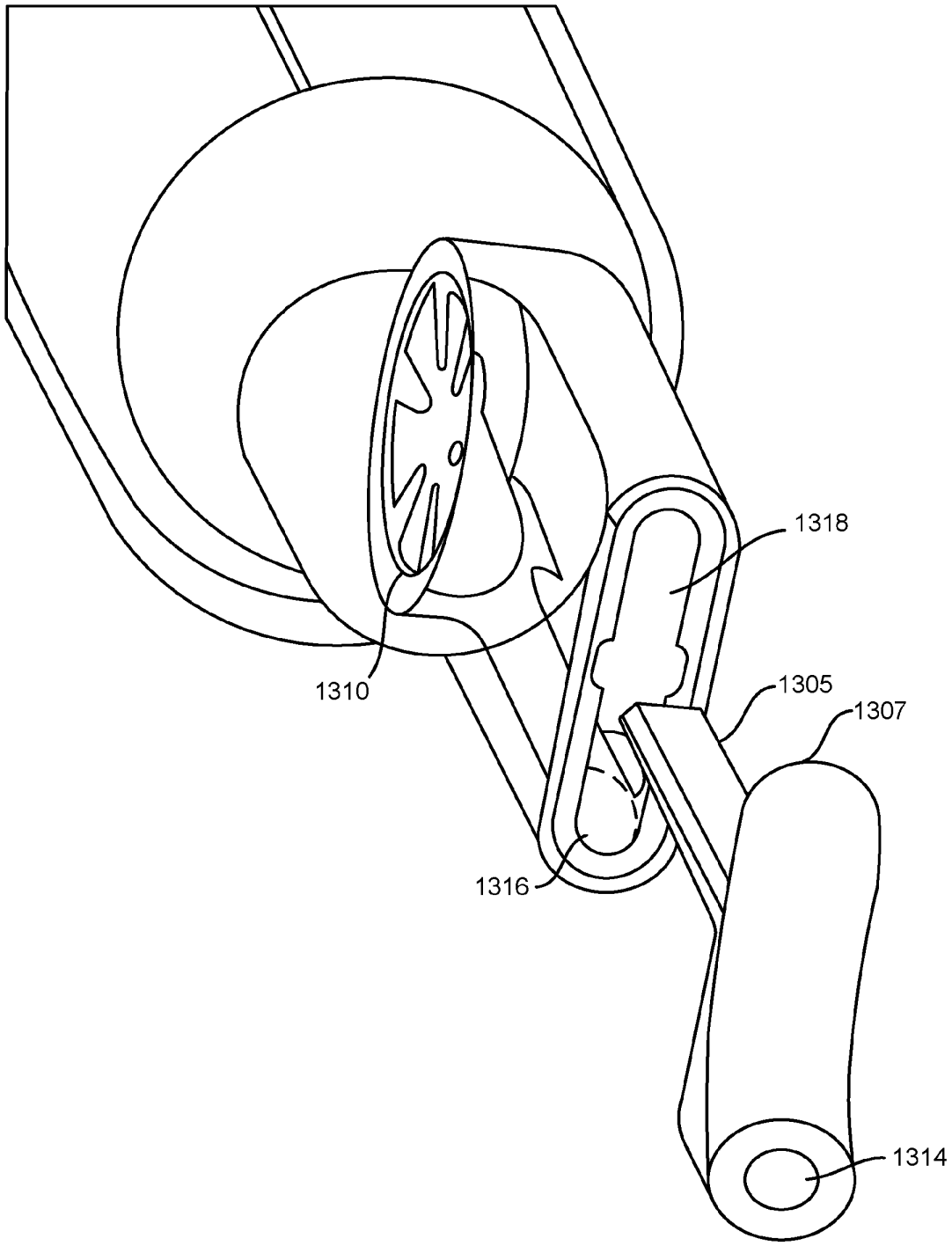


FIG. 13C

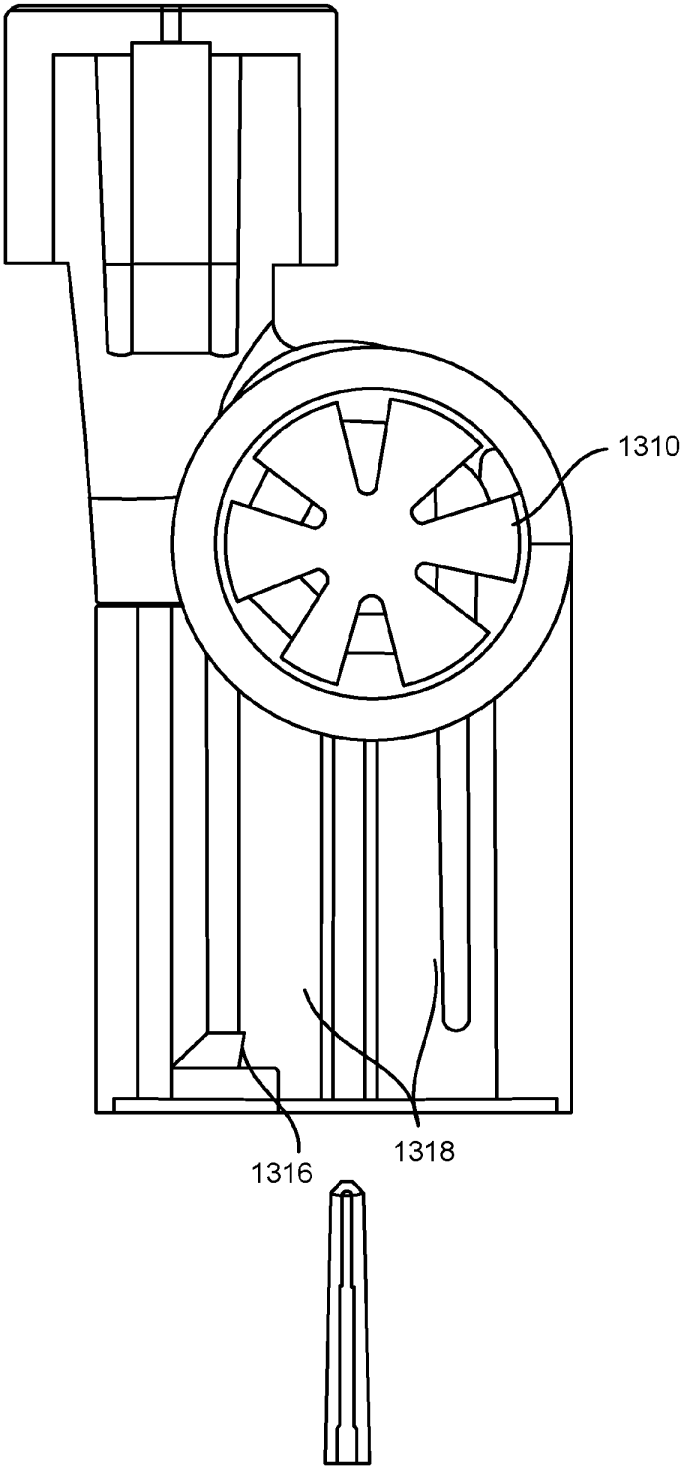


FIG. 13D

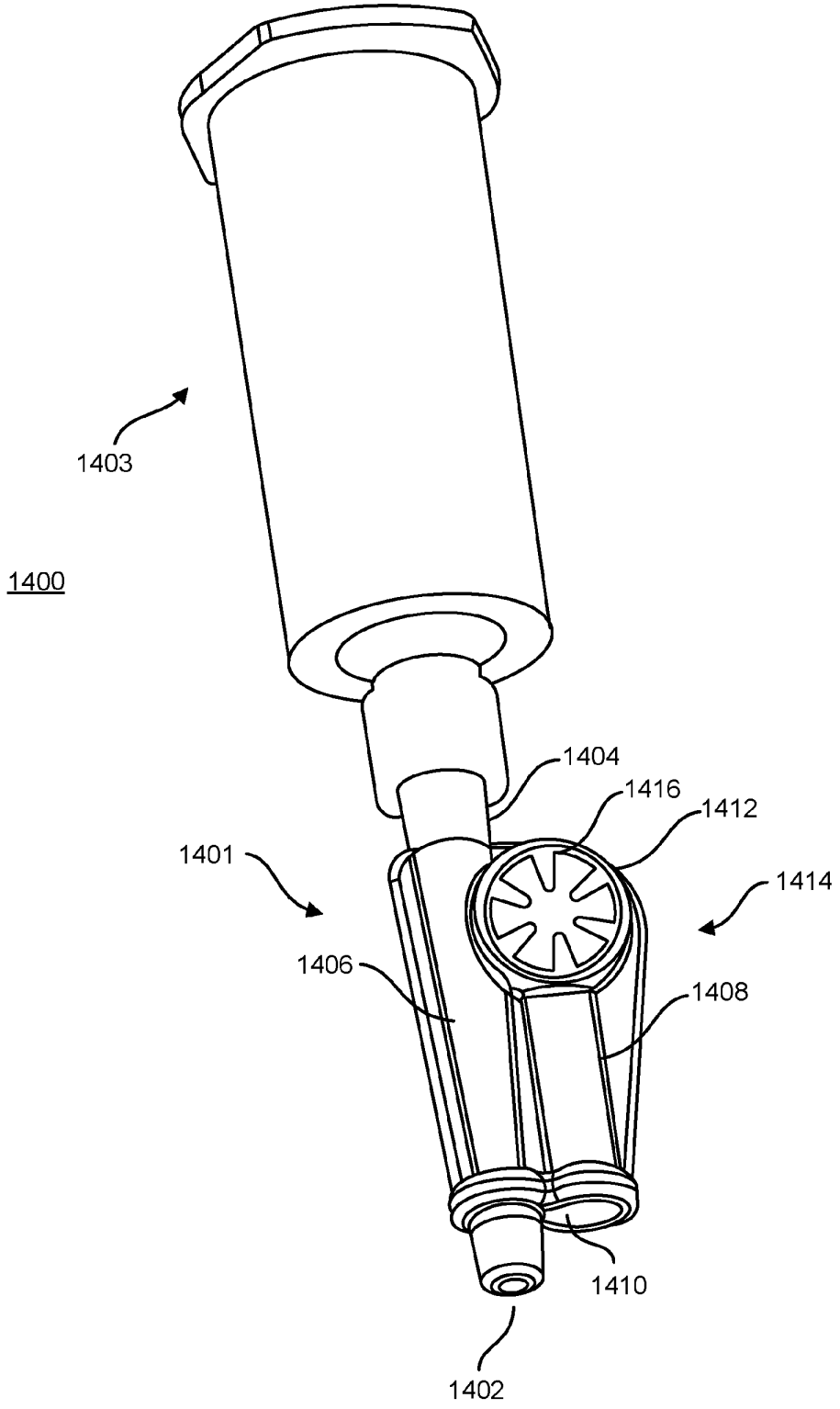


FIG. 14A

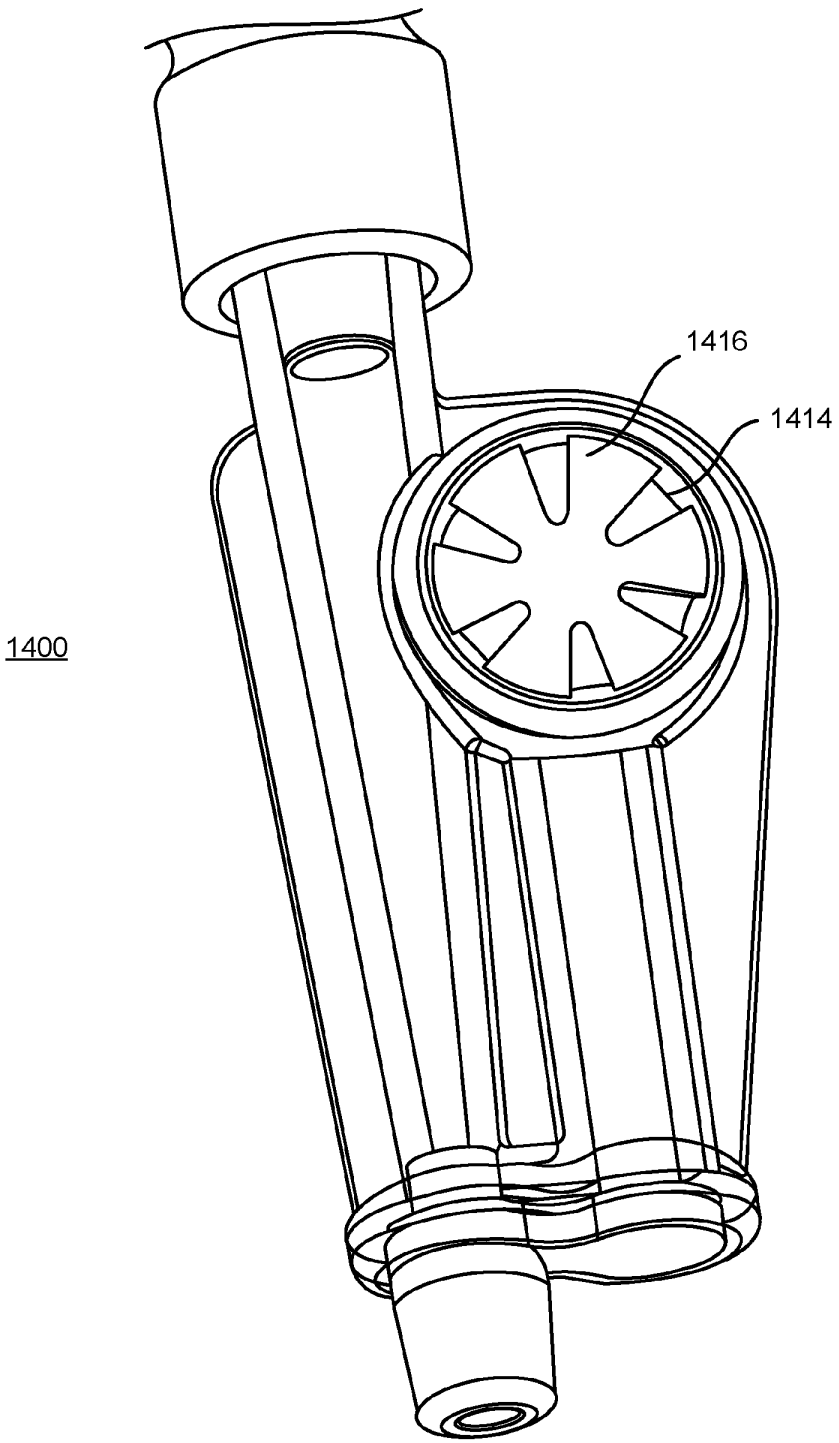


FIG. 14B

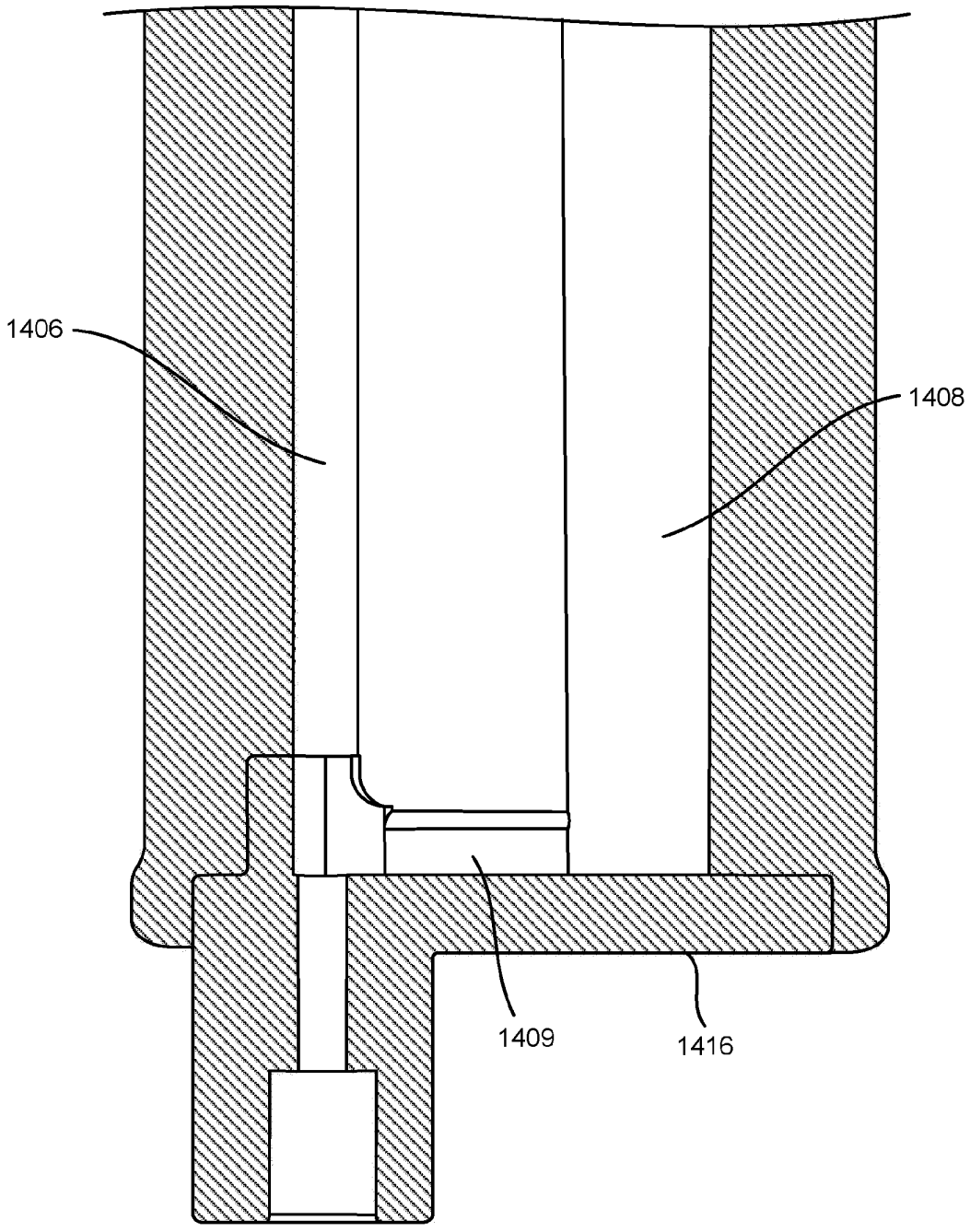


FIG. 14C

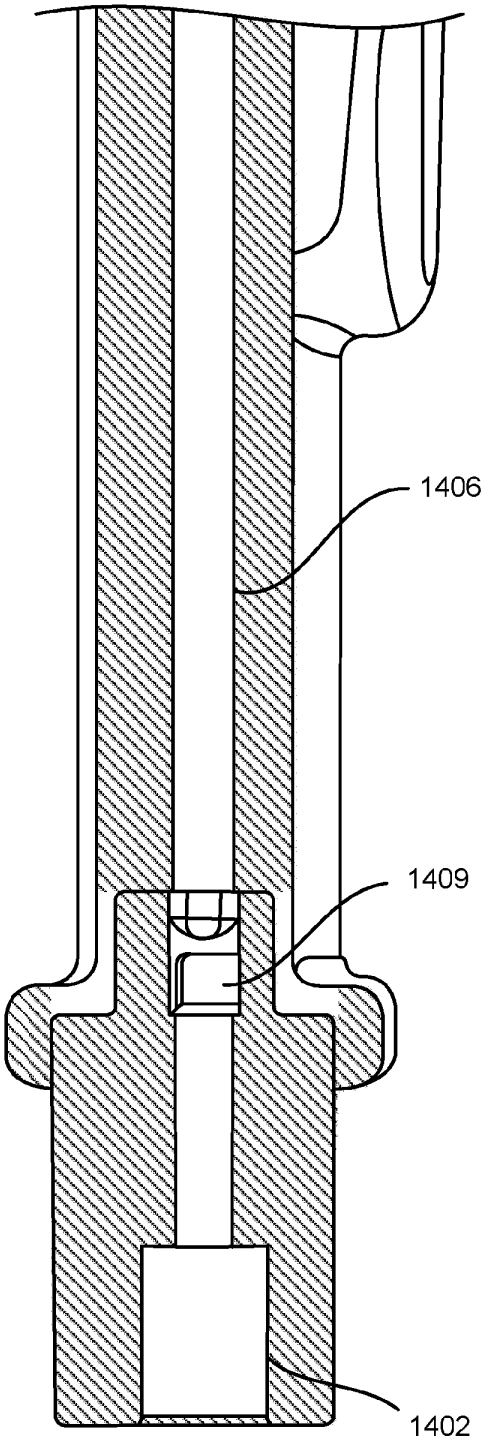


FIG. 14D

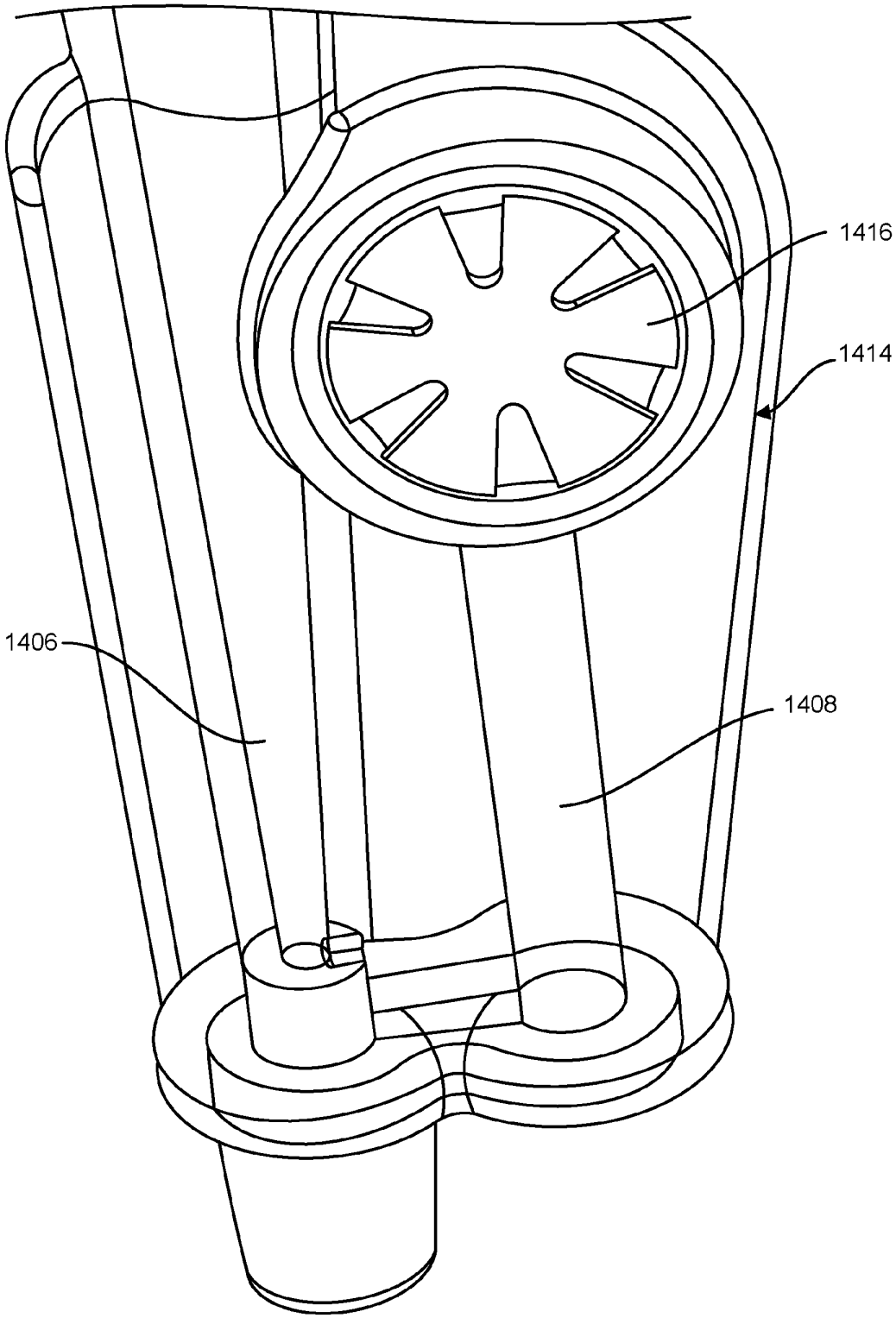


FIG. 14E

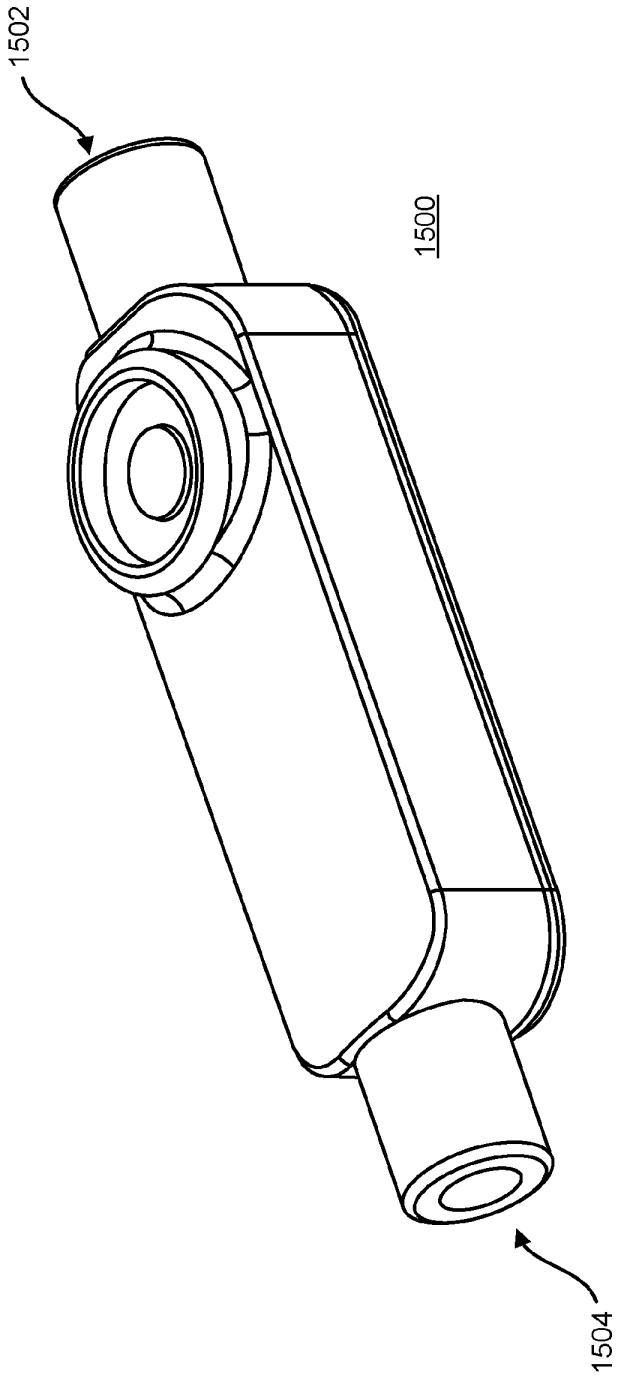


FIG. 15A

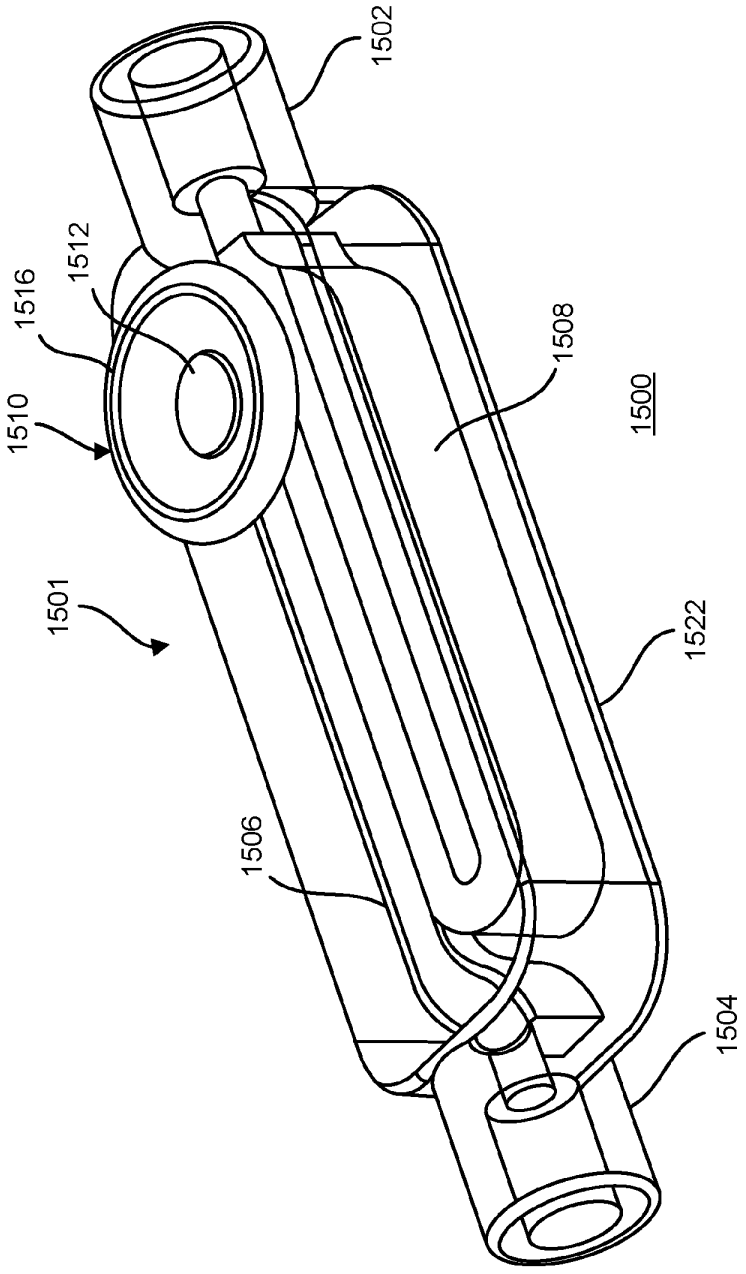


FIG. 15B

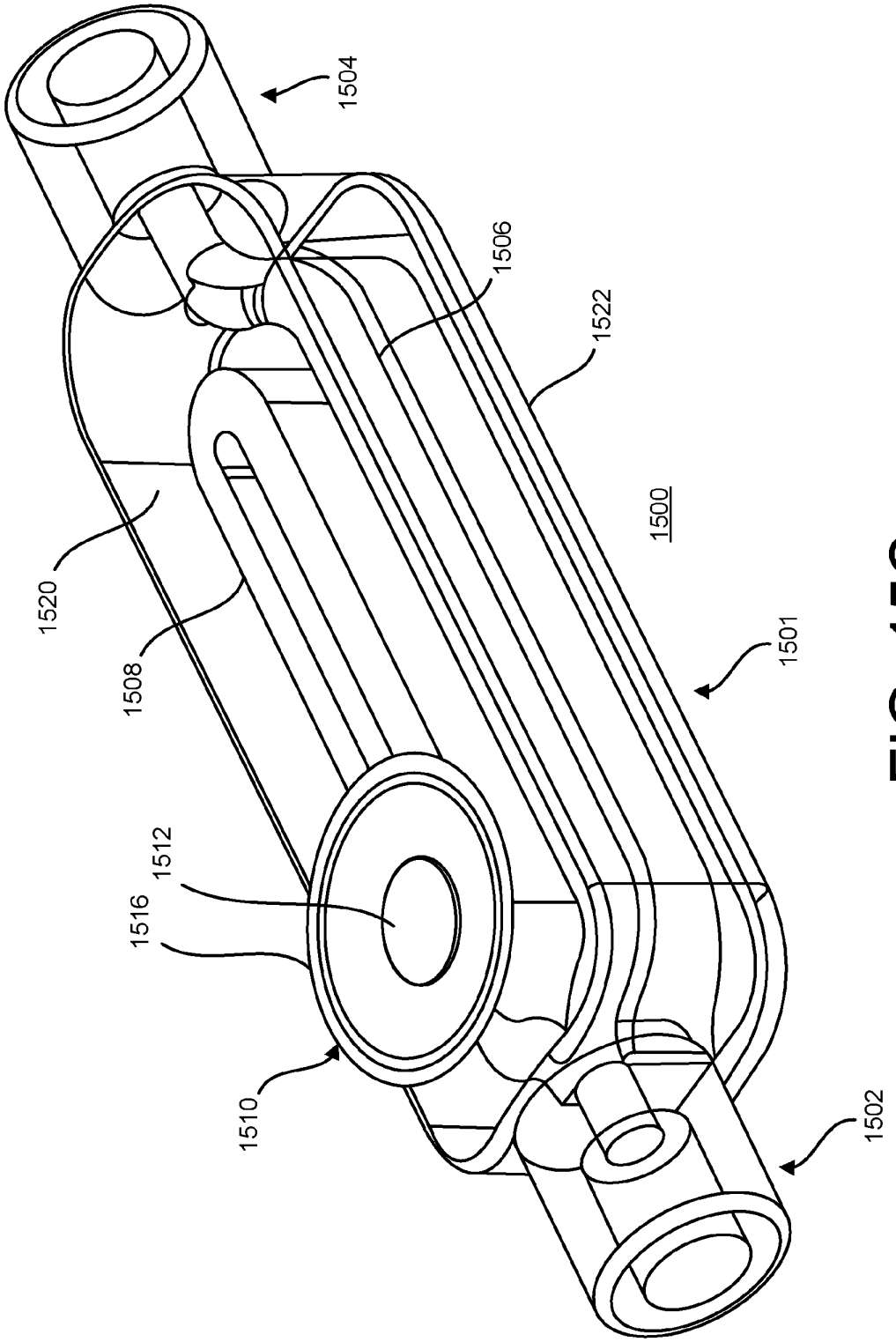


FIG. 15C

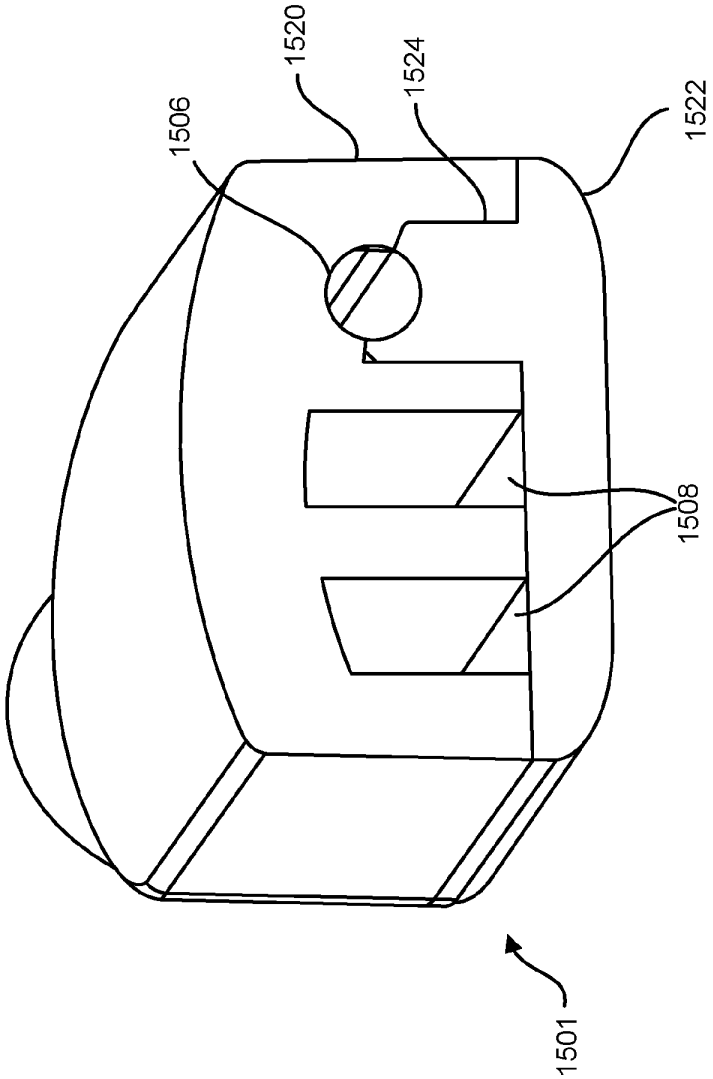


FIG. 15D

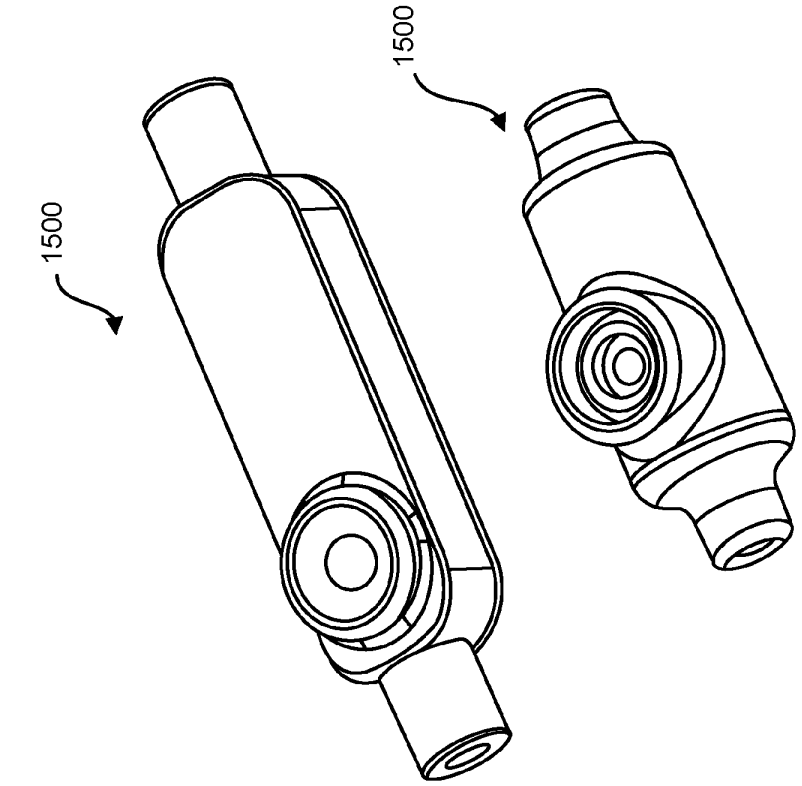


FIG. 15F

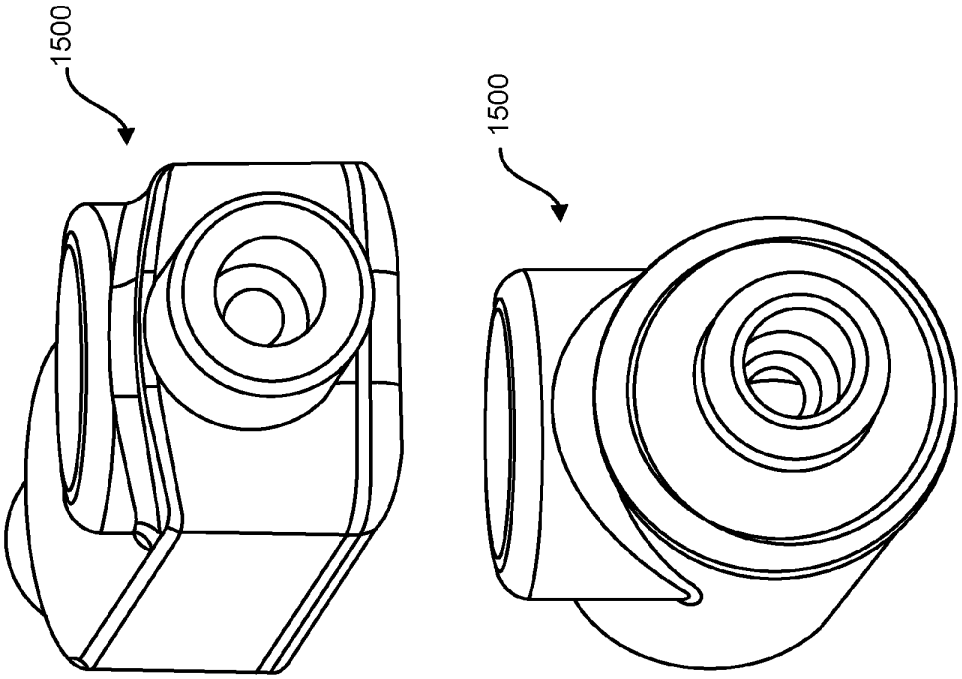


FIG. 15E

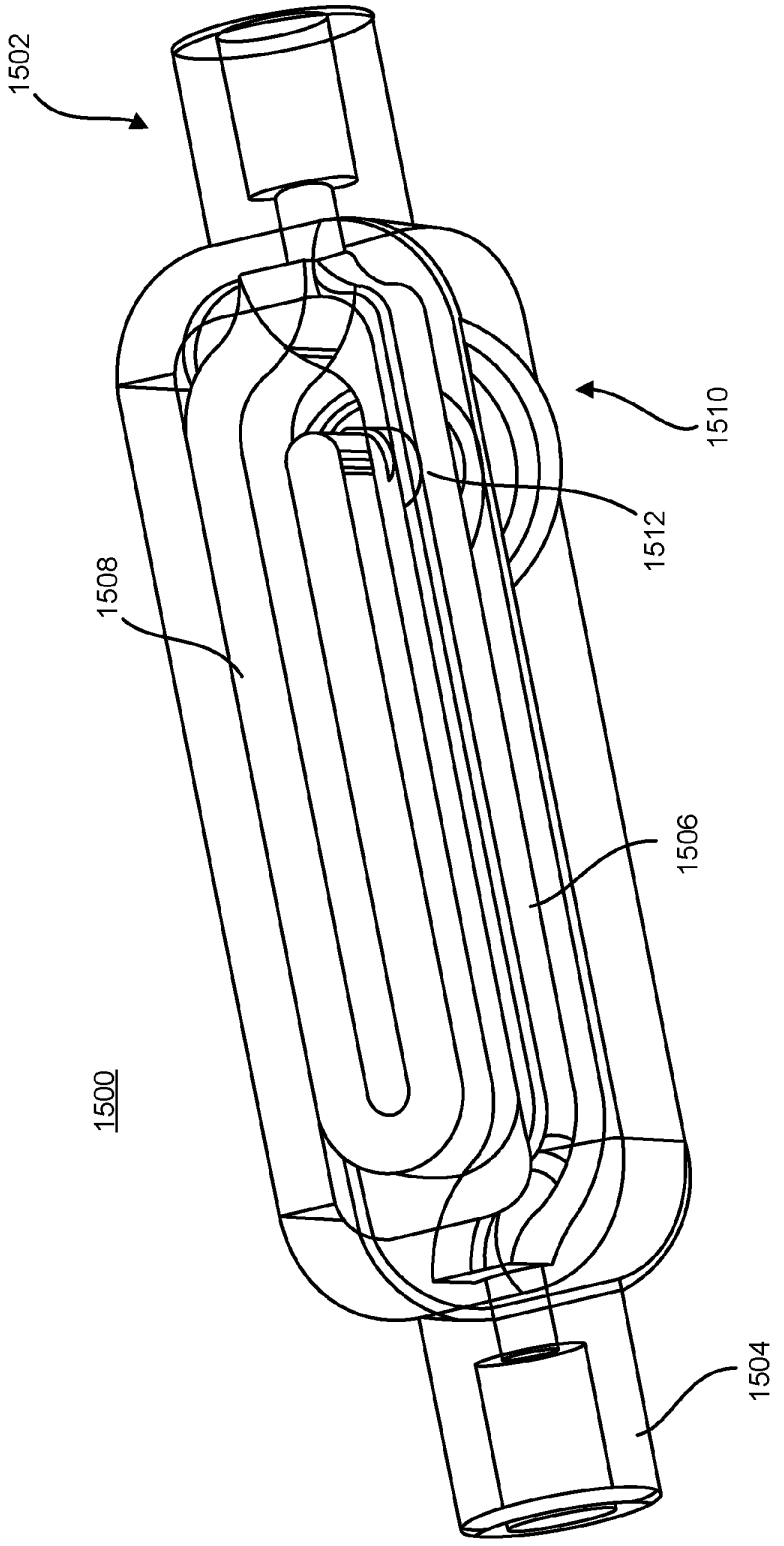


FIG. 15G

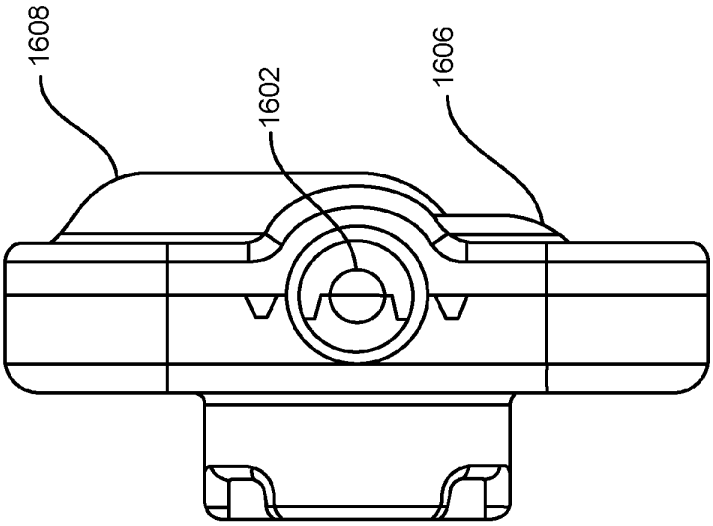


FIG. 16C

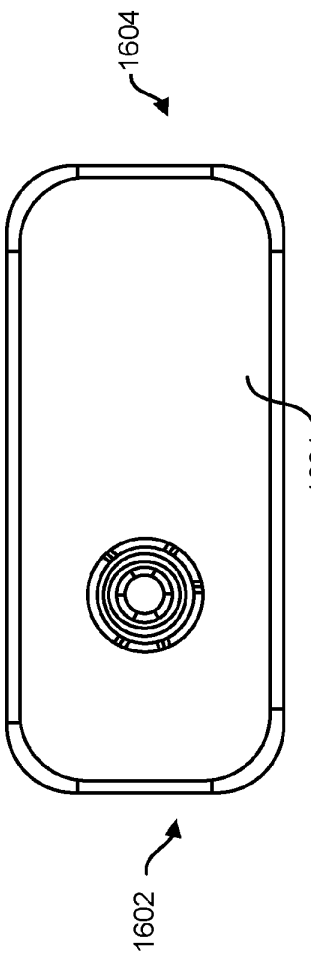


FIG. 16A

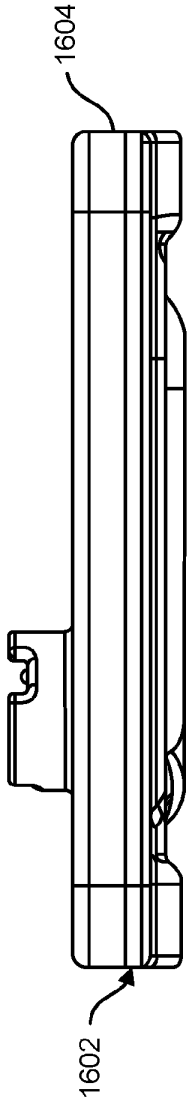


FIG. 16B

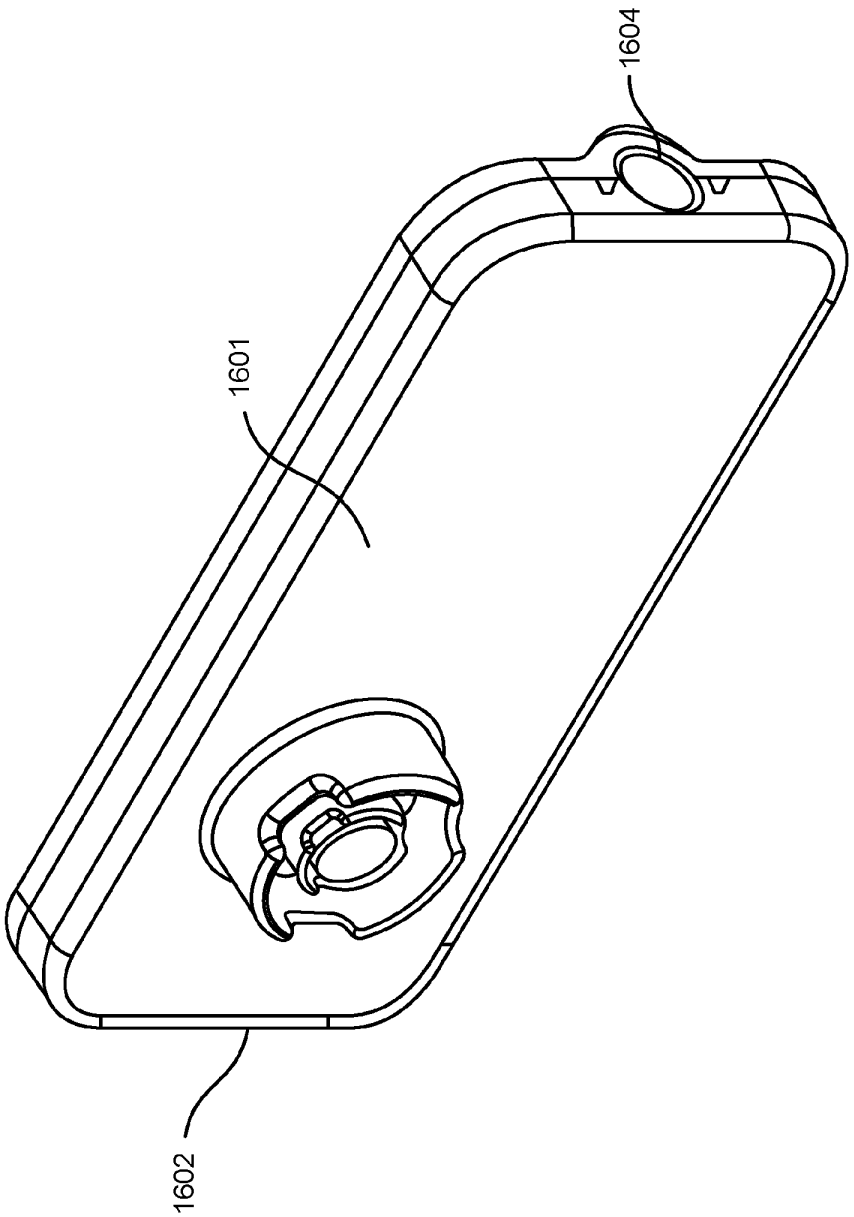


FIG. 16D

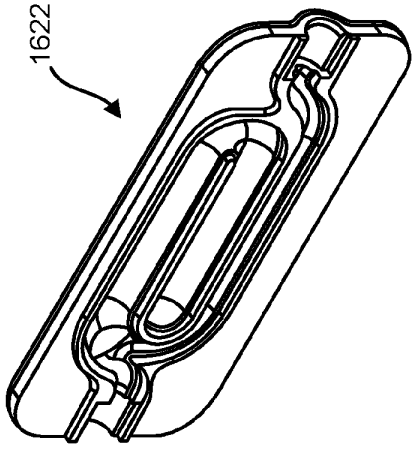


FIG. 17B

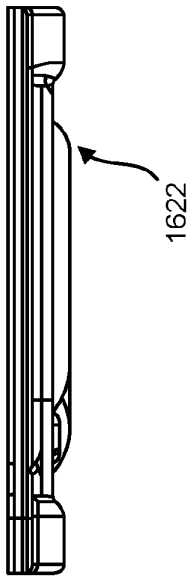


FIG. 17E

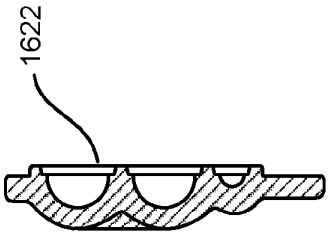


FIG. 17D

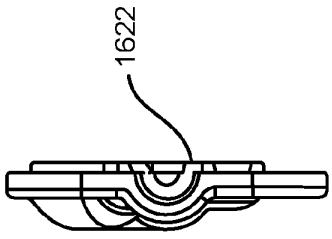


FIG. 17C

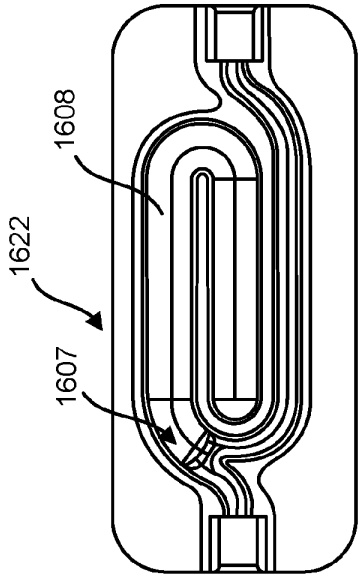


FIG. 17A

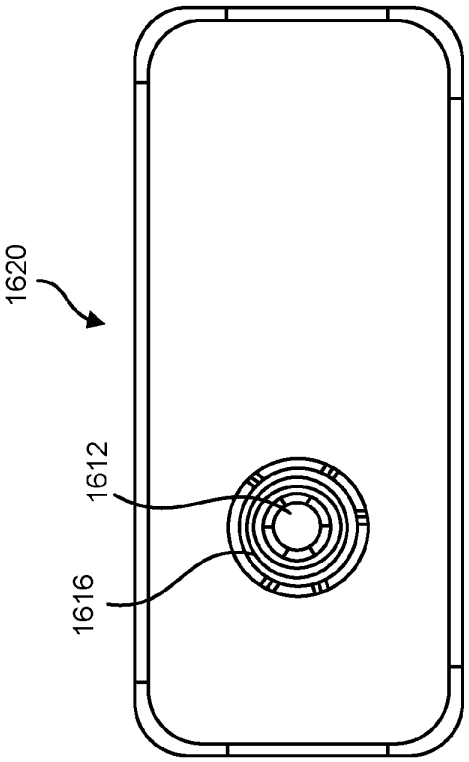


FIG. 18A

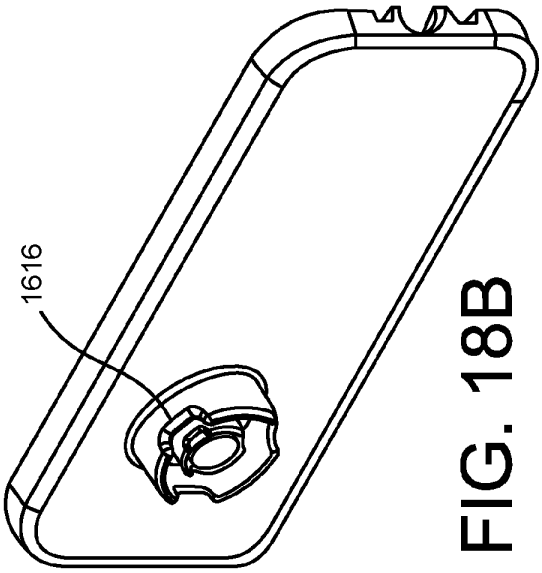


FIG. 18B



FIG. 18C

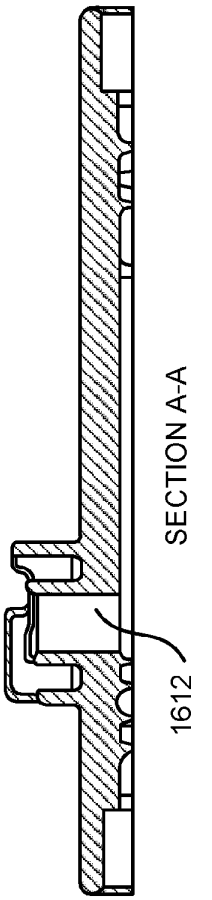


FIG. 18D

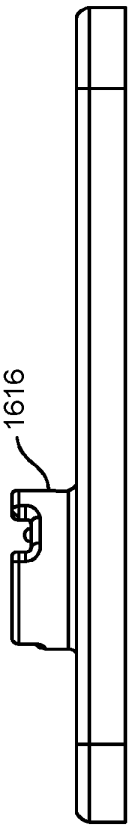


FIG. 18E

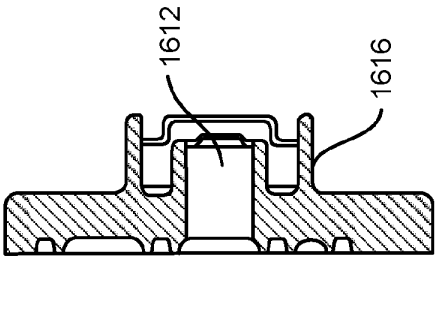


FIG. 18F

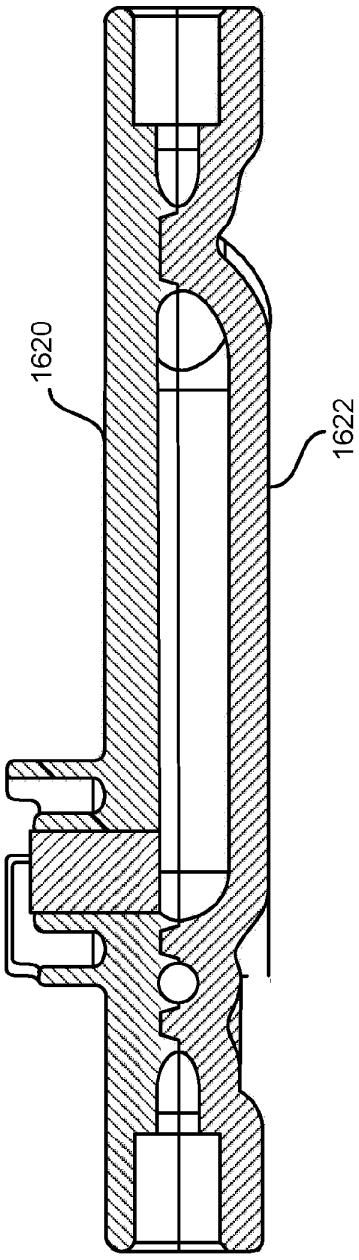


FIG. 19A

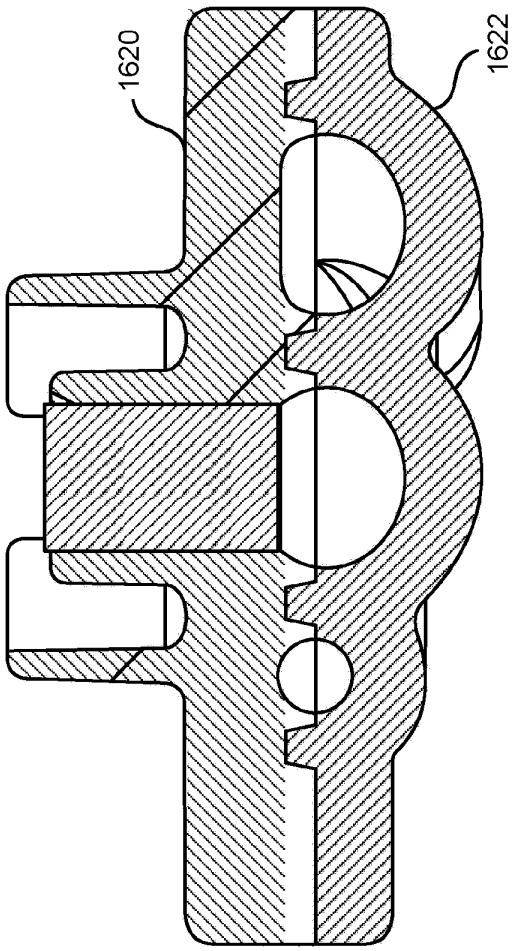


FIG. 19B

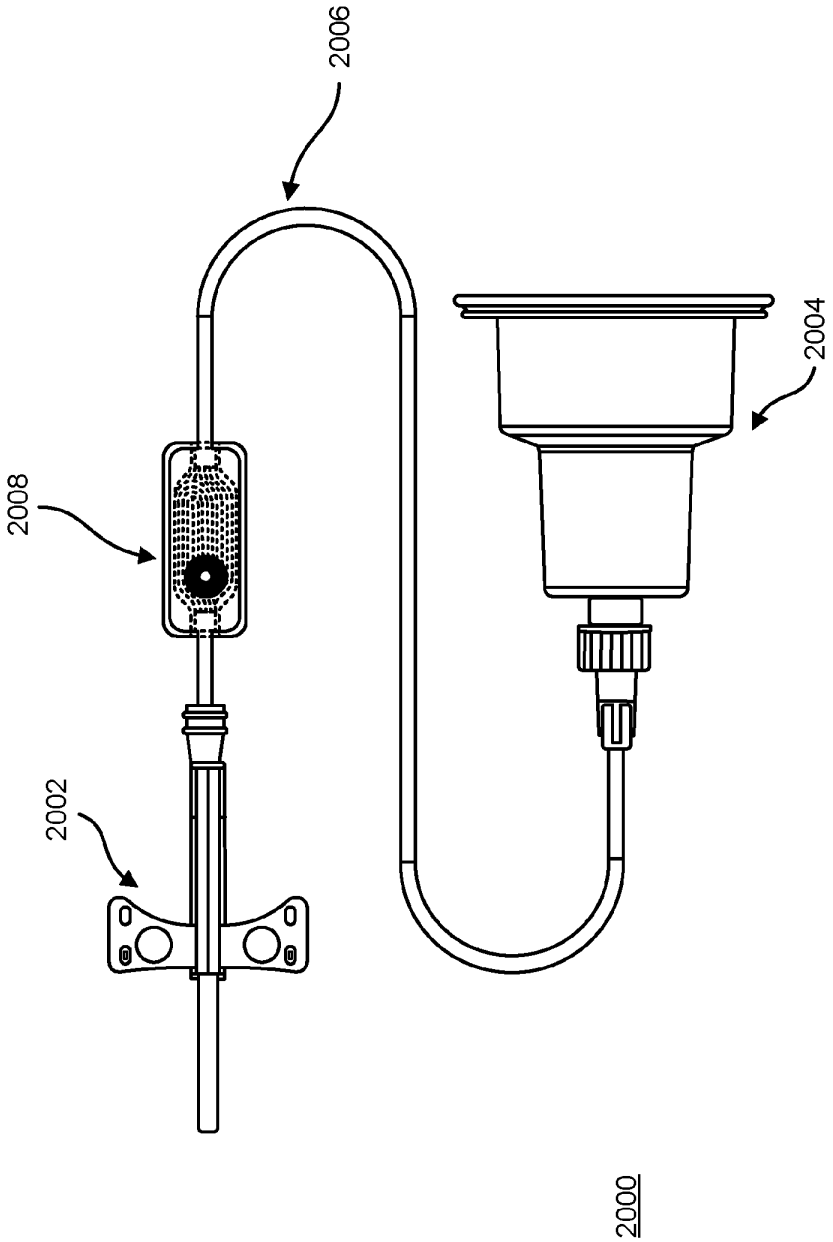


FIG. 20

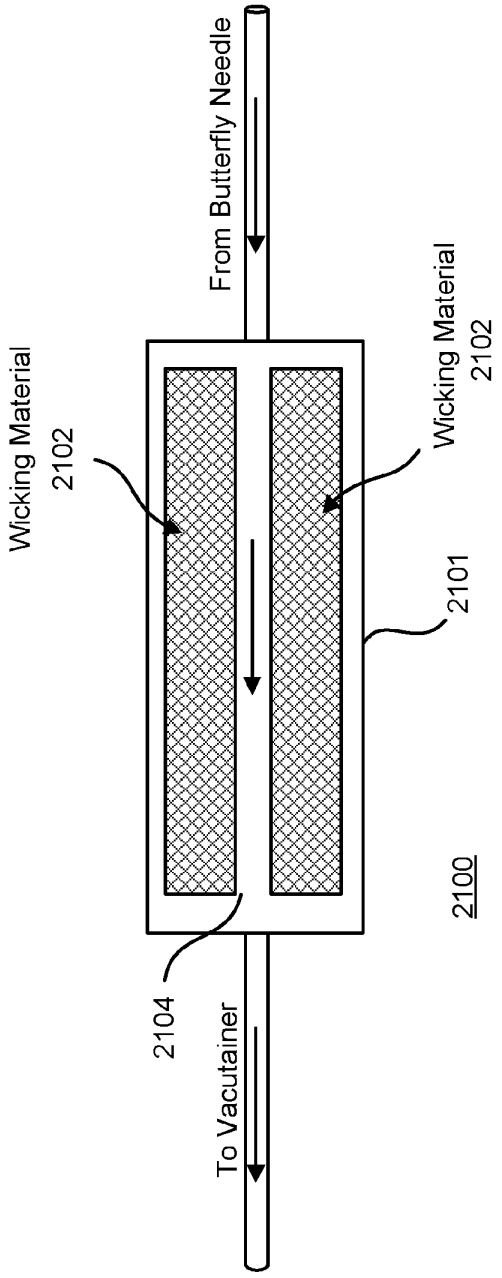

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

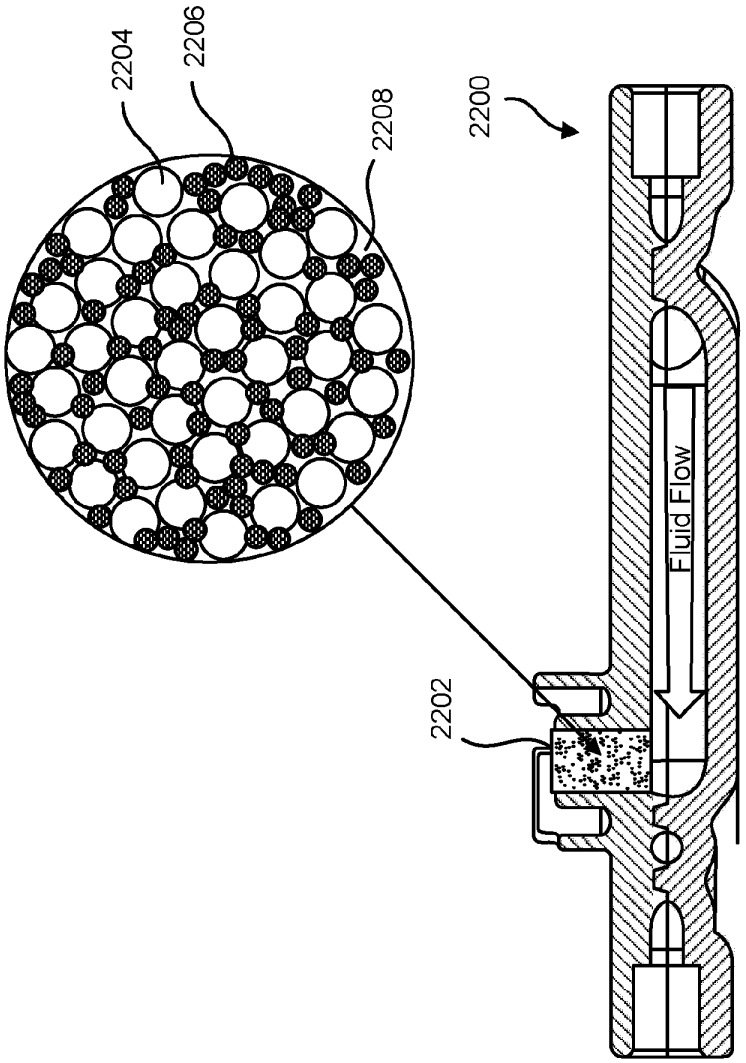


FIG. 22A

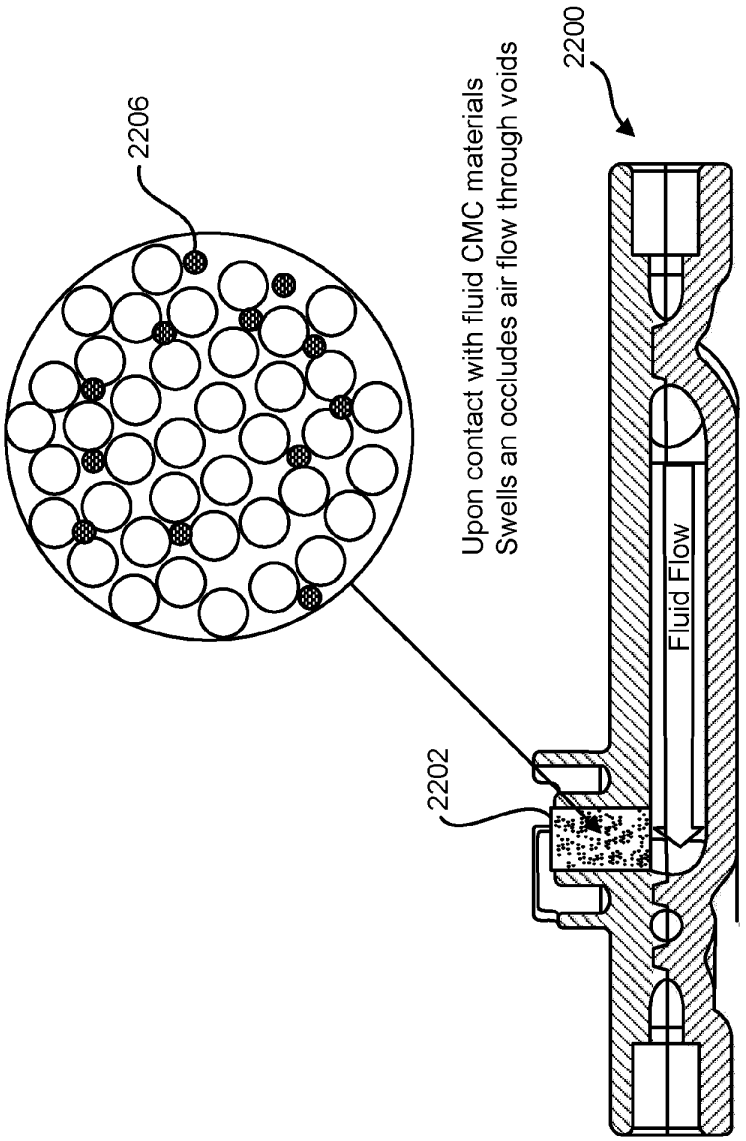

2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2200
2202
Fluid Flow

FIG. 22B

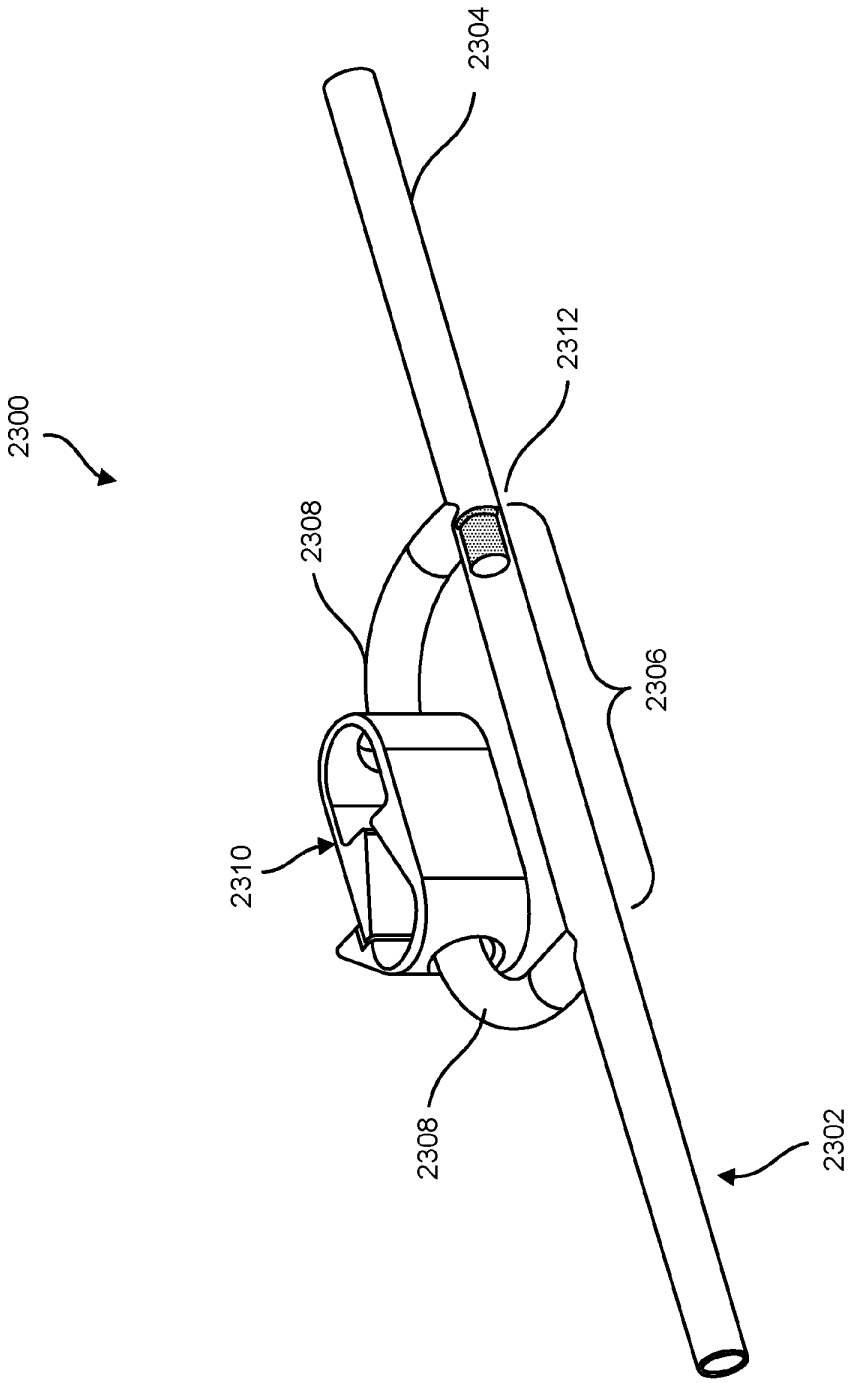


FIG. 23A

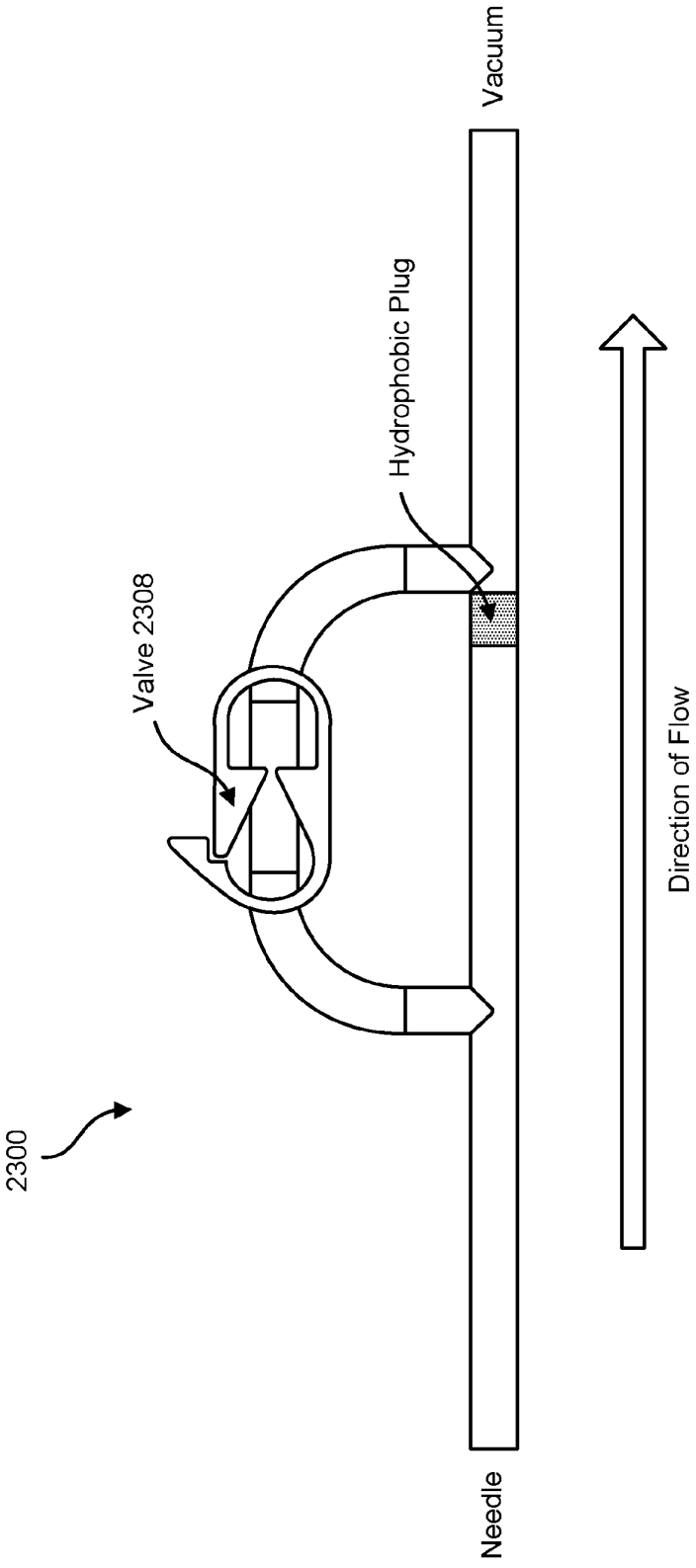

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011 (2011-12-29)	1-5, 7-13, 15-20
A	paragraph [0070] figure 15 abstract	6,14
A	US 2009/227953 A1 (TAN CHEE LEONG [SG] ET AL) 10 September 2009 (2009-09-10) the whole document	1-20
A	JP H08 257018 A (NISSHO KK) 8 October 1996 (1996-10-08) abstract; figures	1-20

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2016	19/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schultz, Ottmar

2

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 416 290 A (LUTKOWSKI LAWRENCE [US]) 22 November 1983 (1983-11-22) abstract; figures	1-20
A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) abstract; figures	1-20
A	EP 1 665 986 A1 (BECTON DICKINSON CO [US]) 7 June 2006 (2006-06-07) figures 13,14	1-20
A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) abstract; figures	1-20
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) paragraphs [0084] - [0094] figures 16-18	1-20

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043709

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		US 2015099996 A1	09-04-2015
		US 2015351678 A1	10-12-2015

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2017 (02.02.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/019552 A1

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A61B 5/15 (2006.01) *A61B 5/154* (2006.01)
A61B 5/153 (2006.01)

(21) International Application Number:
PCT/US2016/043709

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22 July 2016 (22.07.2016)

(25) Filing Language: English

(26) Publication Language: English

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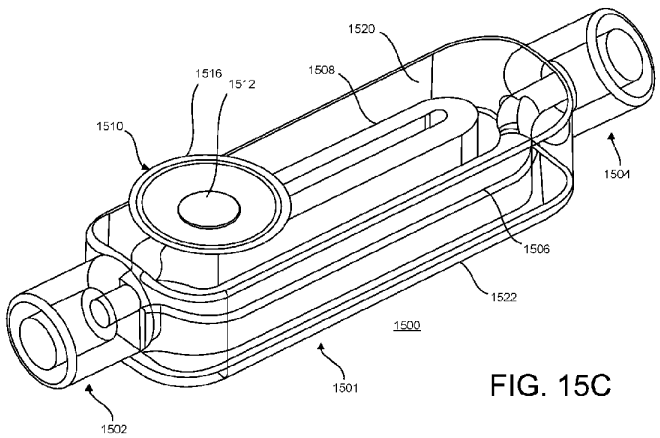


FIG. 15C

(57) Abstract: Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

WO 2017/019552 A1

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Non-Provisional Application Serial No. 15/140,443, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD" and U.S. Non-Provisional Application Serial No. 15/140,448, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD", both of which claim priority to U.S. Provisional Application Serial No. 62/196,797, filed on July 24, 2015 and titled "BLOOD CULTURE IMPROVEMENT SYSTEM AND METHOD"; U.S. Provisional Application Serial No. 62/238,636, filed on October 7, 2015 and titled "BLOOD SEQUESTRATION SYSTEM FOR NON-CONTAMINATED BLOOD SAMPLING"; and U.S. Provisional Application Serial No. 62/318,194, filed on April 4, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

[0002] Bacteraemia is the presence of microorganisms in the blood. Sepsis, on the other hand, is bacteraemia in the presence of clinical symptoms and signs such as fever, tachycardia, tachypnea and hypotension. Bacteraemia and sepsis are associated with a high mortality and an increased incidence and duration of hospital stay and associated costs. Many bacteraemias, sepsis, fungaemias and other pathogens actually occur within a hospital or other healthcare settings with catheters and venipunctures being a source of contamination as potential carriers of these pathogens.

[0003] Blood cultures are the standard test used to detect microbial pathogens related to bacteraemia and sepsis in a patient's blood. The term blood culture refers to a single venipuncture, either from a peripheral site or central or arterial line, with the blood inoculated into one or more blood culture bottles or containers. One bottle is considered a blood culture where two or more are considered a set. Multiple sets may be obtained from multiple venipunctures and are associated with different sites on the patient.

[0004] These methods allow for microbial identification and susceptibility testing to be performed, which is a critical component to managing sepsis, however the lack of rapid results and decreased sensitivity for fastidious pathogens has led to the development of improved systems and adjunctive molecular or proteomic testing.

[0005] Collection of blood samples for conducting blood cultures is a critical component of modern patient care and can either positively affect the patient outcome by providing an accurate diagnosis, or can adversely affect the outcome by prolonging unnecessary antimicrobial therapy, the length of hospital stays, and increasing costs.

[0006] One outcome of collection of blood cultures is contamination. Blood culture contamination can lead to a false positive culture result and/or significant increase in healthcare related costs. Sources of blood culture contamination include improper skin antisepsis, improper collection tube disinfection, and contamination of the initial blood draw which may then skew results.

[0007] Blood culture collection kits generally consist of a "butterfly" set, infusion set, or other type of venipuncture device as offered by companies like BD, Smiths, B. Braun and others, and aerobic and anaerobic blood culture bottles. Various different bottles are also available depending on the test requirements. These bottles are specifically designed to optimize recovery of both aerobic and anaerobic organisms. In conventional kits, a bottle used is known generally as a "Vacutainer," which is a blood collection tube formed of a sterile glass or plastic tube with a closure that is evacuated to create a vacuum inside the tube to facilitate the draw of a predetermined volume of liquid such as blood.

[0008] False positive blood cultures are typically a result of poor sampling techniques. They cause the use of antibiotics when not needed, increasing hospital costs and patient anxiety. Blood cultures are drawn from a needlestick into the skin, and then a Vacutainer is attached to capture a sample of blood. Contamination may occur from improper or incomplete disinfection of the skin area in and around the puncture site. It may also occur from the coring of the skin by the needle during insertion, with the cored skin cells and any associated contamination being pulled into the sample.

[0009] Blood flow through a hypodermic needle is laminar, and as such, a velocity gradient can be developed over the flow tube as a pressure drop is applied to the hypodermic needle. Either forceful aspiration of blood, or using a very small hypodermic needle, can cause lysis and a release of potassium from the red blood cells, thereby rendering the blood samples abnormal.

[0010] In other instances, some patients have delicate veins that can collapse under a pressure drop or vacuum, particularly as applied by a syringe's plunger that is drawn too quickly for the patient's condition. Since such condition is impossible to know beforehand, such vein collapses are a risk and very difficult to control.

[0011] Various strategies have been implemented to decrease blood culture contamination rates, e.g. training staff with regard to aseptic collection technique, feedback with regard to contamination rates and implementation of blood culture collection kits. Although skin antisepsis can reduce the burden of contamination, 20% or more of skin organisms are located deep within the dermis and are unaffected by antisepsis. Changing needles before bottle inoculation is not advisable as it increases the risk to acquire needle stick injuries without decreasing contamination rates.

[0012] Some conventional systems and techniques for reducing blood culture contamination include discarding the initial aliquot of blood taken from central venous catheters, venipunctures, and other vascular access systems. However, these systems require the user to mechanically manipulate an intravascular device, or require a complex series of steps that are difficult to ensure being followed.

SUMMARY

[0013] This document presents systems and methods for reducing blood culture contamination, lysing of cells, and vein collapse. In some implementations, a system and method can eliminate user variability in disinfection, and also eliminate the risk of skin cells getting into the blood culture sample. The systems and methods disclosed herein do not require a change in existing clinical processes, other than to potentially indicate when a vacutainer or other blood collection device (i.e., syringe) should be attached for drawing contaminant-free blood samples.

[0014] In some implementations of the systems and methods disclosed herein the withdrawal of blood is accomplished passively by use of the patient's own blood pressure, thereby reducing the risk of vein collapse and eliminating any additional user steps over current practice. The systems and methods can be applied to accommodate short-path direct stick or butterfly venipuncture systems. They can also be used with samples drawn through a catheter.

[0015] In one aspect, a blood sequestration device is presented. The blood sequestration device includes an inlet port and an outlet port. The blood sequestration device further includes a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port.

[0016] In another aspect, a blood sequestration device connected with a blood sampling pathway is described. The blood sampling pathway has a patient needle and a sample collection device. The blood sequestration device includes an inlet port connected with the patient needle, and a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, and an outlet port connected with a distal end of the sampling channel and with the sample collection device.

[0017] In yet another aspect, a blood sequestration device connected with a blood sampling system is described. The blood sampling system includes a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed and adapted for receiving an evacuated blood collection tube. The blood sequestration device includes an inlet port connected with the patient needle to receive the blood sample from the patient. The blood sequestration device further includes a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed by the evacuated blood collection tube. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a subsequent portion of the blood sample once the sample needle is unsealed by the evacuated blood collection tube. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel for conveying the subsequent portion of the blood sample to the sample needle.

[0018] In yet another aspect, a blood sample optimization system is disclosed and described. The blood sample optimization system includes a blood sampling system for accessing and acquiring one or more samples of a patient's blood, and a blood sequestration device for receiving and sequestering a first portion of the one or more samples of the patient's blood which might be contaminated by a venipuncture process and which could result in a false positive identification of a pathogen in the patient's blood.

[0019] The blood sampling system includes a patient needle configured for a venipuncture of a patient to access a sample of blood of a patient, a blood sampling pathway connected with the patient needle for conveying the sample of blood, and a sample needle configured for receiving an evacuated blood collection container to collect and contain a subsequent portion of the sample of blood.

[0020] In yet another aspect, a blood sequestration device is disclosed and described. In some implementations, the blood sequestration device can include an inlet port, an outlet port connected with the inlet port, and a sequestration chamber connected with the inlet port. The sequestration chamber can have a vent comprising an air permeable blood barrier.

[0021] The blood sequestration device is connected along the blood sampling pathway between the patient needle and the sample needle, and includes an inlet port for receiving the sample of blood. The blood sequestration device further includes a sequestration chamber connected with the inlet port for receiving a first amount of the sample of blood, the sequestration chamber having a vent comprising an air permeable blood barrier for sequestering at least a first portion of the first amount of the sample of blood. The blood sequestration device may further include a sampling channel having a proximal end connected with the inlet port, the sampling channel conveying a subsequent amount of the sample of blood to the evacuated blood collection container upon the sequestration chamber sequestering at least the first portion of the first amount of the sample of blood. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel, the outlet port for outputting the subsequent amount of the sample of blood.

[0022] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features and advantages will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other aspects will now be described in detail with reference to the following drawings.

[0024] FIG. 1 illustrates a blood sample optimization system.

[0025] FIG. 2 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0026] FIG. 3 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0027] FIG. 4 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0028] FIG. 5 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0029] FIG. 6 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0030] FIG. 7 is a flowchart of a method for optimizing a quality of a blood culture.

[0031] FIGS. 8A – 8E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with some implementations.

[0032] FIG. 9 illustrates a pathway splitter for use in a blood sequestrations system.

[0033] FIGS. 10A – 10D illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with alternative implementations.

[0034] FIGS. 11A – 11E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with other alternative implementations.

[0035] FIGS. 12A-12D illustrate a blood sample optimization system including a blood sequestration device in accordance with yet other alternative implementations.

[0036] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet another alternative implementations.

[0037] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample.

[0038] FIGS. 15A-15G illustrate a blood sequestration device and method of using the same, in accordance with yet another implementation.

[0039] FIGS. 16A-16D illustrate a blood sequestration device in accordance with yet another implementation.

[0040] FIGS. 17A – 17E illustrate a bottom member of a housing for a blood sequestration device.

[0041] FIGS. 18A – 18F illustrate a top member of a housing for a blood sequestration device.

[0042] FIGS. 19A and 19B illustrate a blood sequestration device having a top member mated with a bottom member.

[0043] FIG. 20 shows a blood sample optimization system including a blood sequestration device.

[0044] FIG. 21 illustrates a non-vented blood sequestration device using a wicking material chamber.

[0045] FIGS. 22A and 22B illustrate a material makeup of a filter for sequestering blood in a sequestration chamber of a blood sequestration device.

[0046] FIGS. 23A and 23B illustrate another implementation of a blood sequestration device that uses a vacuum force from a blood collection device.

[0047] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0048] This document describes blood sample optimization systems and methods for reducing or eliminating contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. In some implementations, a blood sample optimization system includes a patient needle for vascular access to a patient's bloodstream, a sample needle for providing a blood sample to a blood collection container, such as an evacuated blood collection container or tube like a Vacutainer™ or the like, or other sampling device, and a blood sequestration device located between the patient needle and the sample needle. The blood sequestration device includes a sequestration chamber for sequestering an initial, potentially contaminated

aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

[0049] FIG. 1 illustrates a blood sample optimization system in accordance with some implementations. The system includes a patient needle 1 to puncture the skin of a patient to access the patient's vein and blood therein. The system further includes a sample needle (i.e., a resealably closed needle for use with Vacutainers™ or the like) 5, which may be contained within and initially sealed by a resealable boot 10, a Luer activated valve, or another collection interface or device. The resealable boot 10 can be pushed aside or around the sample needle 5 by application of a Vacutainer™ bottle (not shown) for drawing the patient's blood. The system can further include a low volume chamber 30 that leads to the sample needle 5, but also includes an orifice or one or more channels 45 that lead to a sequestration chamber 55 formed by a housing 50.

[0050] The sequestration chamber 55 is a chamber, channel, pathway, lock, or other structure for receiving and holding a first aliquot of the patient's blood, which may be in a predetermined or measured amount, depending on a volume of the sequestration chamber 55. The first draw of blood typically contains or is more susceptible to containing organisms that cause bacteraemia and sepsis or other pathogens than subsequent blood draws. The sequestration chamber 55 can be a vessel encased in a solid housing, formed in or defined by the housing itself, or can be implemented as tubing or a lumen. The sequestration chamber 55, regardless how formed and implemented, may have a predetermined volume. In some implementations, the predetermined volume may be based on a volume of the patient needle, i.e. ranging from less than the volume of the patient needle to any volume up to or greater than 20 times or more of the volume of the patient needle. The predetermined volume of the sequestration chamber 55 may also be established to economize or minimize an amount of blood to be sequestered and disposed of.

[0051] The sequestration chamber 55 can be formed, contained or housed in a chamber housing 50, and can be made of plastic, rubber, steel, aluminum or other suitable material. For example, the sequestration chamber 55 could be formed of flexible tubing or

other elastomeric materials. The sequestration chamber 55 further includes an air permeable blood barrier 20 that allows air to exit the sequestration chamber 55. As used herein the term "air permeable blood barrier" means an air permeable but substantially blood impermeable substance, material, or structure. Examples may include hydrophobic membranes and coatings, a hydrophilic membrane or coating combined with a hydrophobic membrane or coating, mesh, a filter, a mechanical valve, antimicrobial material, or any other means of allowing air to be displaced from the sequestration chamber 55 as it is filled with blood. In various exemplary embodiments, an air permeable blood barrier may be formed by one or more materials that allow air to pass through until contacted by a liquid, such material then becomes completely or partially sealed to prevent or inhibit the passage of air and/or liquid. In other words, prior to contact with liquid, the material forms a barrier that is air permeable. After contact with a liquid, the material substantially or completely prevents the further passage of air and/or liquid.

[0052] The orifice or channel 45 can be any desired length, cross-sectional shape or size, and/or can be formed to depart from the low volume chamber 30 at any desired angle or orientation. The orifice or channel 45 may also include a one-way flap or valve 60 that maintains an initial aliquot of blood sample within the sequestration chamber 55. In some specific implementations, the orifice or channel 45 can include a "duck bill" or flapper valve 60, or the like, for one-way flow of blood from low volume chamber 30 to the sequestration chamber 55. The air permeable blood barrier 20 can also be constructed of a material that allows air to exit but then seals upon contact with blood, thereby not allowing external air to enter sequestration chamber 55. This sealing would eliminate the need for a valve.

[0053] Valve 60 can be any type of valve or closing mechanism. Chamber 30 is designed to hold virtually no residual blood, and can be designed to be adapted to hold or allow pass-through of a particular volume or rate of blood into sequestration chamber 55. Likewise, sequestration chamber 55 may also include any type of coating, such as an anti-microbial coating, or a coating that aids identification and/or diagnosis of components of the first, sequestered blood draw.

[0054] Housing 50 and 40 can be formed of any suitable material, including plastic, such as acrylonitrile butadiene styrene (ABS) or other thermoplastic or polymeric material, rubber, steel, or aluminum. The air permeable blood barrier 20 can include a color-providing substance, or other signaling mechanism, that is activated upon contact with blood from the initial blood draw, or when air displacement is stopped, or any combination of events with blood in the sequestration chamber 55. The air permeable barrier may also include an outer layer such as a hydrophobic membrane or cover that inhibits or prevents the inadvertent or premature sealing of the filter by an external fluid source, splash etc. Sequestration chamber 55 can also be translucent or clear to enable a user to visually confirm the chamber is filled.

[0055] FIG. 2 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown in FIG. 2, a sequestration chamber 55, or waste chamber, surrounds the patient needle 1, with an open-ended cuff or housing connected with the waste chamber and encircling the sample needle housing base and housing. The patient needle 1 and sample needle 5 are connected together by a boot 56, which forms a continuous blood draw channel therethrough. The boot 56 includes a single orifice or channel leading from the blood draw channel into sequestration chamber 55. The device can include more than one single orifice or channel, in other implementations. Each orifice or channel can include a one-way valve, and can be sized and adapted for predetermined amount of blood flow.

[0056] The sequestration chamber 55 includes an air permeable blood barrier. The filter can further include a sensor or indicator to sense and/or indicate, respectively, when a predetermined volume of blood has been collected in the sequestration chamber 55. That indication will alert a user to attach an evacuated blood collection tube or bottle, such as a Vacutainer™ to the sample needle 5. The housing for the sequestration chamber 55 can be any size or shape, and can include any type of material to define an interior space or volume therein. The interior space is initially filled only with air, but can also be coated with an agent or substance, such as a decontaminate, solidifying agent, or the like. Once evacuated blood collection tube is attached to the sample needle 5, blood will flow automatically into the patient needle 1, through the blood draw channel and sample needle 5, and into the bottle.

The sample needle 5 is covered by a resealable boot, coating or membrane that seals the sample needle when a blood collection bottle is not attached thereon or thereto.

[0057] FIG. 3 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is surrounded by a resealable boot or membrane, and is further connected with a patient needle 1. A blood flow channel is formed through the sample needle and the patient needle. The connection between the sample needle and patient needle includes a "T" or "Y" connector 102, which includes a channel, port or aperture leading out from the main blood flow channel to a sequestration chamber 104.

[0058] The T or Y connector 102 may include a flap or one-way valve, and have an opening that is sized and adapted for a predetermined rate of flow of blood. The sequestration chamber 104 can be formed from tubing, or be formed by a solid housing, and is initially filled with air. The sequestration chamber 104 will receive blood that flows out of a patient automatically, i.e. under pressure from the patient's own blood pressure. The sequestration chamber 104 includes an air permeable blood barrier 106, preferably at the distal end of tubing that forms the sequestration chamber 104, and which is connected at the proximal end to the T or Y connector 102. The T or Y connector 102 can branch off at any desired angle for most efficient blood flow, and can be formed so as to minimize an interface between the aperture and channel and the main blood flow channel, so as to minimize or eliminate mixing of the initial aliquot of blood with main blood draw samples.

[0059] In some alternative implementations, the sample needle may be affixed to a tubing of any length, as shown in FIG. 4, connecting at its opposite end to the T or Y connector 102. The sequestration chamber 104 can be any shape or volume so long as it will contain a predetermined amount of blood sample in the initial aliquot. The T or Y connector 102 may also include an opening or channel that is parallel to the main blood flow channel. The air permeable blood barrier may further include an indicator 107 or other mechanism to indicate when a predetermined amount of blood has been collected in the sequestration chamber, or when air being expelled reaches a certain threshold, i.e. to zero. The tubing can also include a clip 109 that can be used to pinch off and prevent fluid flow therethrough.

[0060] Once the air permeable blood barrier and primary chamber are sealed the initial aliquot of blood is trapped in the sequestration chamber 104, an evacuated blood collection tube, such as a Vacutainer™ bottle may be attached to the sample needle 5 to obtain the sample. The blood collection tube can be removed, and the sample needle 5 will be resealed. Any number of follow-on blood collection tubes can then be attached for further blood draws or samples. Upon completion of all blood draws, the system can be discarded, with the initial aliquot of blood remaining trapped in the sequestration chamber 104.

[0061] FIG. 5 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is connected with a patient needle by tubing. A "T" or "Y" connector 120 is added along the tubing at any desired location, and includes an aperture, port or channel leading to a sequestration chamber 204, substantially as described above.

[0062] FIG. 6 illustrates a blood sample optimization system in accordance with some alternative implementations, in which a sequestration chamber 304, formed as a primary collection channel, receives an initial aliquot of blood, and is provided adjacent to the blood sampling channel. The sequestration chamber 304 can encircle the blood sampling channel, the patient needle 1, and/or the sample needle 5. The primary collection channel can include a T or Y connector 120, or other type of aperture or channel. The sequestration chamber 304 includes an air permeable blood barrier, which can also include an indicator of being contacted by a fluid such as blood, as described above.

[0063] In some implementations, either the patient needle 1 or the sample needle 5, or both, can be replaced by a Luer lock male or female connector. However, in various implementations, the connector at a sample needle end of the blood sample optimization system is initially sealed to permit the diversion of the initial aliquot of blood to the sequestration chamber, which is pressured at ambient air pressure and includes the air outlet of the air permeable blood barrier. In this way, the system passively and automatically uses a patient's own blood pressure to overcome the ambient air pressure of the sequestration chamber to push out air through the air permeable blood barrier and displace air in the sequestration chamber with blood.

[0064] FIG. 7 is a flowchart of an exemplary method for optimizing the quality of a blood culture. At 702, a clinician places a needle into a patient's vein. At 704, blood then flows into a sequestration chamber, pushing the air in the sequestration chamber out of the sequestration chamber through an air permeable blood barrier. In some implementations, the volume of the sequestration chamber is less than 0.1 to more than 5 cubic centimeters (cc's), or more. The sequestration chamber is sized and adapted to collect a first portion of a blood sample, which is more prone to contamination than secondary and other subsequent portion of the blood sample or subsequent draws. Since the sequestration chamber has an air-permeable blood barrier through which air can be displaced by blood pushed from the patient's vein, such blood will naturally and automatically flow into the sequestration chamber before it is drawn into or otherwise enters into a Vacutainer or other bottle for receiving and storing a blood sample.

[0065] When the sequestration chamber fills, the blood will gather at or otherwise make contact with the air permeable blood barrier, which will inhibit or prevent blood from passing therethrough. At 706, when the blood comes into contact with the entire internal surface area of the air permeable blood barrier, the air permeable blood barrier is then closed and air no longer flows out or in. At 708, the clinician may be provided an indictor or can see the full chamber, to indicate the evacuated blood collection tube, such as a Vacutainer™ can be attached. The indicator can include visibility into the primary chamber to see whether it is full, the blood barrier changing color, for example, or other indicator. The fill time of the sequestration chamber may be substantially instantaneous, so such indicator, if present, may be only that the sequestration chamber is filled.

[0066] Prior to an evacuated blood collection tube being attached, communication between the needle, sampling channel, and the sequestration chamber is restricted by the sealing of the sequestration chamber blood barrier thereby not permitting air to reenter the system through the sequestration. Sealing the communication path could also be accomplished with a mechanical twist or other movement, a small orifice or tortuous pathway, eliminating the need for a separate valve or mechanical movement or operation by the clinician. At 710, once the evacuated blood collection tube is removed, the self-sealing membrane closes the sample needle, and at 712, additional subsequent evacuated blood

collection tubes may be attached. Once samples have been taken, at 714 the device is removed from the patient and discarded.

[0067] FIGS. 8A – 8E illustrate an exemplary blood sample optimization system 800 for non-contaminated blood sampling, in accordance with some implementations. The blood sample optimization system 800 includes an inlet port 802 that can be connected to tubing, a patient needle (or both), or other vascular or venous access device, and a pathway splitter 804 having a first outlet to a sequestration chamber tubing 806 and a second outlet to sample collection tubing 808. One or both of the sequestration chamber tubing 806 and the sample collection tubing 808 can be formed of tubing. In some implementations, the sequestration chamber tubing 806 is sized so as to contain a particular volume of initial blood sample. The sample collection tubing 808 will receive a blood sample once the sequestration chamber tubing 806 is filled. The sample collection tubing 808 can be connected to a Vacutainer™ base or housing 810, or other blood sample collection device.

[0068] The blood sequestration system 800 further includes a blood sequestration device 812 which, as shown in more detail in FIGS. 8B – 8D, includes a housing 818 that includes a sampling channel 820 defining a pathway for the non-contaminated sample collection tubing 808 or connected at either end to the non-contaminated sample collection tubing 808. The sampling channel 820 can be curved through the housing 818 so as to better affix and stabilize the housing 818 at a location along the non-contaminated sample collection tubing 808.

[0069] The blood sequestration device 812 further includes a sequestration chamber 822 connected with the sequestration chamber tubing 806 or other chamber. The sequestration chamber 822 terminates at an air permeable blood barrier 824. The air permeable blood barrier 824 can also include a coloring agent that turns a different color upon full contact with blood, as an indicator that the regular collection of blood samples (i.e. the non-contaminated blood samples) can be initiated. Other indicators may be used, such as a small light, a sound generation mechanism, or the like. In some implementations, the air permeable blood barrier is positioned at a right angle from the direction of sequestration chamber 822, but can be positioned at any distance or orientation in order to conserve space

and materials used for the housing 818. The housing 818 and its contents can be formed of any rigid or semi-rigid material or set of materials.

[0070] FIG. 9 illustrates a pathway splitter 900 for use in a blood sequestrations system, such as those shown in FIGS. 8A – 8E, for example. The pathway splitter 900 includes an inlet port 902, a main line outlet port 904, and a sequestration channel outlet port 906. The inlet port 902 can be connected to main tubing that is in turn connected to a patient needle system, or directly to a patient needle. The main line outlet port 904 can be connected to main line tubing to a blood sampling system, such as a vacutainer base or housing, or directly to such blood sampling system. The sequestration channel outlet port 906 can be connected to sequestration tubing for receiving and sequestering a first sample of blood, up to a measured amount or predetermined threshold. Alternatively, the sequestration channel outlet port 906 can be connected to a sequestration chamber. The sequestration channel outlet port 906 is preferably 20-70 degrees angled from the main line outlet port 904, which in turn is preferably in-line with the inlet port 902. Once the predetermined amount of initial blood sample is sequestered in the sequestration tubing or chamber, in accordance with mechanisms and techniques described herein, follow-on blood samples will flow into the inlet port 902 and directly out the main line outlet port 904, without impedance.

[0071] FIGS. 10A – 10D illustrate a blood sequestration device 1000 in accordance with alternative implementations. The blood sequestration device 1000 includes an inlet port 1002, a main outlet port 1004, and a sequestration channel port 1006. The inlet port 1002 can be connected to a patient needle or related tubing. The main outlet port 1004 can be connected to a blood sample collection device such as a Vacutainer, associated tubing, or a Luer activated valve, or the like. The sequestration channel port 1006 splits off from the main outlet port 1004 to a sequestration chamber 1008. In some implementations, the sequestration chamber 1008 is formed as a helical channel within a housing or other container 1001.

[0072] The sequestration chamber 1008 is connected at the distal end to an air permeable blood barrier 1010, substantially as described above. Air in the sequestration chamber 1008 is displaced through the air permeable blood barrier 1010 by an initial aliquot

of blood that is guided into the sequestration channel port 1006. Once the sequestration chamber 1008 is filled, further blood draws through the main outlet port 1004 can be accomplished, where these samples will be non-contaminated.

[0073] FIGS. 11A – 11E illustrate a blood sequestration device 1100 in accordance with other alternative implementations. The blood sequestration device 1100 includes an inlet port 1102, similar to the inlet ports described above, a main outlet port 1104, and a sequestration channel port 1106 that splits off from the main outlet port 1104 and inlet port 1102. The sequestration channel port is connected to a sequestration chamber 1108. In the implementation shown in FIGS. 11A – 11E, the blood sequestration device includes a base member 1101 having a channel therein, which functions as the sequestration chamber 1108. The channel can be formed as a tortuous path through the base member 1101, which is in turn shaped and formed to rest on a limb of a patient.

[0074] A portion of the sequestration chamber 1108 can protrude from the base member or near a top surface of the base member, just before exiting to an air permeable blood barrier 1110, to serve as a blood sequestration indicator 1109. The indicator 1109 can be formed of a clear material, or a material that changes color when in contact with blood.

[0075] In some implementations, the blood sequestration device 1100 can include a blood sampling device 1120 such as a normally closed needle, Vacutainer™ shield or other collection device. The blood sampling device 1120 can be manufactured and sold with the blood sequestration device 1100 for efficiency and convenience, so that a first aliquot of blood that may be contaminated by a patient needle insertion process can be sequestered. Thereafter, the blood sampling device 1120 can draw non-contaminated blood samples to reduce the risk of false positive testing and ensure a non-contaminated sample.

[0076] FIGS. 12A-12D illustrate a blood sample optimization system 1200 in accordance with yet other alternative implementations. The system 1200 includes a blood sequestration device 1202 for attaching to a blood sampling device 1204, such as a Vacutainer™ or other collection and sampling device. The blood sequestration device 1202 is configured and arranged to receive, prior to a Vacutainer™ container or vial being attached to a collection needle of the blood sampling device 1204, a first aliquot or amount of blood,

and sequester that first aliquot or amount in a sequestration channel of the blood sequestration device 1202.

[0077] In some implementations, the blood sequestration device 1202 can include an inlet port 1212, a main outlet port, and a sequestration channel port. The inlet port 1212 can be connected to a patient needle or related tubing. The main outlet port 1214 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port splits off from the main outlet port to a sequestration chamber 1218.

[0078] In some implementations, the sequestration chamber 1218 is formed as a channel within the body of a sequestration device 1202. The sequestration chamber 1218 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel. The sequestration device 1202 can include a housing or other containing body, and one or more channels formed therein. As shown in FIGS. 12A and 12B, the sequestration device 1202 includes a main body 1206 and a cap 1208. The main body 1206 is formed with one or more cavities or channels, which are further formed with one or more arms 1210 that extend from the cap 1208, and which abut the cavities or channels in the main body 1206 to form the primary collection port and main outlet port.

[0079] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet other alternative implementations. The system 1300 includes a blood sequestration device 1302 for attaching to a blood sampling device 1304, such as a Vacutainer or other bodily fluid collection and sampling device. The blood sequestration device 1302 is configured and arranged to receive, prior to a Vacutainer container or vial being attached to a collection needle of the blood sampling device 1304, a first aliquot or amount of blood, and to sequester that first aliquot or amount of blood or other bodily fluid in a sequestration channel of the blood sequestration device 1302.

[0080] The blood sequestration device 1302 includes a housing 1301 having an inlet port 1314, a main outlet port 1312, and a sequestration channel port 1316. The inlet port 1314 can be connected to a patient needle or associated tubing. The main outlet port 1312

can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port 1316 splits off from the main inlet port 1314 to a sequestration chamber 1318.

[0081] In the implementation shown in FIGS. 13A-D, the sequestration chamber 1318 is formed as a cavity or chamber within housing 1301 or formed by walls that define housing 1301. The sequestration chamber 1318 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel, that is defined by the cooperation and connection of housing 1301 with cap 1307 which cap 1307 can include a protrusion 1305 that provides one or more walls or directors for the winding channel in the sequestration chamber 1318. The protrusion 1305 from the cap 1307 can be straight or curved, and may have various channels, apertures or grooves embedded therein, and can extend from the cap 1307 any angle or orientation. When the cap 1307 is connected with the housing 1301 to complete the formation of the sequestration chamber 1318, the protrusion 1305 forms at least part of the winding channel to sequester a first aliquot or amount of blood or other bodily fluid in a sequestration channel formed in the sequestration chamber 1318 and by the winding channel.

[0082] The sequestration chamber 1318 includes an air permeable blood barrier 1310, substantially as described above. Air in the sequestration chamber 1318 is displaced through the air permeable blood barrier 1310 by an initial aliquot of blood that is provided into the sequestration chamber 1318 by the blood pressure of the patient. Once the sequestration chamber 1318 is filled and the air in the sequestration chamber 1318 displaced, the blood pressure of the patient will be insufficient to drive or provide further blood into the blood sequestration device 1302, and in particular the outlet port 1312, until a force such as a vacuum or other pressure, such as provided by the blood sample collection device like Vacutainer is provided to draw out a next aliquot or amount of blood or bodily fluid. Further blood draws through the main outlet port 1312 can be accomplished, where these samples will be non-contaminated since any contaminants would be sequestered in the sequestration chamber 1318 with the first aliquot of blood.

[0083] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system 1400 to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample. The blood sampling system 1400 includes a blood sequestration device 1401 that can be connected between a blood sample collection device 1403 and a patient needle (not shown). The blood sample collection device 1403 can be a Vacutainer or the like. The blood sequestration device 1401 includes an inlet port 1402 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1402 may also be connected with tubing or other conduit that is in turn connected with the patient needle.

[0084] The inlet port 1402 defines an opening into the blood sequestration device 1401, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more. The blood sequestration device 1401 further includes an outlet port 1404, which defines an opening out of the blood sequestration device 1401 and to the blood sample collection device 1403. The outlet port 1404 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device 1403. The outlet port 1404 can further include a connector device such as a threaded cap, a Luer connector (male or female), a non threaded interference or glue joint fitting for attachment of various devices including but not limited to tubing, or the like.

[0085] The blood sequestration device 1401 further includes a sampling channel 1406 between the inlet port 1402 and the outlet port 1404, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1406 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1406 has a substantially similar cross sectional area as the opening of the inlet port 1402. In other implementations, the sampling channel 1406 can gradually widen from the inlet port 1402 to the outlet port 1404.

[0086] The blood sequestration device 1401 further includes a sequestration chamber 1408 that is connected to and split off or diverted from the sampling channel 1406 at any point between the inlet port 1402 and the outlet port 1404, but preferably from a proximal end of the sampling channel 1406 near the inlet port 1402. The sequestration chamber 1408 is at first maintained at atmospheric pressure, and includes an air outlet 1412 at or near a distal end of the sequestration chamber 1408 opposite the diversion point from the sampling channel 1406. The air outlet 1412 includes an air permeable blood barrier 1412. As shown in FIG. 14B, the air permeable blood barrier 1412 can be overlaid with a protective cover 1416. The protective cover 1416 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1412 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1412 as the air is displaced from the sequestration chamber 1408 by blood being forced into the sequestration chamber 1408 by a patient's own blood pressure. In addition the protective cover 1416 can be constructed to inhibit or prevent accidental exposure of the air permeable blood barrier to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0087] As shown in FIGS. 14C and 14D, the sampling channel 1406 can be cylindrical or frusto-conical in shape, going from a smaller diameter to a larger diameter, to minimize a potential to lyse red blood cells. Likewise, the sampling channel 1406 is formed with a minimal amount of or no sharp turns or edges, which can also lyse red blood cells. The sampling channel 1406 splits off to the sequestration chamber 1408 near the inlet port 1402 via a diversion pathway 1409. The diversion pathway 1409 can have any cross-sectional shape or size, but is preferably similar to the cross-sectional shape of at least part of the inlet port 1402.

[0088] In some implementations, the sampling channel 1406 and the sequestration chamber 1408 are formed by grooves, channels, locks or other pathways formed in housing 1414. The housing 1414 can be made of plastic, metal or other rigid or semi-rigid material. The housing 1414 can have a bottom member that sealably mates with a top member. One or both of the bottom member and the top member can include the sampling channel 1406 and the sequestration chamber 1408, as well as the diversion pathway 1409, the inlet port 1402,

and the outlet port 1404. In some other implementations, one or more of the diversion pathway 1409, the inlet port 1402, and/or the outlet port 1404 can be at least partially formed by a cap member that is connected to either end of the housing 1414. In some implementations, the top member and the bottom member, as well as the cap member(s), can be coupled together by laser welding, heat sealing, gluing, snapping, screwing, bolting, or the like. In other implementations, some or all of the interior surface of the diversion pathway 1409 and/or sequestration chamber 1408 can be coated or loaded with an agent or substance, such as a decontaminate, solidifying agent, or the like. For instance, a solidifying agent can be provided at the diversion pathway 1409 such that when the sequestration chamber 1408 is filled and the initial aliquot of blood backs up to the diversion pathway 1409, that last amount of sequestered blood could solidify, creating a barrier between the sequestration chamber 1408 and the sampling channel 1406.

[0089] FIGS. 15A-15G illustrate a blood sequestration device 1500. The blood sequestration device 1500 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like.

[0090] The blood sequestration device 1500 includes an inlet port 1502 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1502 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1502 defines an opening into the blood sequestration device 1500, which opening may be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[0091] The inlet port 1502 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1502, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner,

the blood sequestration device 1500 can be fabricated and sold with the patient needle as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1500 at the time of blood draw or sampling.

[0092] The blood sequestration device 1500 further includes an outlet port 1504, which defines an opening out of the blood sequestration device 1500 and to the blood sample collection device. The outlet port 1504 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1500 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1500 at the time of blood draw or sampling.

[0093] The blood sequestration device 1500 further includes a sampling channel 1506 between the inlet port 1502 and the outlet port 1504, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1506 can be any sized, shaped or configured channel or conduit. In some implementations, the sampling channel 1506 has a substantially similar cross sectional area as the opening of the inlet port 1502. In other implementations, the sampling channel 1506 can gradually widen from the inlet port 1502 to the outlet port 1504.

[0094] The blood sequestration device 1500 further includes a sequestration chamber 1508 that is connected to and split off or diverted from the sampling channel 1506 at any point between the inlet port 1502 and the outlet port 1504, but preferably from a proximal end of the sampling channel 1506 near the inlet port 1502. In some implementations, the diversion includes a Y-shaped junction. The sequestration chamber 1508 is preferably maintained at atmospheric pressure, and includes a vent 1510 at or near a distal end of the sequestration chamber 1508. The vent 1510 includes an air permeable blood barrier 1512. FIG. 15C illustrates the blood sequestration device 1500 with the sequestration chamber 1508 filled with a first aliquot or sample of blood from the patient.

[0095] The air permeable blood barrier 1512 can be covered with a protective cover 1516. The protective cover 1516 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1512 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1512 as the air is displaced from the sequestration chamber 1508 by blood being forced into the sequestration chamber 1508 by a patient's own blood pressure. The protective cover 1516 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0096] FIG. 15B is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating an initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before a sample collection device is activated. FIG. 15G is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and bottom side of the housing 1501 of the blood sequestration device 1500, and illustrating the initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before the sample collection device is activated. FIG. 15C is another perspective view of the blood sequestration device 1500 from the inlet port 1502 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating blood now being drawn through sampling channel 1506 while the sequestered blood remains substantially in the sequestration chamber 1508.

[0097] FIG. 15D is a cross section of the blood sequestration device 1500 in accordance with some implementations, showing the housing 1501 that defines the sampling channel 1506 and the sequestration chamber 1508. FIGS. 15E and 15F illustrate various form factors of a housing for a blood sequestration device, in accordance with one or more implementations described herein.

[0098] The sequestration chamber 1508 can have a larger cross-sectional area than the sampling channel 1506, and the cross-sectional area and length can be configured for a predetermined or specific volume of blood to be sequestered or locked. The sampling

channel 1506 can be sized to be compatible with tubing for either or both of the patient needle tubing or the blood collection device tubing.

[0099] The housing 1501 can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIG. 15D, the housing 1501 includes a top member 1520 and a bottom member 1522 that are mated together, one or both of which having grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc. The top member 1520 can be connected with the bottom member 1522 by any mating or connection mechanism, such as by laser welding, thermal bonding, ultrasonic welding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like.

[00100] In some implementations, such as shown in FIG. 15D, the top member 1520 can include the grooves, channels, locks, conduits or other pathways, while the bottom member 1522 can include a protrusion 1524 that is sized and adapted to fit into at least one of the grooves, channels, locks or other pathways of the top member 1520. The protrusion 1524 can provide a surface feature, such as a partial groove or channel, for instance, to complete the formation of either the sampling channel 1506 and/or the sequestration chamber 1508. In some implementations, the protrusion 1524 can be formed with one or more angled sides or surfaces for a tighter fit within the corresponding groove, channel, lock or other pathway. In yet other implementations, both the top member 1520 and the bottom member can include grooves, channels, locks or other pathways, as well as one or more protrusions 1524.

[00101] In some implementations, the sampling channel 1506 and the sequestration chamber 1508 are formed by grooves, channels, locks or other pathways formed in housing 1501. The housing 1501 can be made of any suitable material, including rubber, plastic, metal or other material. The housing 1501 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1501 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1506 and/or the sequestration chamber 1508 is clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 1508 is first filled to the

extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1506. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1512 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00102] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will make its way into the input port 1502 blood sequestration device 1500 and flow into the sequestration chamber 1508 by following the path of least resistance, as the patient's own blood pressure overcomes the atmospheric pressure in the sequestration chamber 1508 to displace air therein through the air permeable blood barrier 1512. The patient's blood pressure will not be sufficient to overcome the air pressure that builds up in the sealed sampling channel 1506. Eventually, the sequestration chamber 1508, which has a predetermined volume, is filled with blood that displaces air through the air permeable blood barrier 1512. Once the blood hits the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1512 material to completely or partially seal the vent 1510. A signal or indication may be provided that the practitioner can now utilize the Vacutainer capsule or other blood sample collection device to acquire a next amount of the patient's blood for sampling. The blood in the sequestration chamber 1508 is now effectively sequestered in the sequestration chamber.

[00103] Upon filling the blood sequestration pathway 1508 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1506, possibly resulting in a small amount of blood moving past the diversion point to the sequestration chamber 1508 and into the sampling channel 1506, queuing up the uncontaminated blood to be drawn through the sampling channel 1506.

[00104] FIGS. 16-19 illustrate yet another implementation of a blood sequestration device. FIGS. 16A-16D illustrate a blood sequestration device 1600 that can be connected

between a blood sample collection device, such as an evacuated blood collection container like a Vacutainer™ (not shown), and a patient needle (not shown) and/or associated tubing. FIG. 17 illustrates a bottom member of the blood sequestration device, and FIG. 18 illustrates a top member of the blood sequestration device, which top member and bottom member can be mated together to form an input port, and output port, a sequestration chamber and a sampling channel, as explained more fully below. FIGS. 19A and B show the top member and bottom member mated together. It should be understood that FIGS. 16-19 illustrate one exemplary manner of constructing a blood sequestration device as described herein, and other forms of construction are possible.

[00105] Referring to FIGS. 16A – D, the blood sequestration device 1600 includes an inlet port 1602 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1602 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1602 defines an opening into the blood sequestration device 1600, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[00106] The inlet port 1602 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1602, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1600 at the time of blood draw or sampling.

[00107] The blood sequestration device 1600 further includes an outlet port 1604, which defines an opening out of the blood sequestration device 1600 and to the blood sample collection device. The outlet port 1604 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing

or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1600 at the time of blood draw or sampling.

[00108] The blood sequestration device 1600 further includes a sampling channel 1606 between the inlet port 1602 and the outlet port 1604, and a sequestration chamber 1608 that is connected to and split off or diverted from the sampling channel 1606 at any point between the inlet port 1602 and the outlet port 1604. The sampling channel 1606 functions as a blood sampling pathway once a first aliquot of blood has been sequestered in the sequestration chamber 1608. The sampling channel 1606 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1606 has a substantially similar cross sectional area as the opening of the inlet port 1602. In other implementations, the sampling channel 1606 can gradually widen from the inlet port 1602 to the outlet port 1604. The sequestration chamber 1608 may have a larger cross section to form a big reservoir toward the sequestration channel path so that the blood will want to enter the reservoir first versus entering a smaller diameter on the sampling channel 1606, as is shown more fully in FIGS. 17 and 19.

[00109] In some exemplary implementations, the diversion between the sampling channel 1606 and the sequestration chamber 1608 is by diverter junction 1607. Diverter junction 1607 may be a substantially Y-shaped, T-shaped, or U-shaped. In some preferred exemplary implementations, and as shown in FIG. 17A – 17B, the diverter junction 1607 is configured such that the flow out of the inlet port 1602 is preferentially directed toward the sequestration chamber 1608. The sequestration chamber 1608 may also include or form a curve or ramp to direct the initial blood flow toward and into the sequestration chamber 1608.

[00110] The sequestration chamber 1608 is preferably maintained at atmospheric pressure, and includes a vent 1610 at or near a distal end of the sequestration chamber 1608. The vent 1610 may include an air permeable blood barrier 1612 as described above.

[00111] The blood sequestration device 1600 can include a housing 1601 that can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIGS. 17A – 17D and FIGS. 18A – 18F, the housing 1601 includes a top member 1620 and a bottom member 1622 that are mated together. The blood sequestration device 1600 can also include a gasket or other sealing member (not shown) so that when the top member 1620 is mechanically attached with the bottom member 1622, the interface between the two is sealed by the gasket or sealing member. The FIGS. 17A – 17D illustrate a bottom member 1622 of a housing for a blood sequestration device 1600. The bottom member 1622 can include grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc., to form the sampling channel 1606, the sequestration chamber 1608, and diverter junction 1607.

[00112] The sequestration chamber 1608 may have a larger cross section than the sampling channel 1606 so that the blood will preferentially move into the sequestration chamber first versus entering a smaller diameter on the sampling channel 1606.

[00113] FIGS. 18A – 18F illustrate the top member 1620, which can be connected with the bottom member 1622 by any mating or connection mechanism, such as by laser welding, thermal bonding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like. The top member 1620 can include some or all of the grooves, channels, locks, conduits or other pathways to form the sampling channel 1606, the sequestration chamber 1608, and the diverter junction 1607. In yet other implementations, both the top member 1620 and the bottom member 1622 can include the grooves, channels, locks or other pathways.

[00114] In some implementations, the sampling channel 1606 and the sequestration chamber 1608 are formed by grooves, channels, locks or other pathways formed in housing 1601. The housing 1601 can be made of rubber, plastic, metal or any other suitable material. The housing 1601 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1601 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1606 and/or the sequestration chamber 1608 may be clear or translucent, giving a practitioner a

visual cue or sign that the sequestration chamber 1608 is first filled to the extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1606. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1612 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00115] As shown in FIGS. 18A – 18F, the air permeable blood barrier 1612 can be covered with, or surrounded by, a protective member 1616. The protective member 1616 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1612 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1612 as the air is displaced from the sequestration chamber 1608. In some implementations, the protective member 1616 includes a protrusion that extends up from a top surface of the top member 1620 and around the air permeable blood barrier 1612. The protective cover 1616 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[00116] In use, the blood sequestration device 1600 includes a sampling channel 1606 and a sequestration chamber 1608. Both pathways are initially air-filled at atmospheric pressure, but the sampling channel 1606 is directed to an output port 1604 that will be initially sealed by a Vacutainer or other such sealed blood sampling device, and the sequestration chamber 1608 terminates at a vent 1610 to atmosphere that includes an air permeable blood barrier 1612.

[00117] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will pass through input port 1602 of blood sequestration device 1600. This initial volume of potentially contaminated blood will preferentially flow into the sequestration chamber 1608 by finding the path of least resistance. The patient's own blood

pressure overcomes the atmospheric pressure in the vented sequestration chamber 1608 to displace air therein through the air permeable blood barrier 1612, but is not sufficient to overcome the air pressure that builds up in the sealed sampling channel 1606. In various exemplary embodiments, the sequestration chamber 1608 and sampling channel 1606 can be configured such that the force generated by the patient's blood pressure is sufficient to overcome any effect of gravity, regardless of the blood sequestration device's orientation.

[00118] Eventually, the sequestration chamber 1608 fills with blood that displaces air through the air permeable blood barrier 1612. Once the blood contacts the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1612 material to completely or partially seal the vent 1610. A signal or indication may be provided that the practitioner can now utilize the Vacutainer or other blood sampling device.

[00119] Upon filling the blood sequestration pathway 1608 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1606, possibly resulting in a small amount of blood moving past the diversion point into the sampling channel 1606, queuing up the uncontaminated blood to be drawn through the sampling channel 1606.

[00120] FIG. 19A is a side view, and FIG. 19B is a cross-sectional view, of the blood sequestration device 1600, illustrating the top member 1620 mated with the bottom member 1622.

[00121] FIG. 20 shows a blood sample optimization system 2000 that includes a patient needle 2002 for vascular access to a patient's bloodstream, a blood sample collection device 2004 to facilitate the collecting of one or more blood samples, and a conduit 2006 providing a fluid connection between the patient needle 2002 and the blood sample collection device 2004. In some implementations, the blood sample collection device 2004 includes a protective shield that includes a sealed collection needle on which a sealed vacuum-loaded container is placed, which, once pierced by the collection needle, draws in a blood sample under vacuum pressure or force through the conduit 2006 from the patient needle 2002.

[00122] The blood sample optimization system 2000 further includes a blood sequestration device 2008, located at any point on the conduit 2006 between the patient needle 2002 and the blood sample collection device 2004 as described herein.

[00123] FIG. 21 illustrates a non-vented blood sequestration device 2100 using a wicking material chamber. The blood sequestration device 2100 includes a housing 2101 that has a sampling channel 2104 that is at least partially surrounded or abutted by a sequestration chamber 2102 that is filled with a wicking material. An initial aliquot of blood is drawn in from the patient needle into the sampling channel 2104 where it is immediately wicked into the wicking material of the sequestration chamber 2102. The wicking material and/or sequestration chamber 2102 is sized and adapted to receive and hold a predetermined amount of blood, such that follow-on or later blood draws pass by the wicking material and flow straight through the sampling channel 2104 to a sampling device such as a Vacutainer. The wicking material can include a substance such as a solidifier, a decontaminate, or other additive.

[00124] As described herein, an air permeable blood barrier may be created using a wide variety of different structures and materials. As shown in FIGS. 22A and B, an air permeable blood barrier 2202 of a blood sequestration device 2200 can include a polymer bead matrix 2204, in which at least some beads are treated to make them hydrophilic. The air permeable blood barrier 2202 further includes a self-sealing material 2206, such as carboxymethyl cellulose (CMC) or cellulose gum, or other sealing material. The air permeable blood barrier 2202 can further include voids 2208 that permit air flow before contact or during partial contact with a fluid such as blood. As shown in FIG. 22B, contact with a fluid causes the self-sealing material 2206 to swell and close off the voids 2208, occluding air flow through the voids 2208 and creating a complete or partial seal.

[00125] FIGS. 23A and B illustrate yet another implementation of a blood sequestration device 2300, having an inlet port 2302 to connect with a patient needle, an outlet port 2304 to connect with a blood sample collection device, a sequestration chamber 2306, and a sampling channel 2308 that bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be

sequestered. The sequestration chamber 2306 includes a hydrophobic plug 2312 at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302. A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. A small amount of blood may make its way into the sampling channel 2308, which is initially closed off by valve 2308. Upon release of the valve 2308, and under further force of the vacuum or other force, follow-on amounts of blood will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 toward the outlet port 2304 and to the collection device.

[00126] The sampling channel 2308 can have any suitable geometry and can be formed of plastic tubing or any other suitable material. Valve 2308 can be a clip or other enclosing device to pinch, shunt, bend or otherwise close off the sampling channel before the initial aliquot of blood is sequestered in the sequestration chamber 2306.

[00127] Although a variety of embodiments have been described in detail above, other modifications are possible. Other embodiments may be within the scope of the following claims.

CLAIMS

1. A blood sequestration device comprising;

an inlet port;

an outlet port;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

2. The blood sequestration device in accordance with claim 1, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

3. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber includes a sequestration channel defined in the housing.

4. The blood sequestration device in accordance with claim 3, further comprising a blood sampling pathway connected with the inlet port, and wherein the inlet port defined by the housing has a cross-sectional geometry consistent with the blood sampling pathway.

5. The blood sequestration device in accordance with claim 3, wherein the sampling channel defined by the housing has a cross-sectional geometry consistent with the inlet port.

6. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

7. The blood sequestration device in accordance with claim 3, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

8. A blood sequestration device connected with a blood sampling pathway having a patient needle and a sample collection device, the blood sequestration device comprising;

an inlet port connected with the patient needle;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port; and

an outlet port connected with a distal end of the sampling channel and with the sample collection device; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

9. The blood sequestration device in accordance with claim 8, wherein the inlet port is connected with the patient needle via a first portion of the blood sampling pathway.

10. The blood sequestration device in accordance with claim 8, wherein the outlet port is connected with the sample collection device via a second portion of the blood sampling pathway.

11. The blood sequestration device in accordance with claim 8, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

12. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber includes a sequestration channel defined in the housing.

13. The blood sequestration device in accordance with claim 12, wherein the sequestration channel has a proximal end connected with the inlet port, and a distal end having the vent comprising an air permeable blood barrier.

14. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

15. The blood sequestration device in accordance with claim 8, wherein the sampling channel has a substantially uniform cross-sectional geometry that is consistent with the blood sampling pathway.

16. The blood sequestration device in accordance with claim 15, wherein the sequestration chamber includes a sequestration chamber that has a cross-sectional area that is larger than the cross-sectional geometry of the sampling channel.

17. A blood sequestration device connected with a blood sampling system comprising a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed, the blood sequestration device comprising;

an inlet port connected with the patient needle to receive the blood sample from the patient;

a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed; and

a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a second portion of the blood sample once the sample needle is unsealed;

an outlet port connected with a distal end of the sampling channel for conveying the second portion of the blood sample to the sample needle; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

18. The blood sequestration device in accordance with claim 17, wherein the sequestration chamber is at ambient air pressure, and wherein the sequestration chamber receives the first portion of the blood sample by blood pressure of the patient overcoming the ambient air pressure in the sequestration chamber.

19. The blood sequestration device in accordance with claim 17, wherein the sampling channel causes the second portion of the blood sample to bypass the sequestered first portion of blood, and exit the outlet port for conveyance to a blood collection device.

20. The blood sequestration device in accordance with claim 17, wherein the air permeable blood barrier includes an air permeable material that seals upon contact with blood.

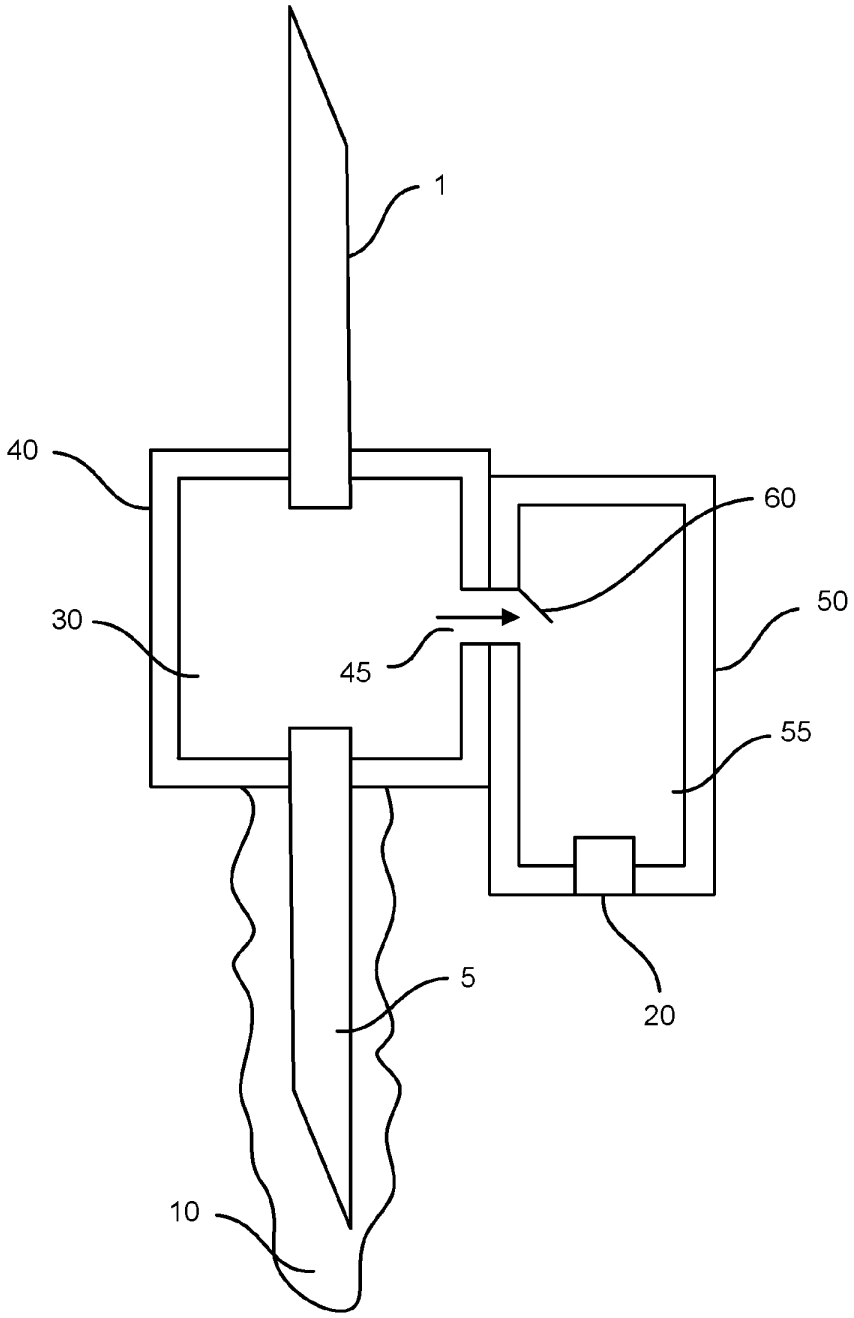


FIG. 1

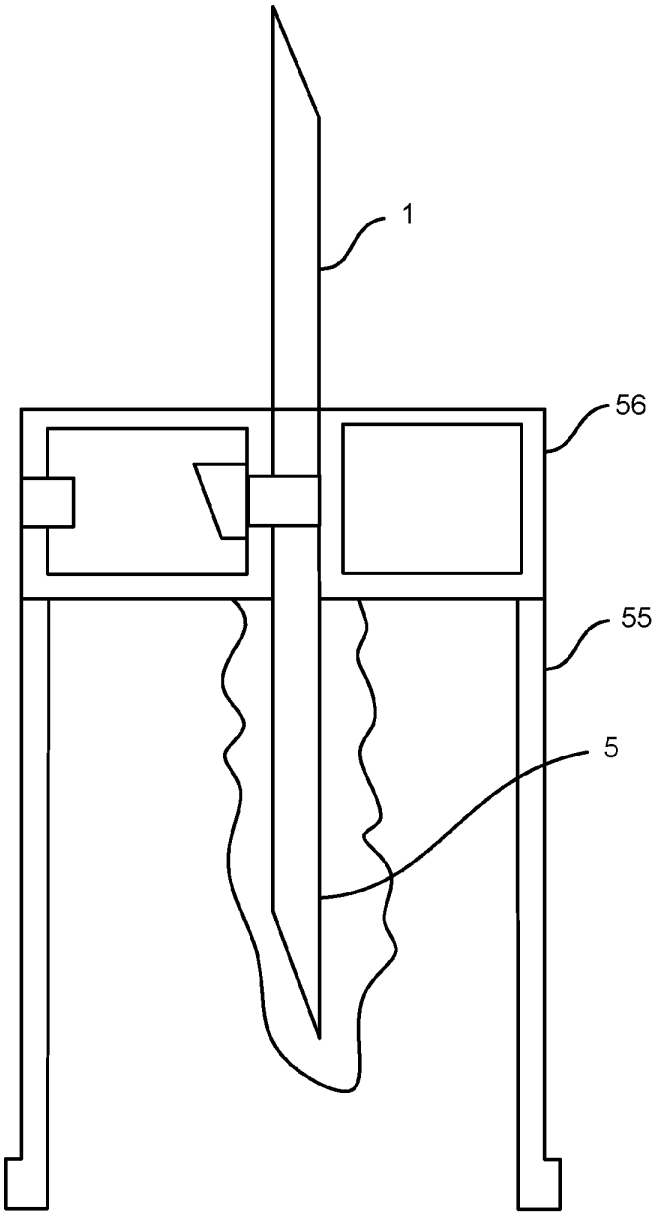


FIG. 2

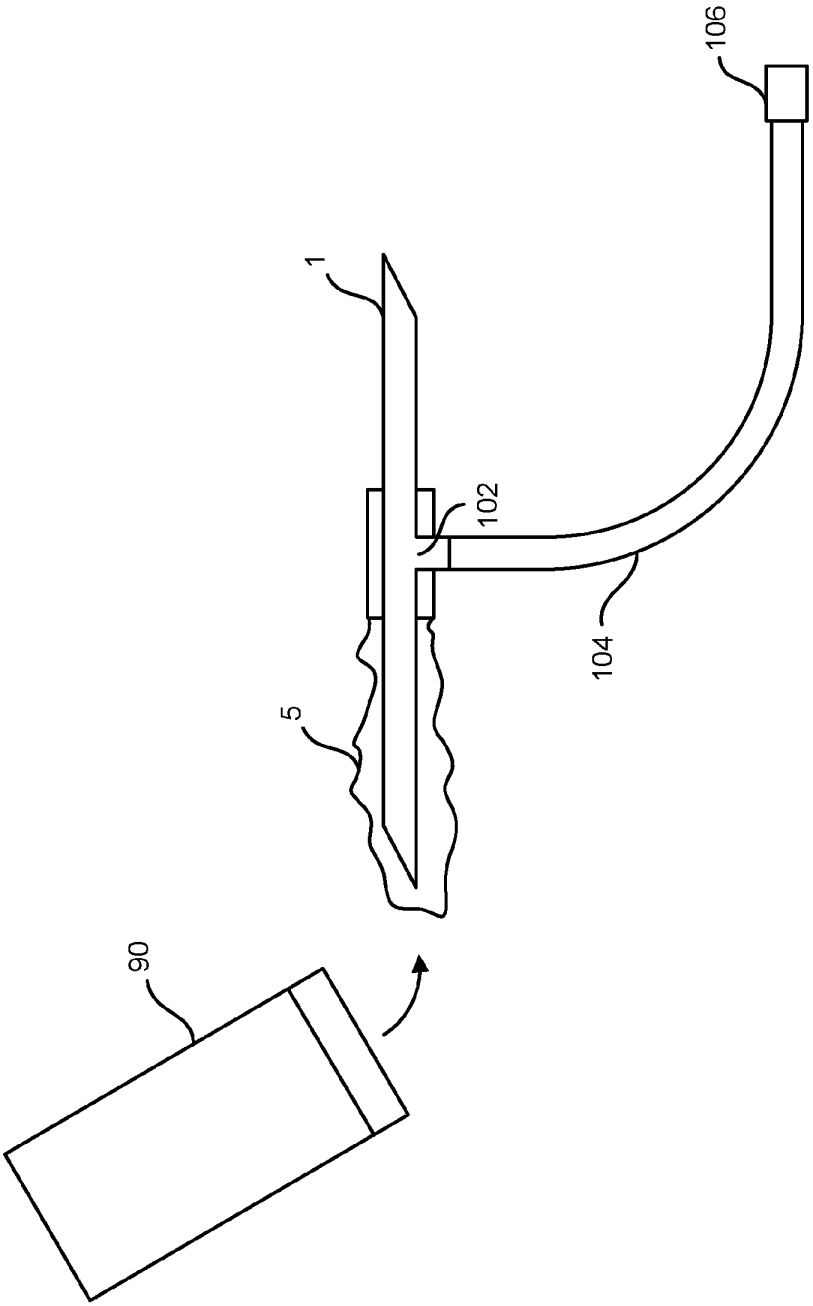


FIG. 3

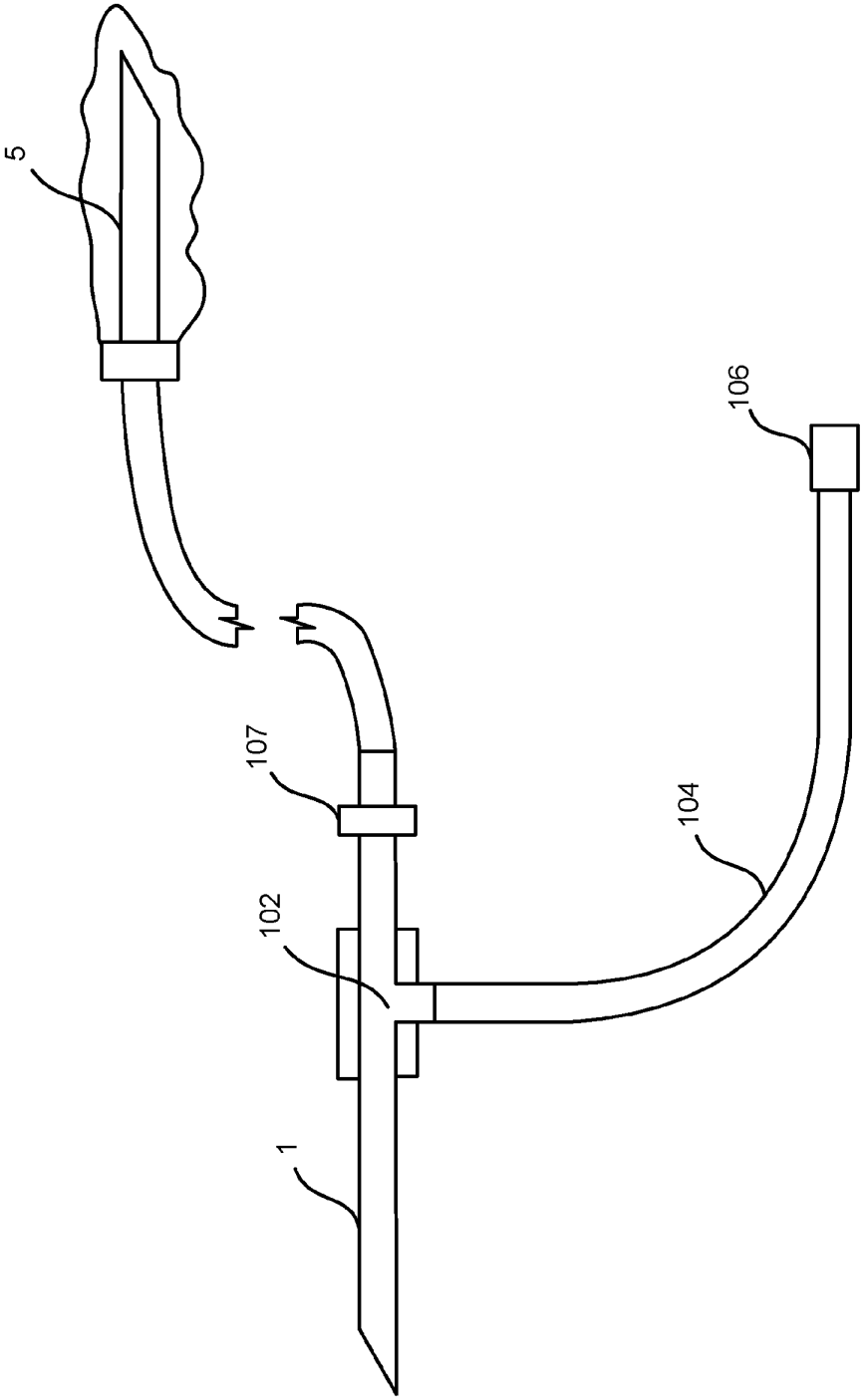


FIG. 4

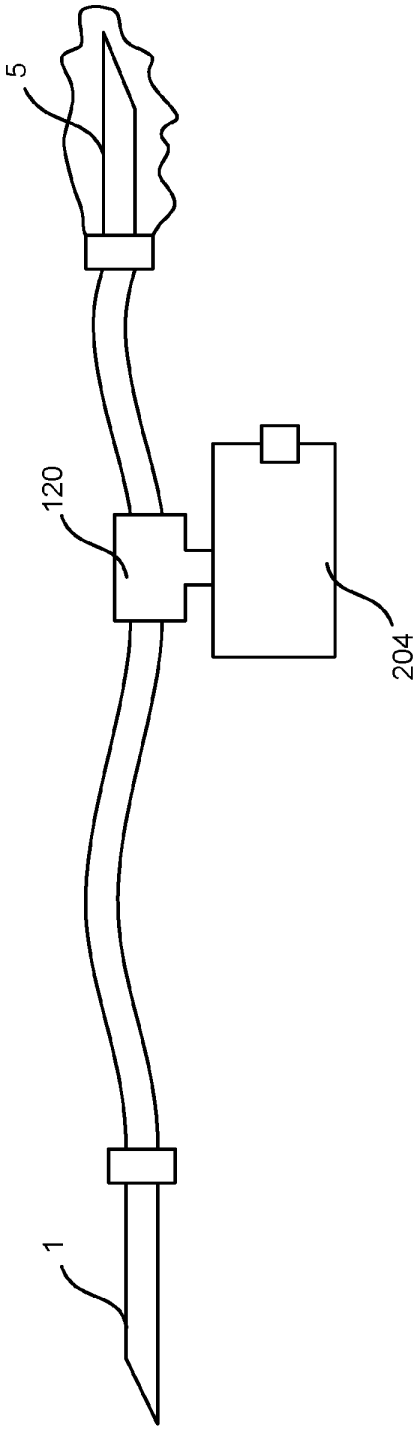


FIG. 5

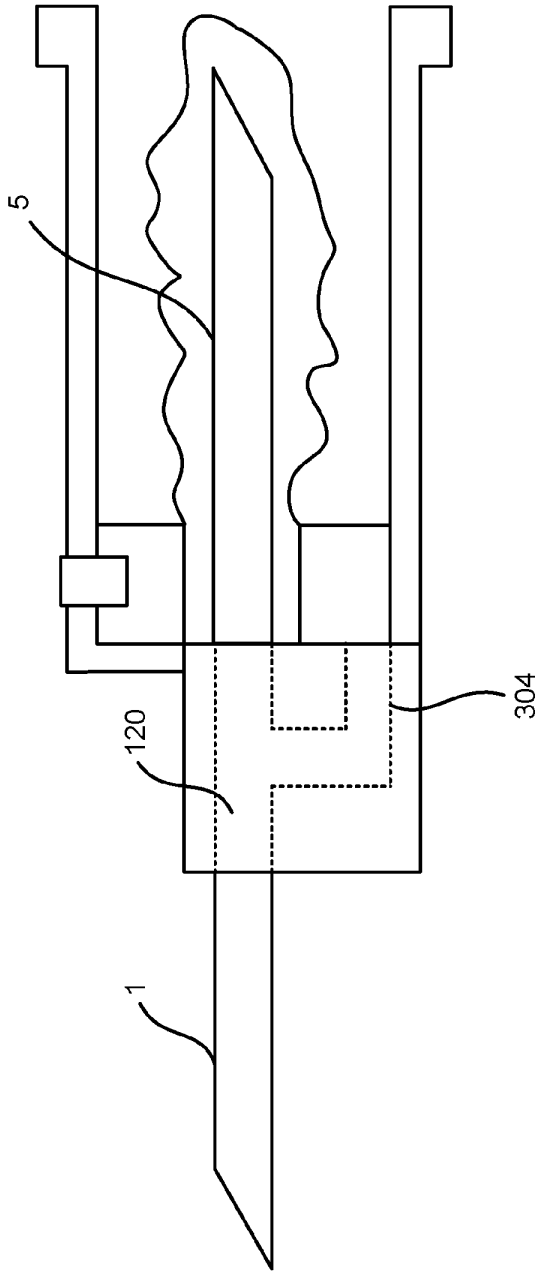


FIG. 6

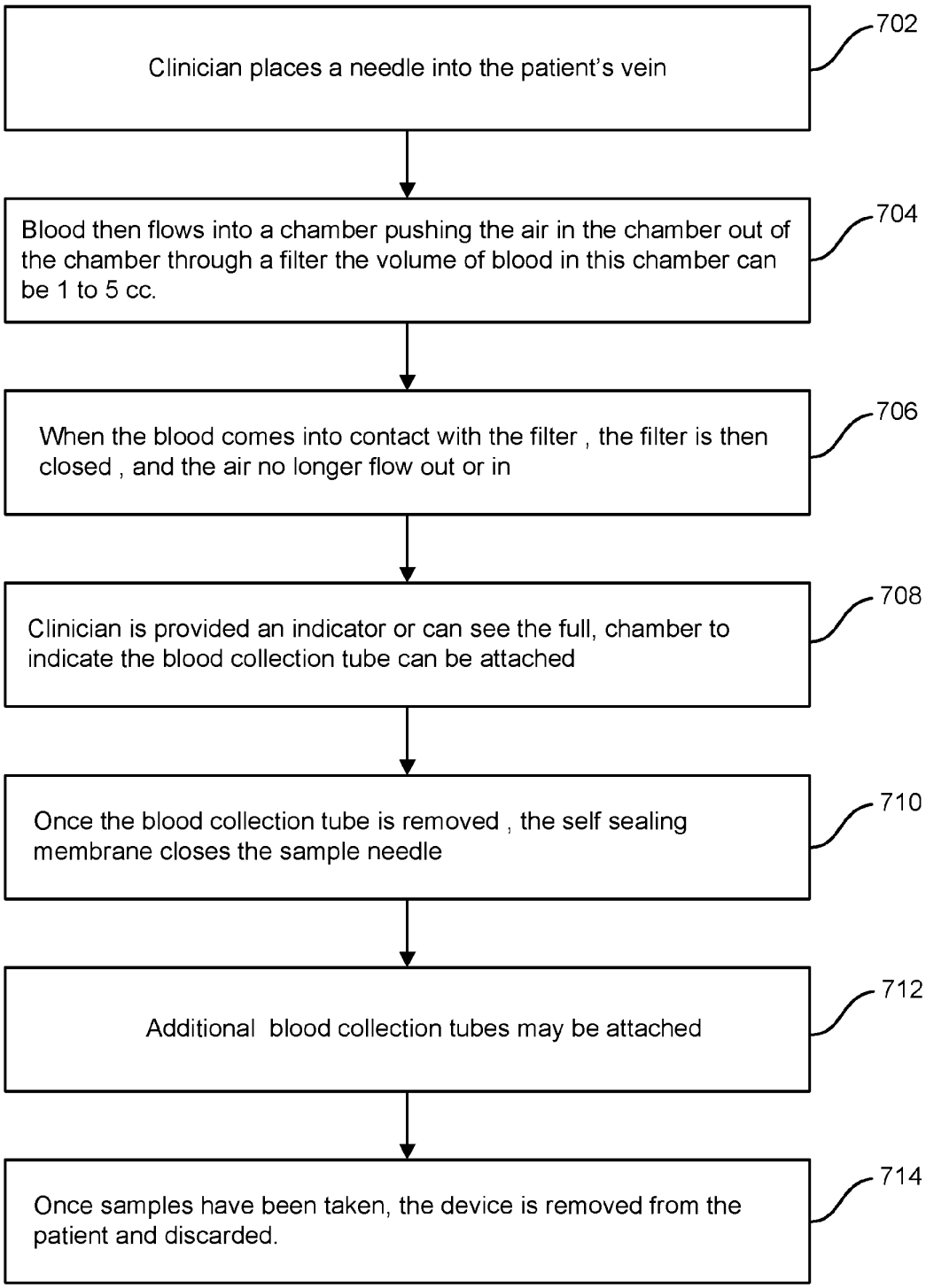

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air no longer flow out or in
706
Clinician is provided an indicator or can see the full, chamber to indicate the blood collection tube can be attached
708
Once the blood collection tube is removed , the self sealing membrane closes the sample needle
710
Additional blood collection tubes may be attached
712
Once samples have been taken, the device is removed from the patient and discarded.
714

FIG. 7

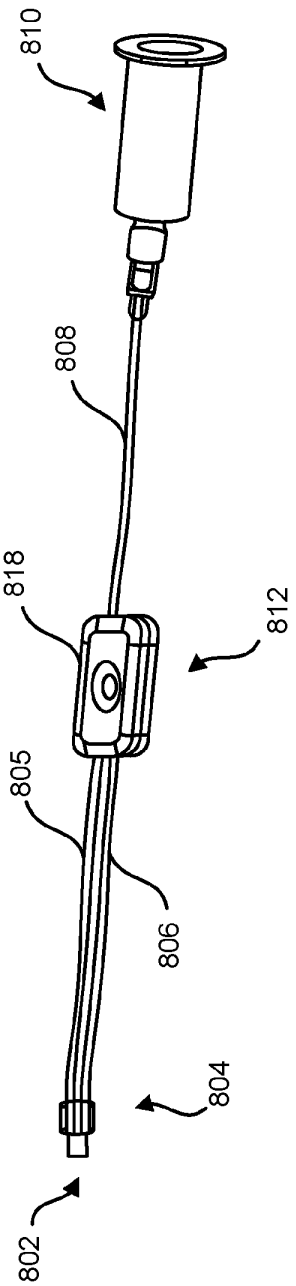


FIG. 8A

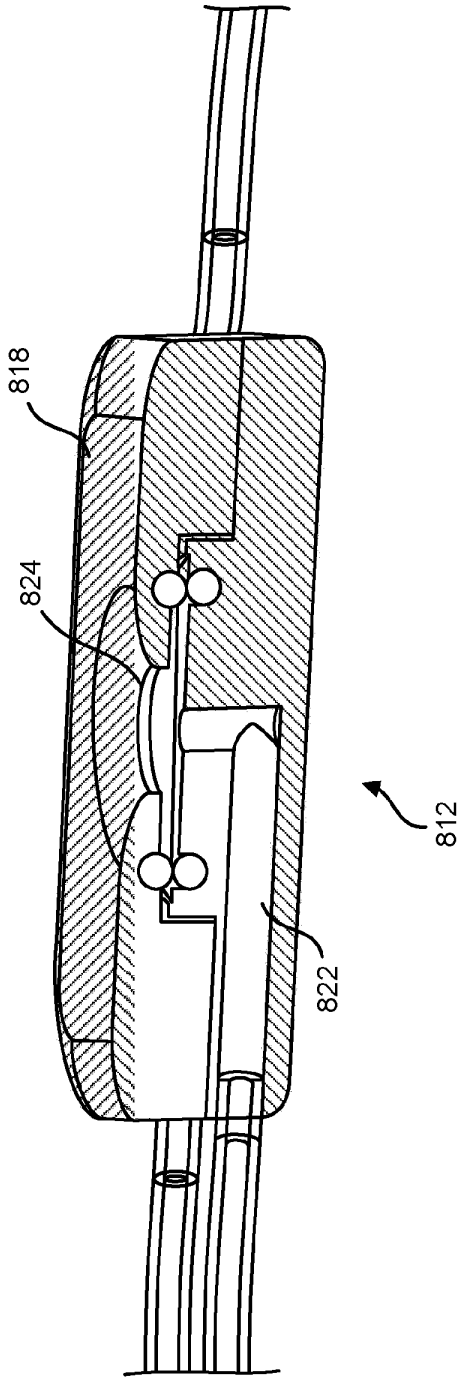


FIG. 8B

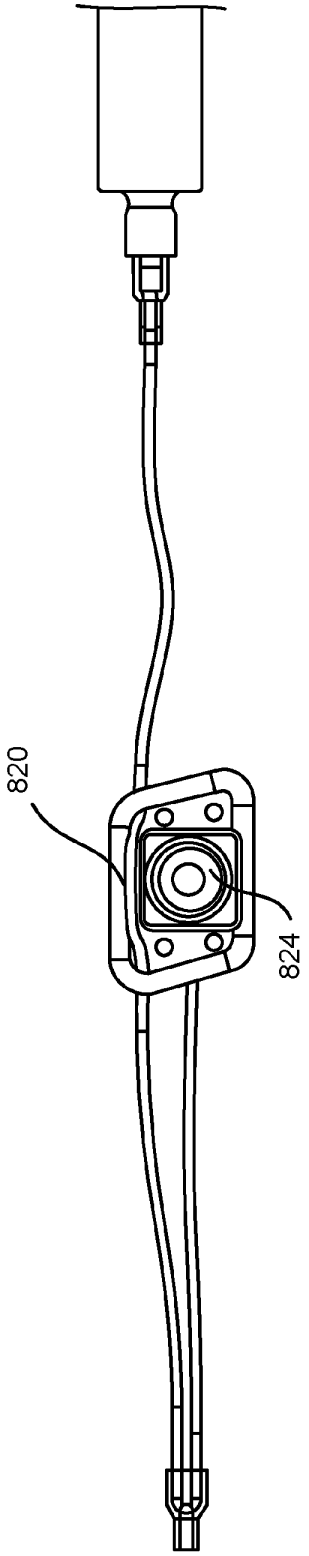


FIG. 8C

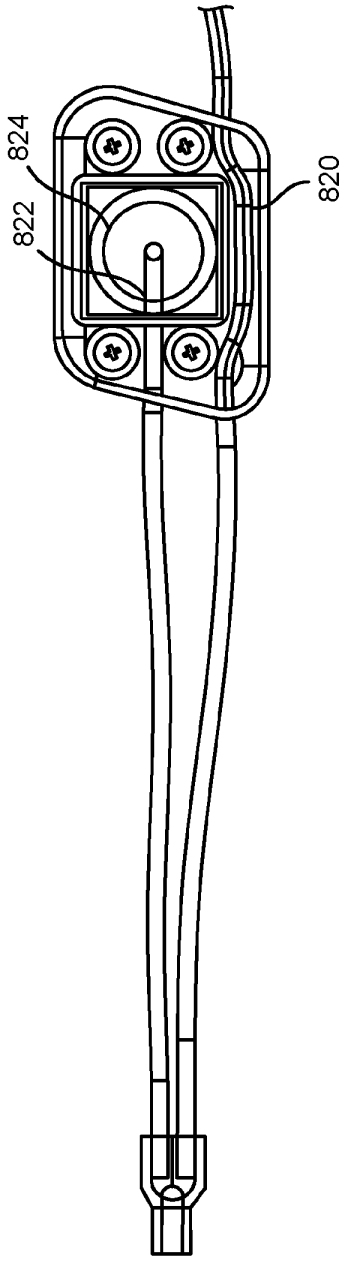


FIG. 8D

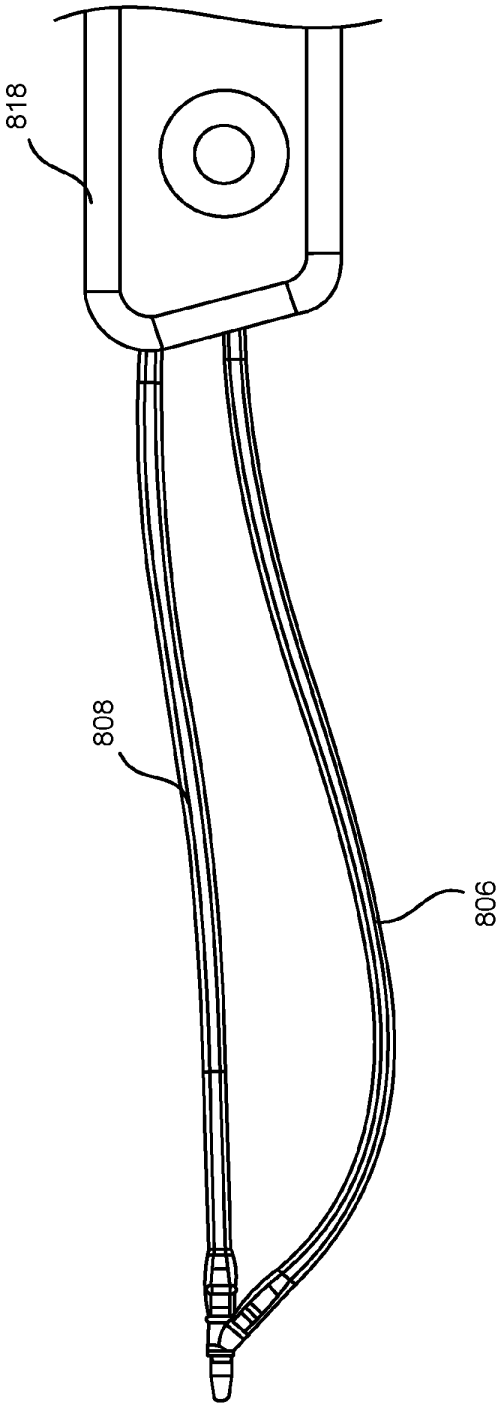


FIG. 8E

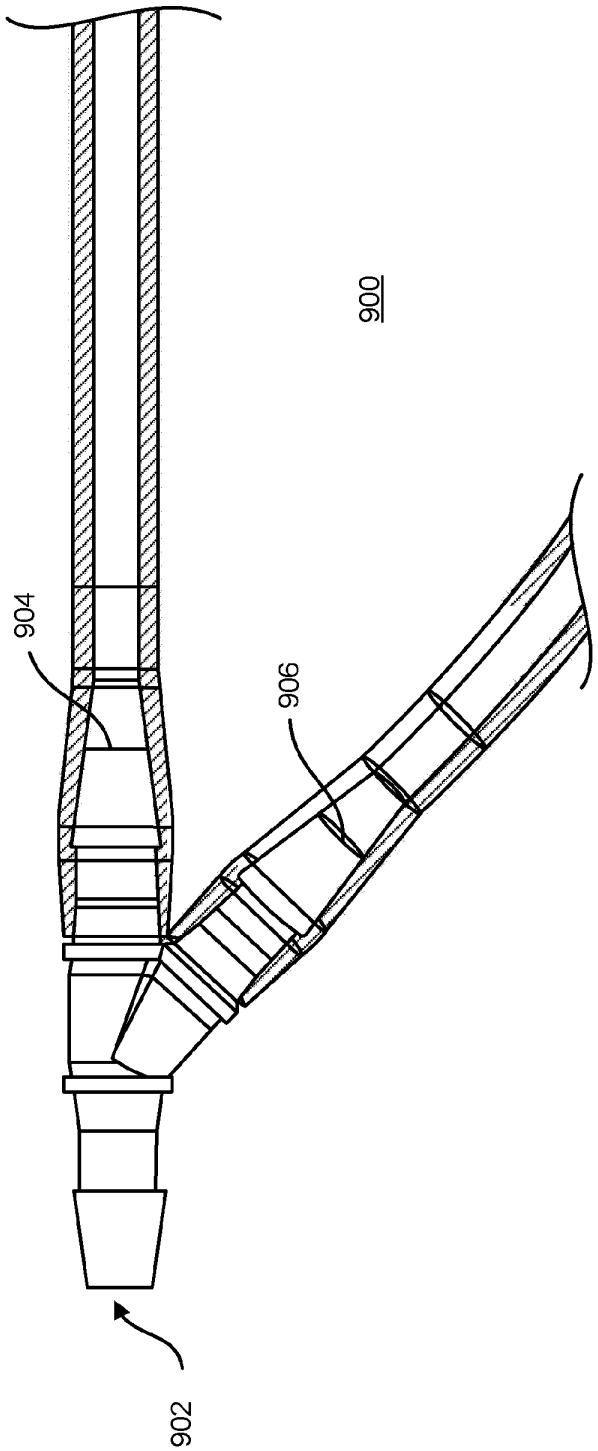


FIG. 9

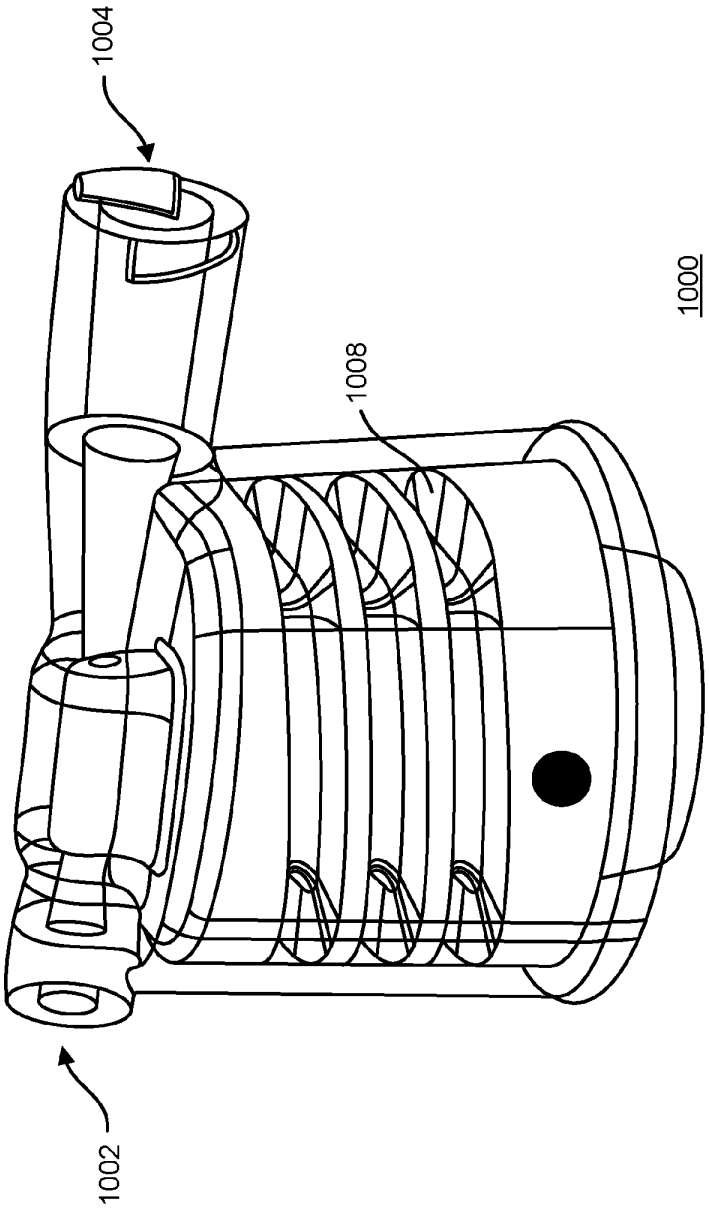


FIG. 10A

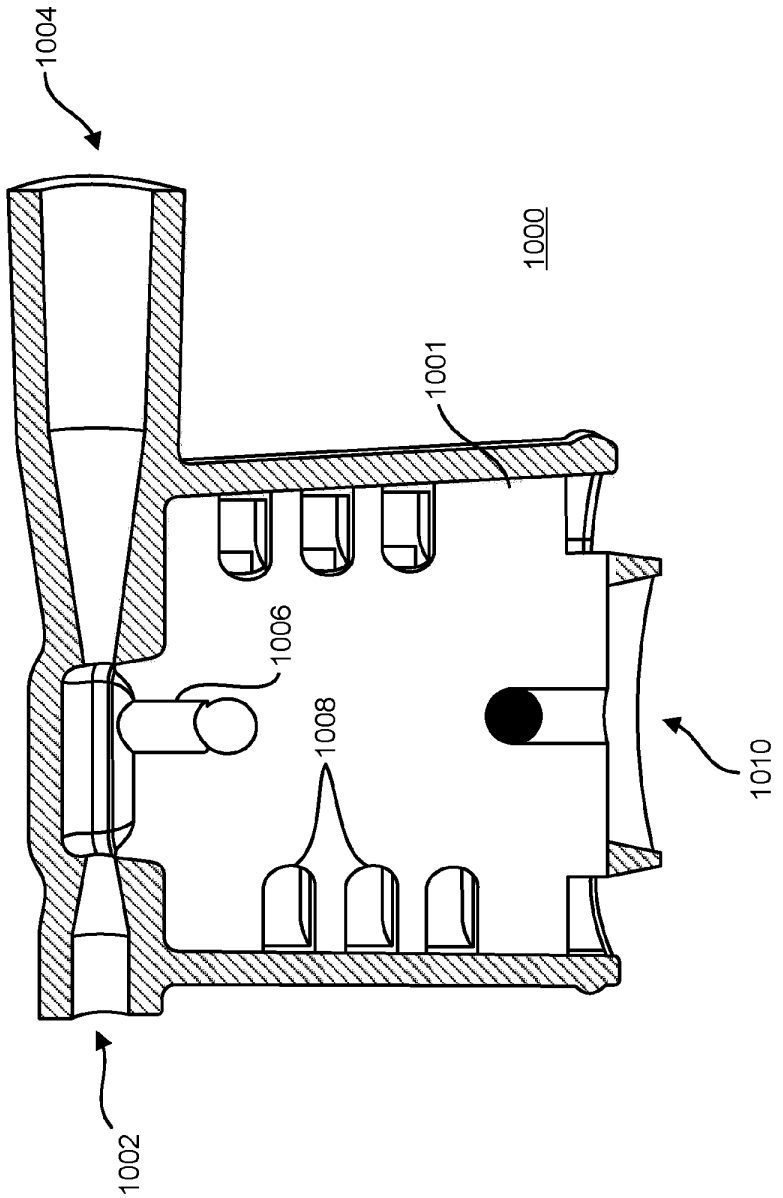


FIG. 10B

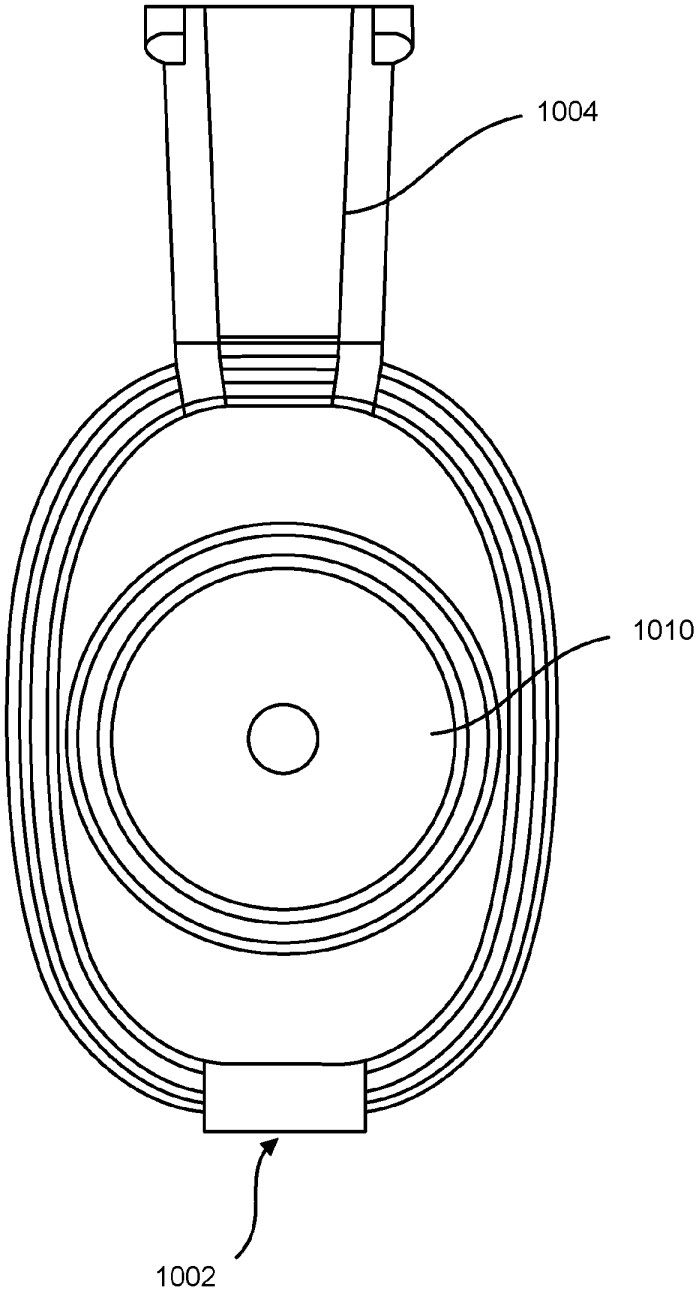


FIG. 10C

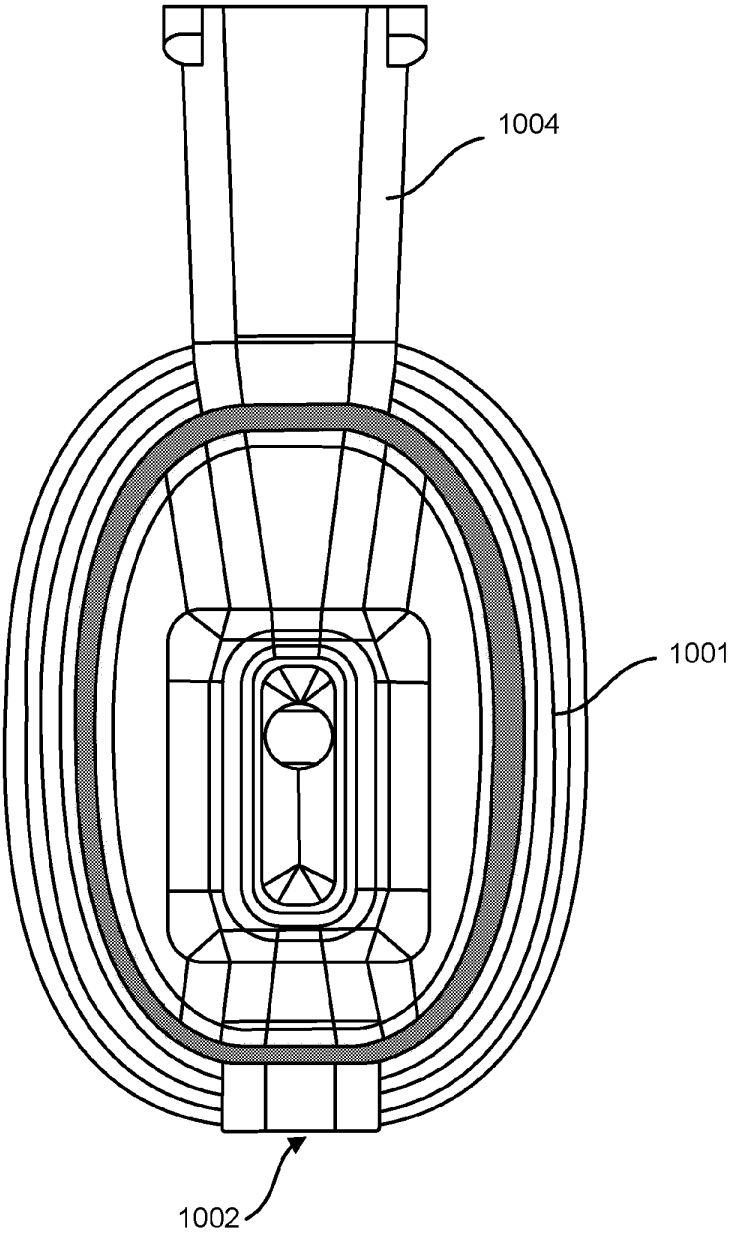


FIG. 10D

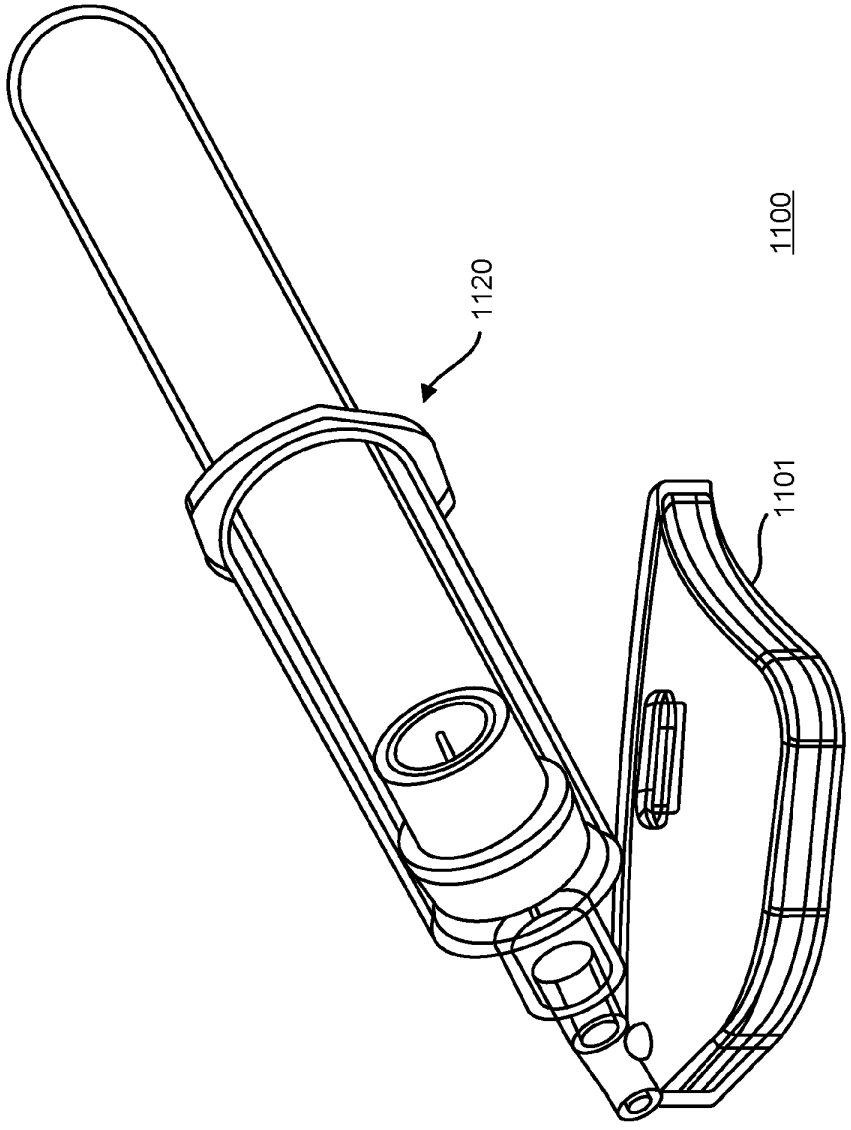


FIG. 11A

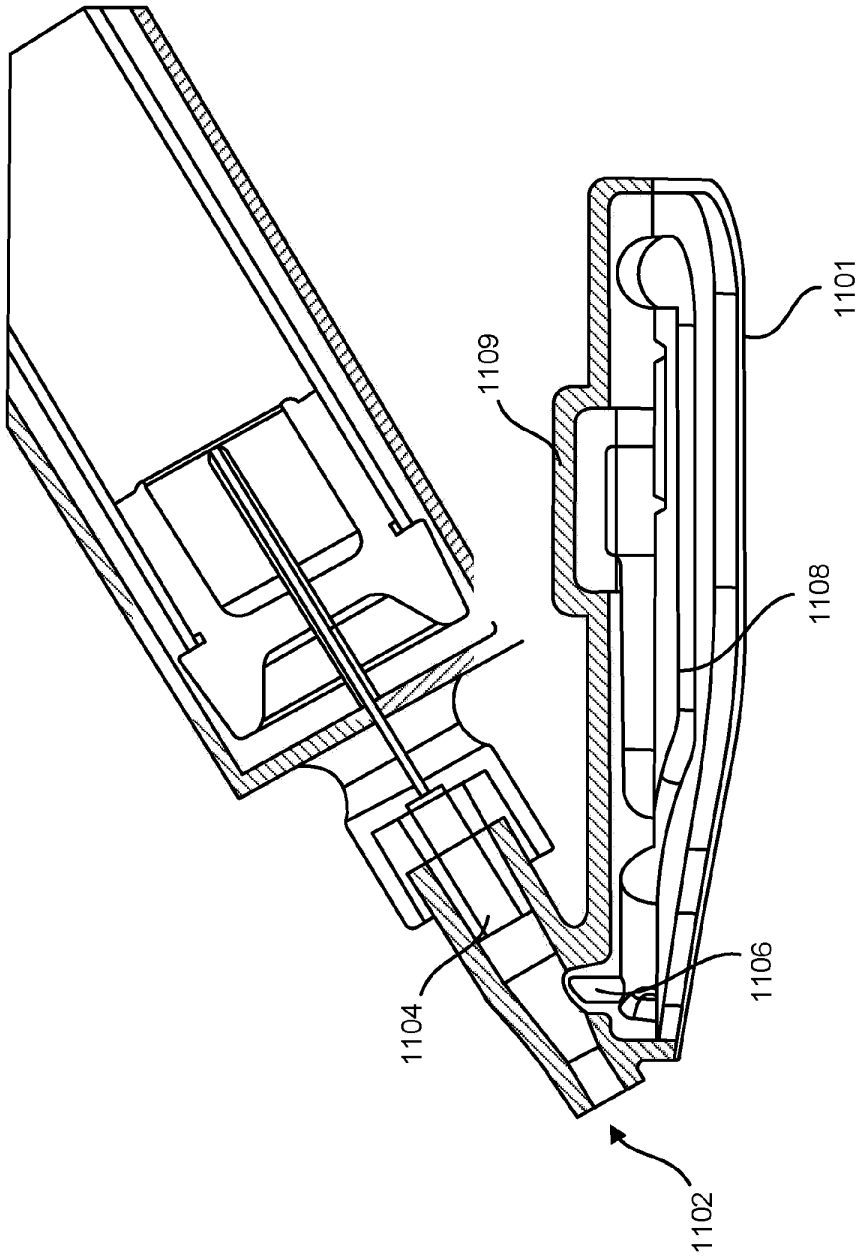


FIG. 11B

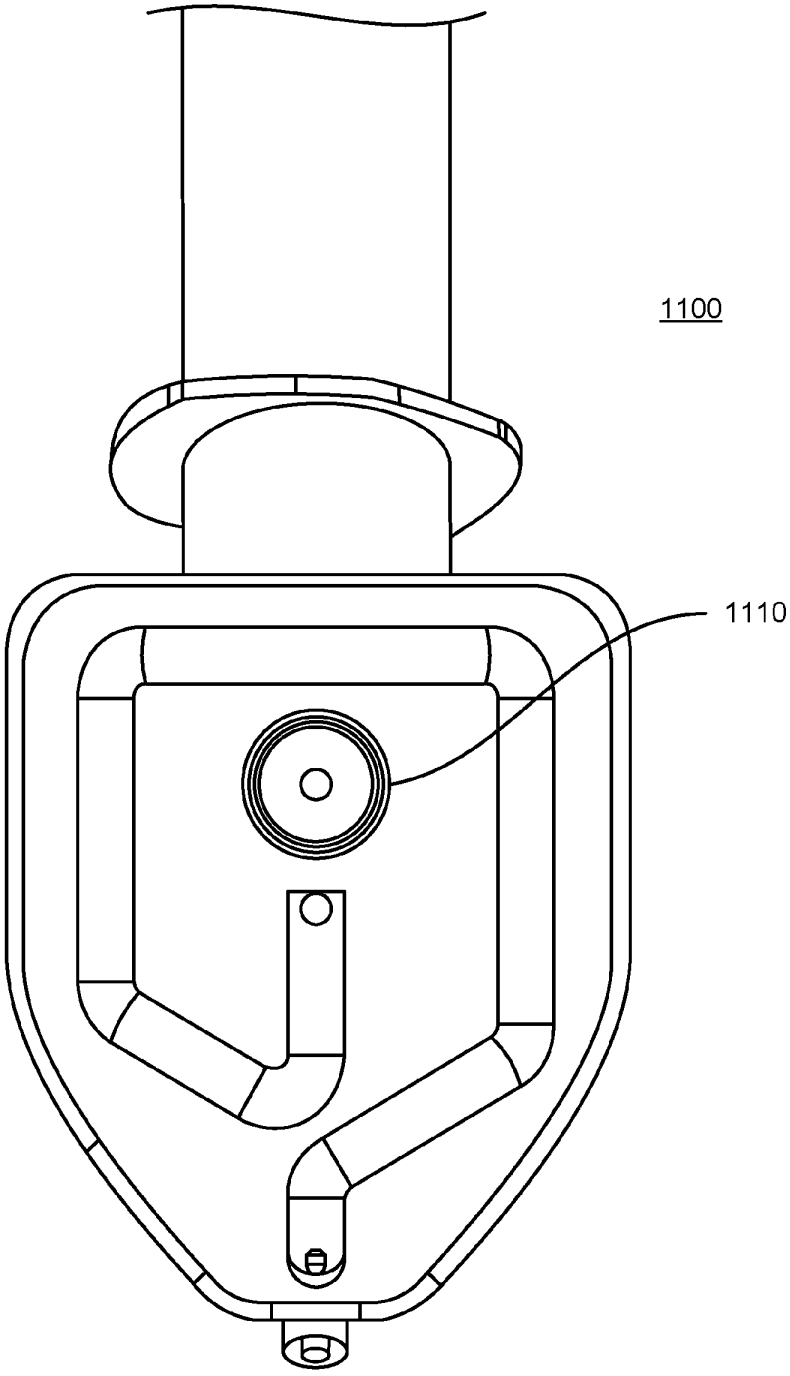


FIG. 11C

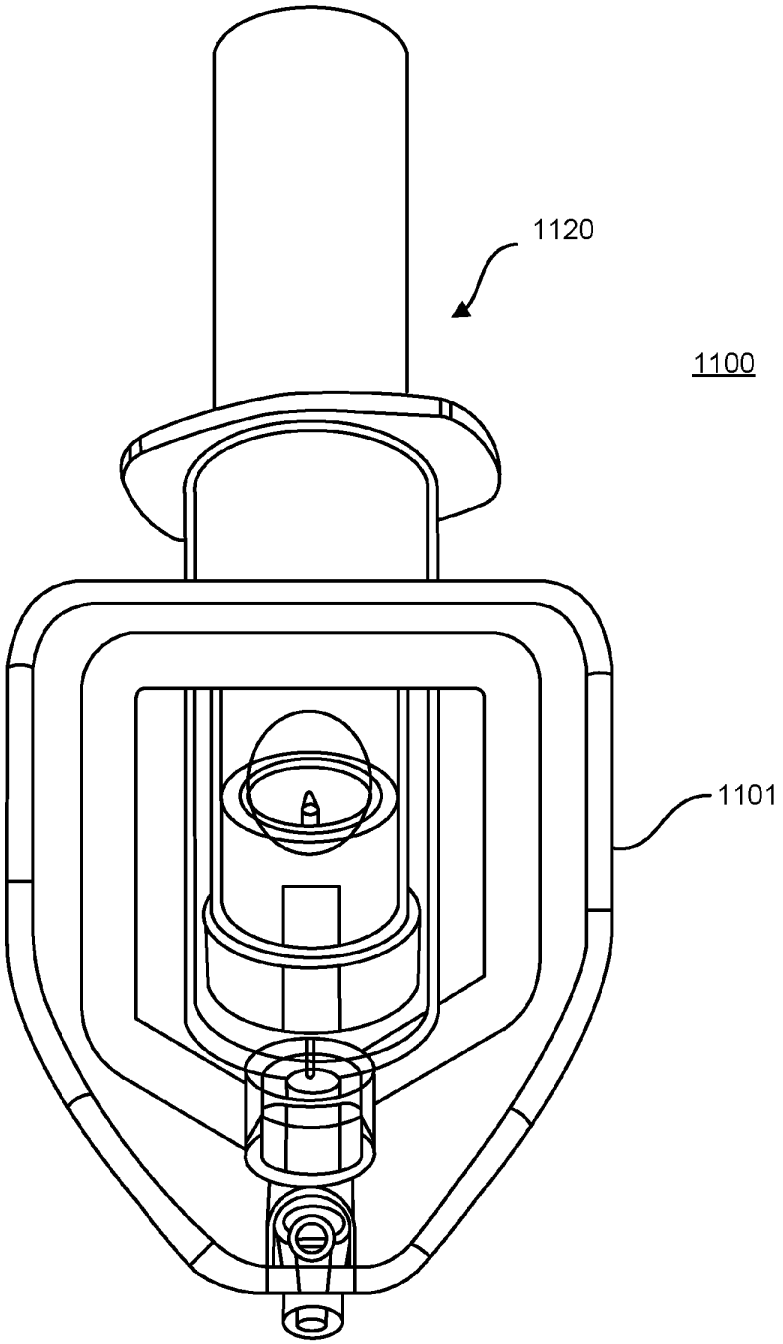


FIG. 11D

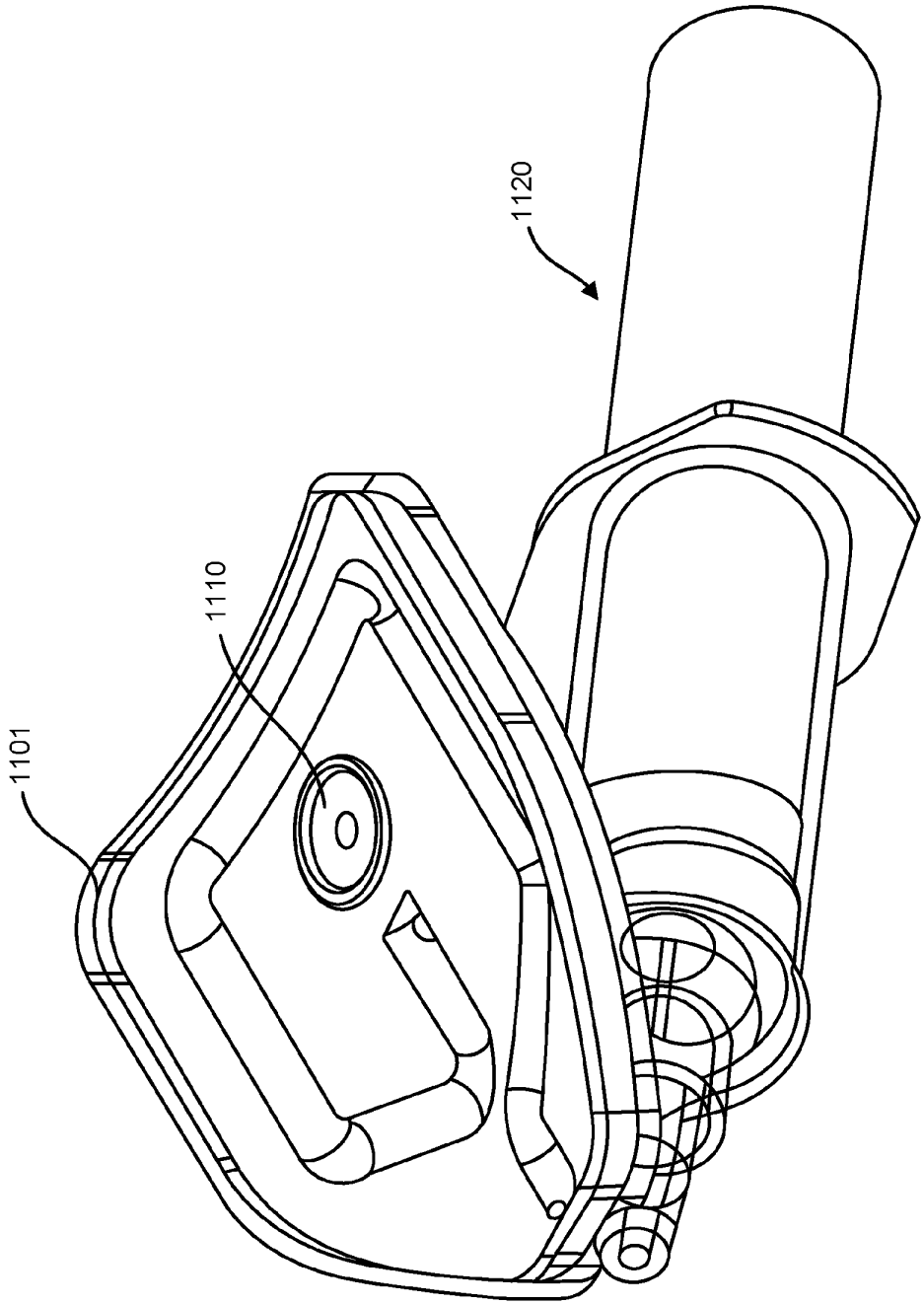


FIG. 11E

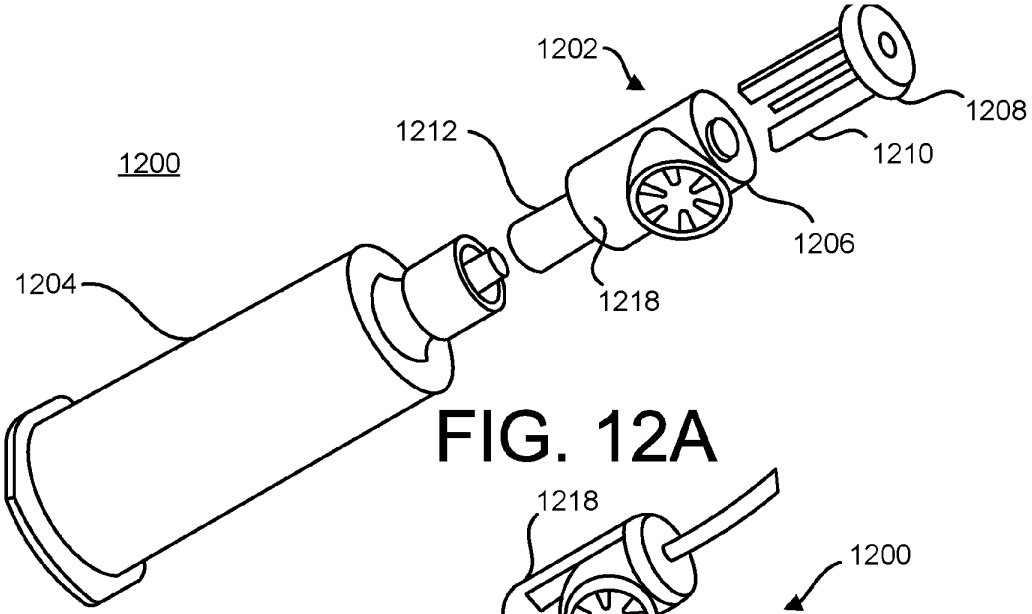


FIG. 12A

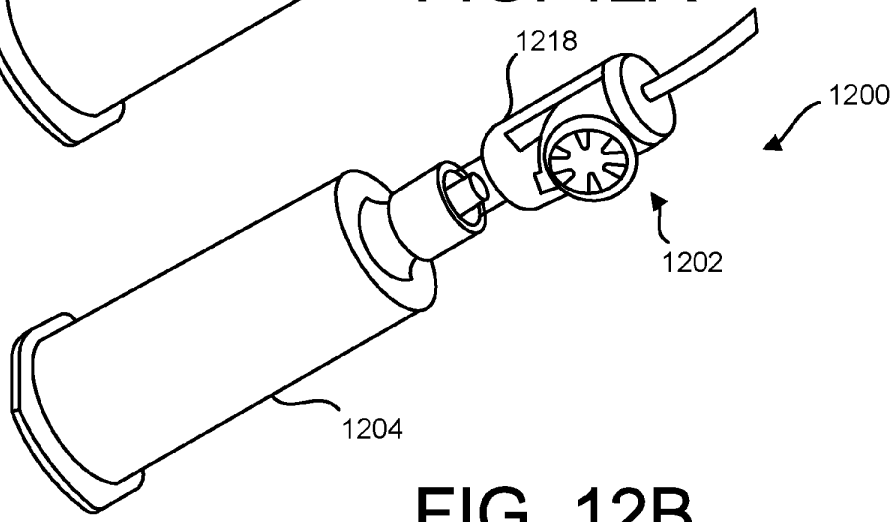


FIG. 12B

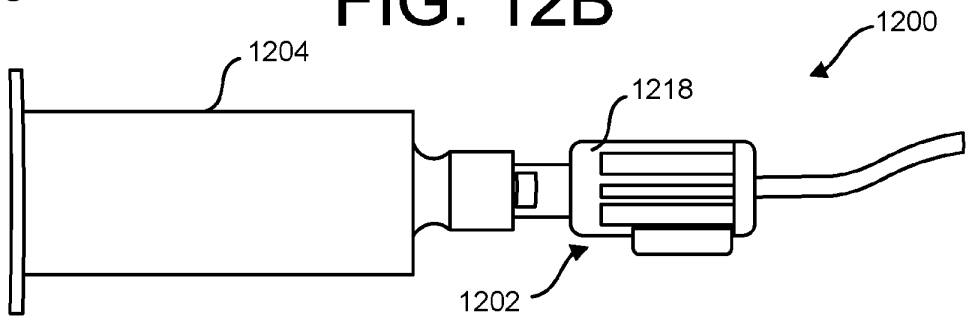


FIG. 12C

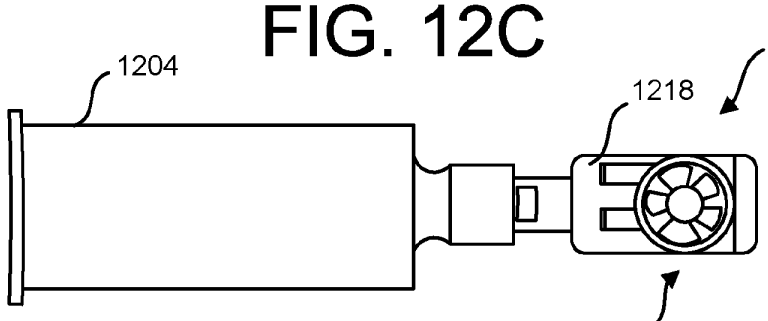


FIG. 12D

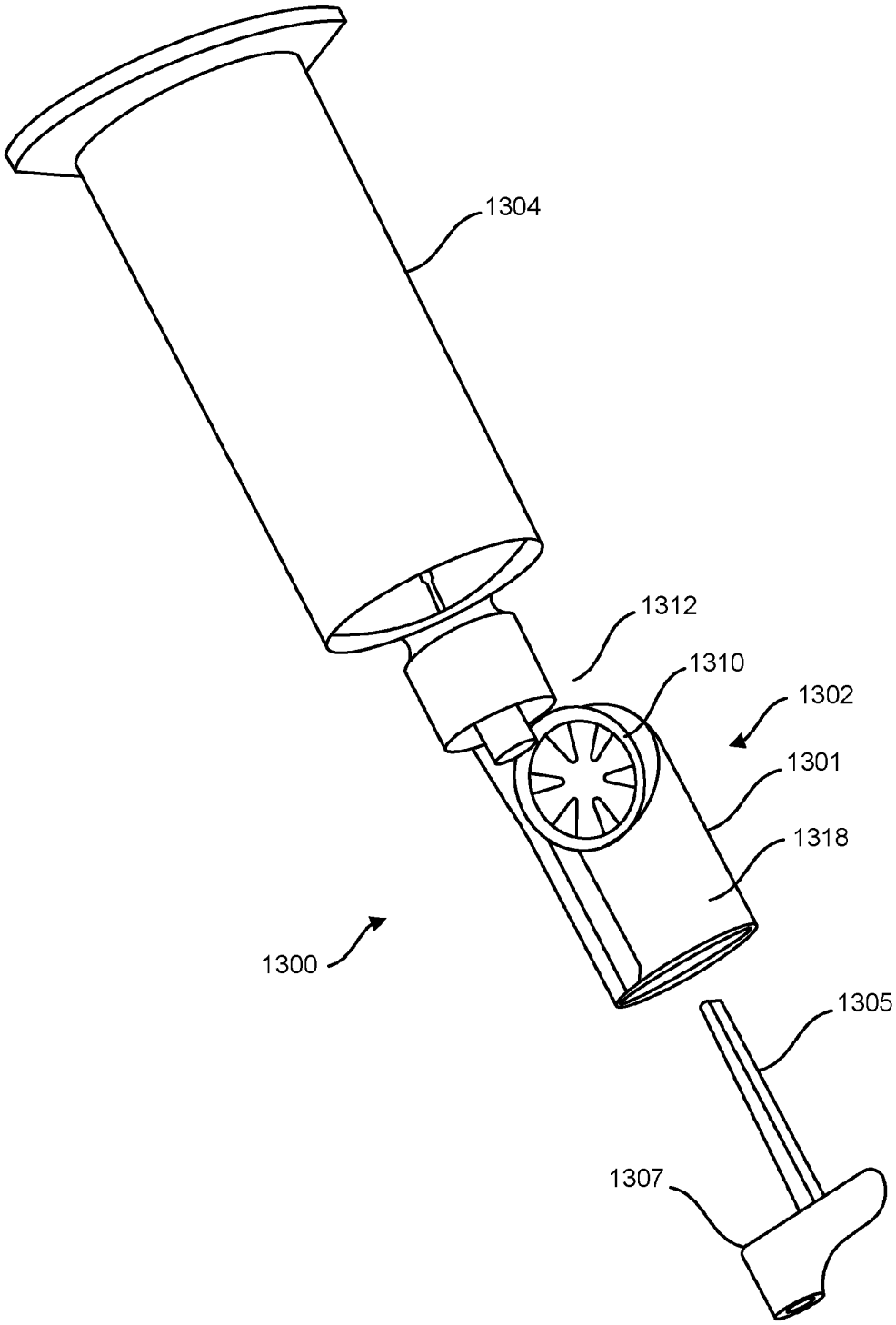


FIG. 13A

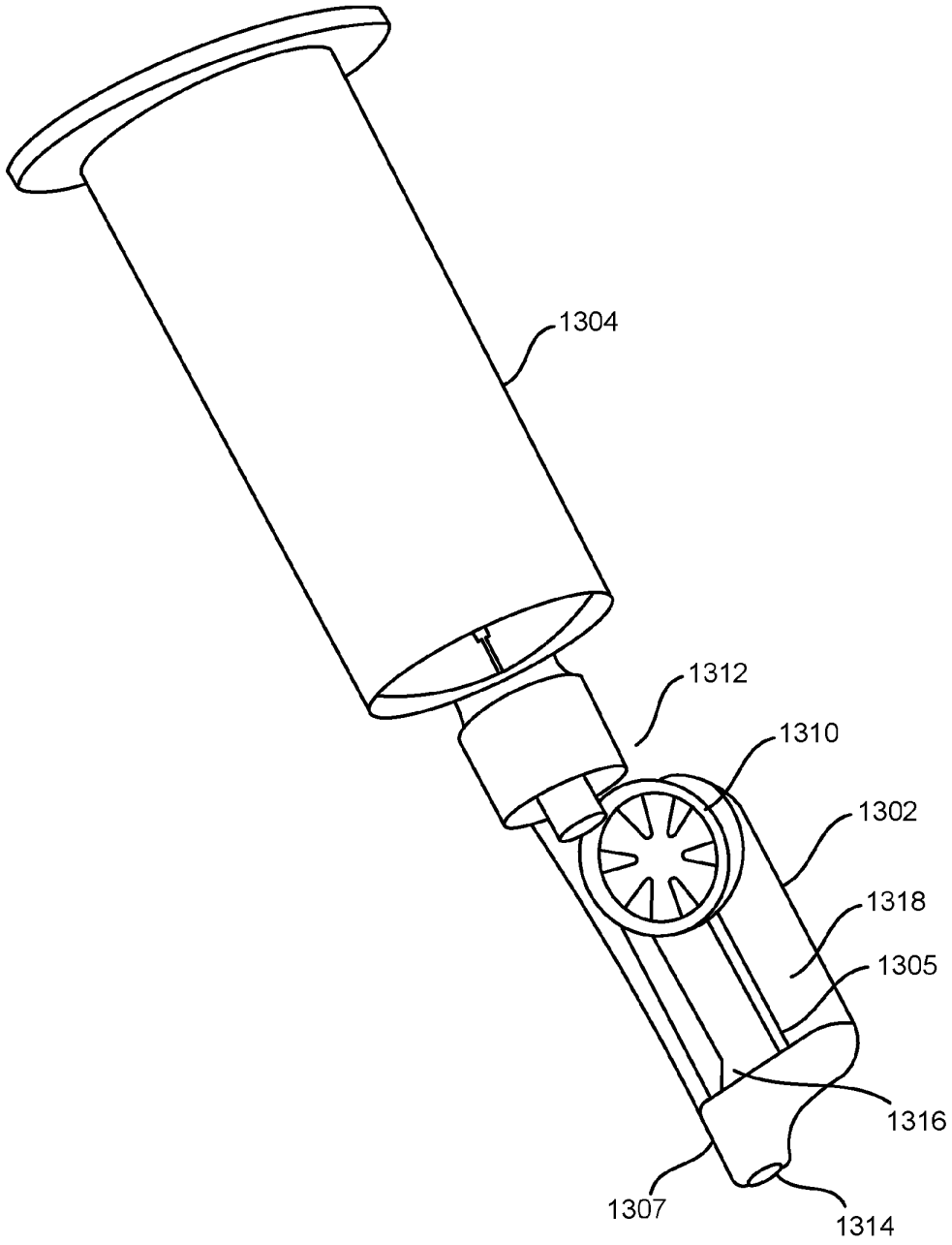


FIG. 13B

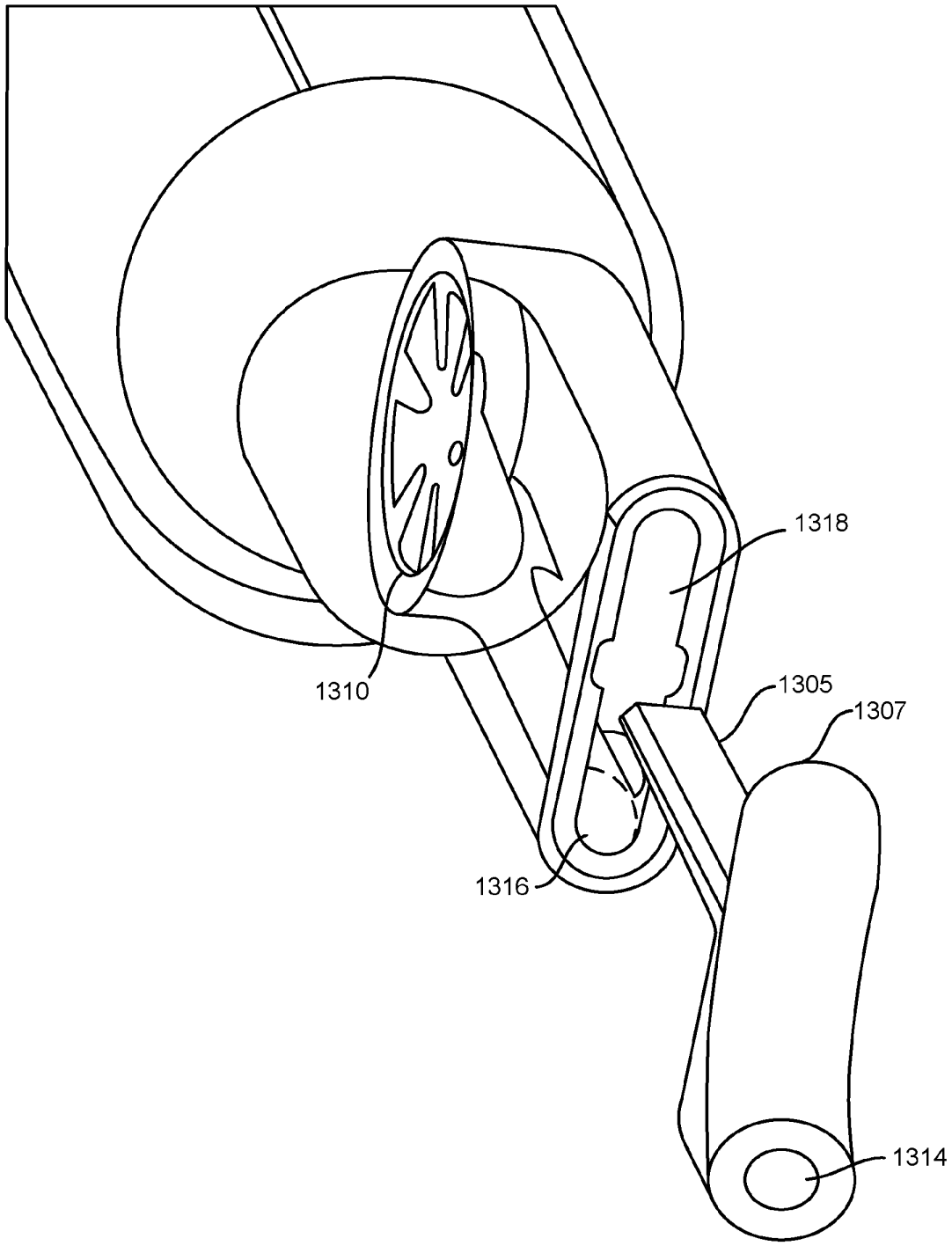


FIG. 13C

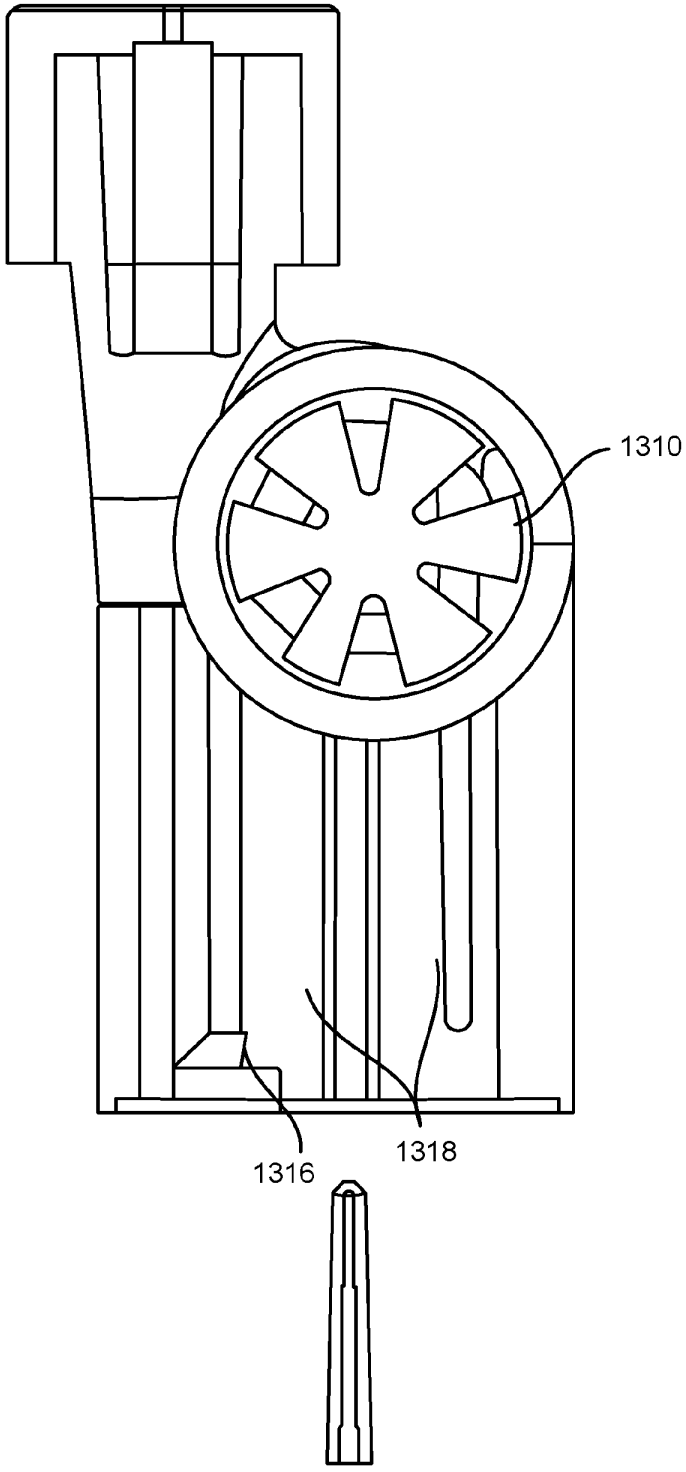


FIG. 13D

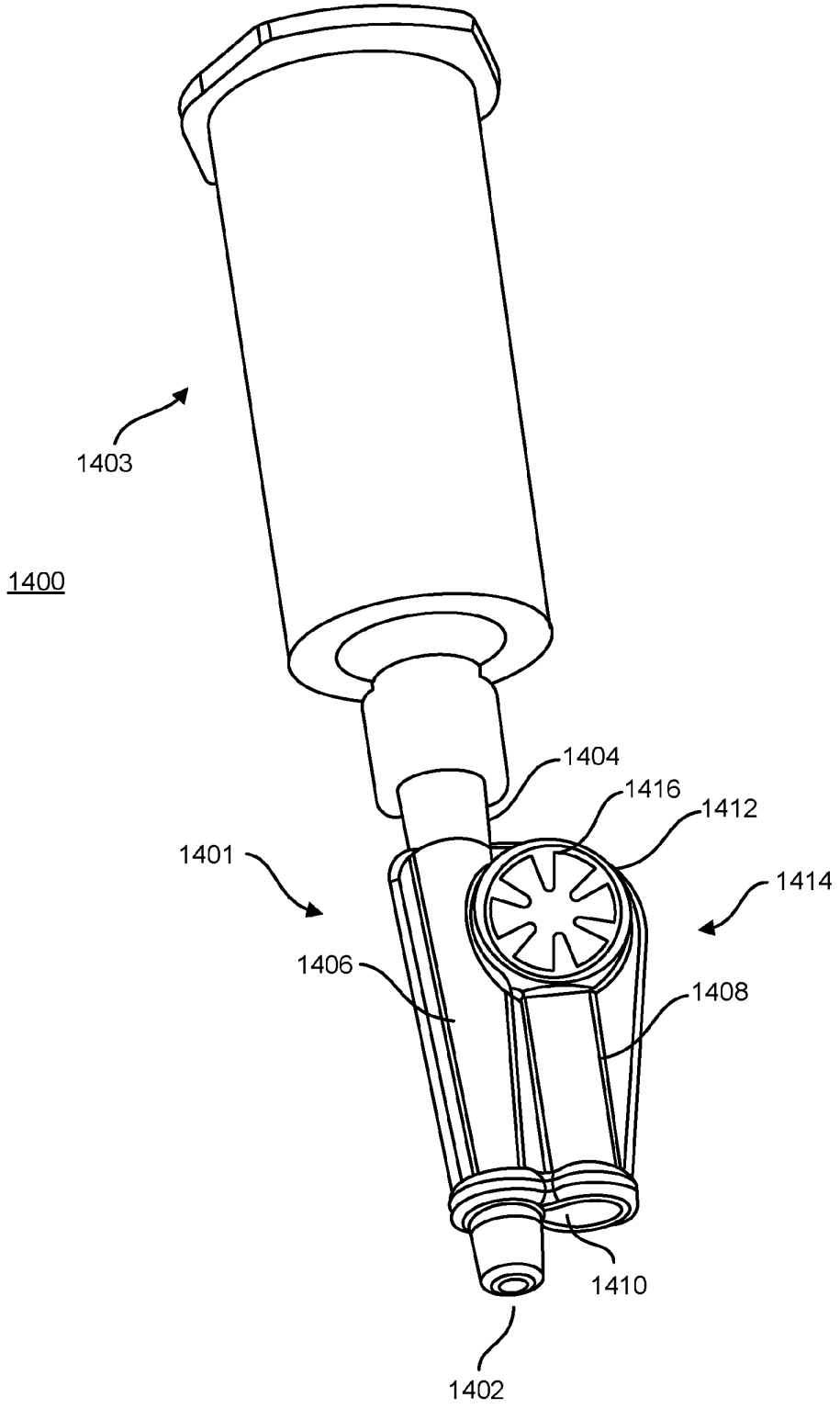


FIG. 14A

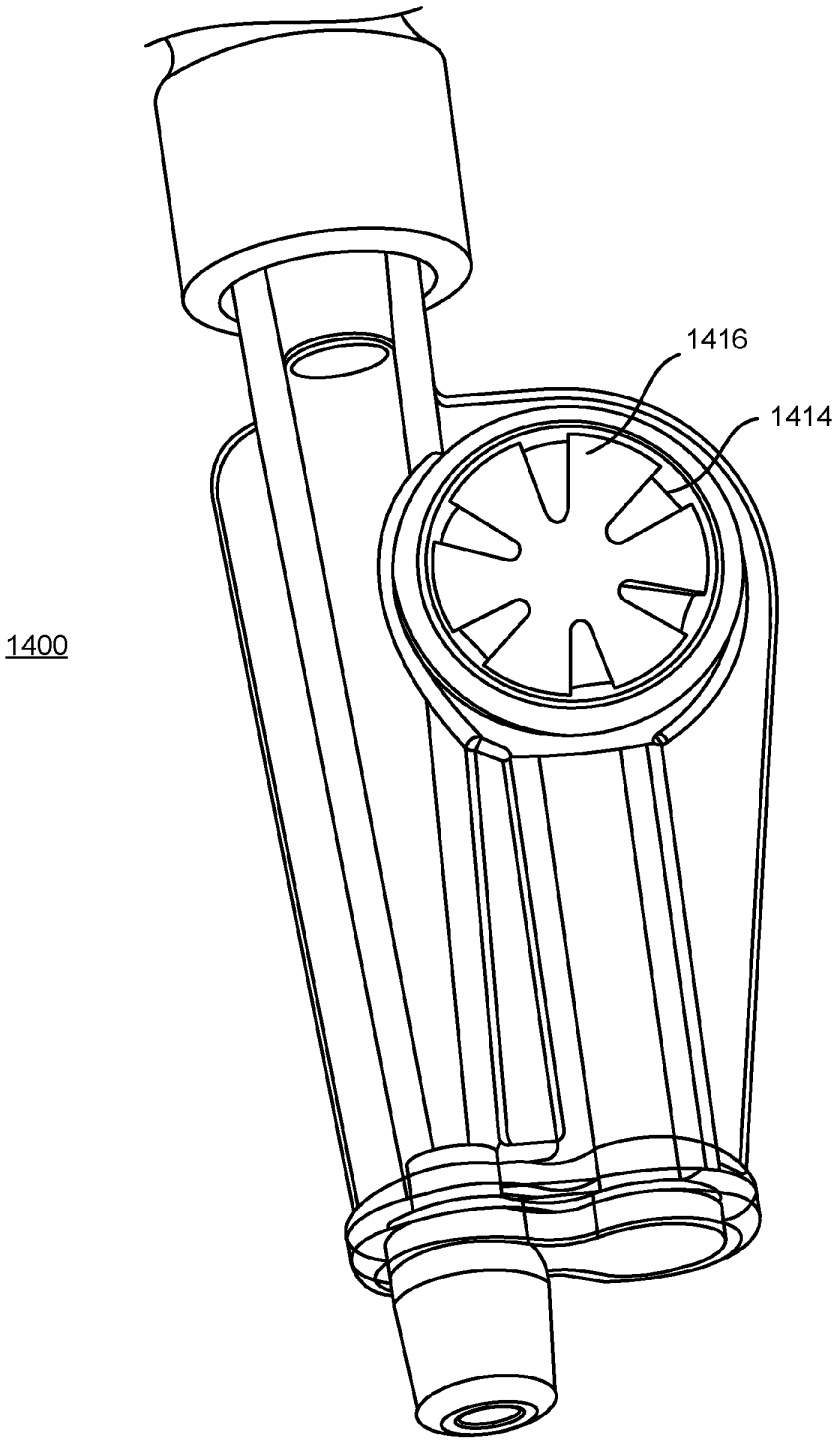


FIG. 14B

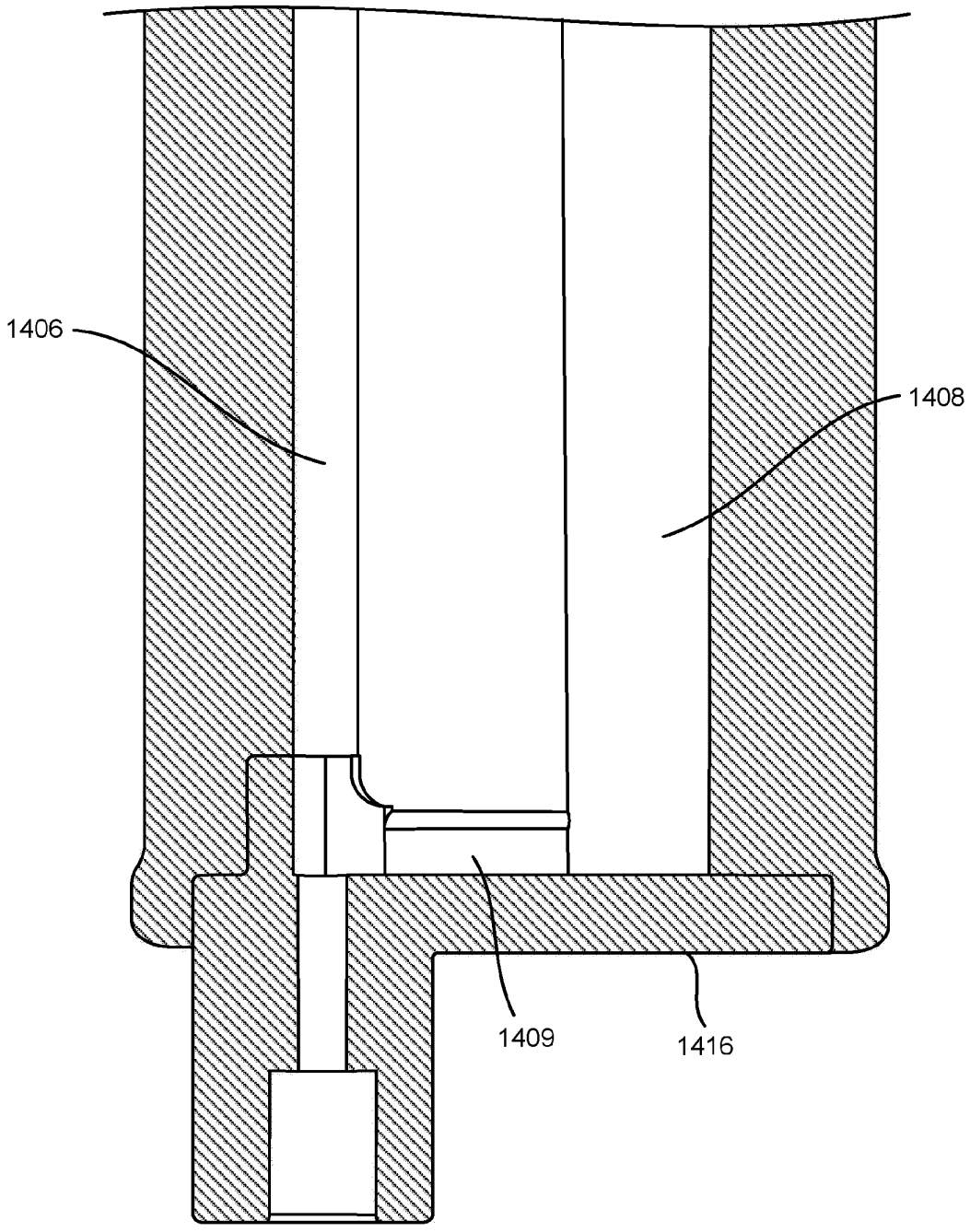


FIG. 14C

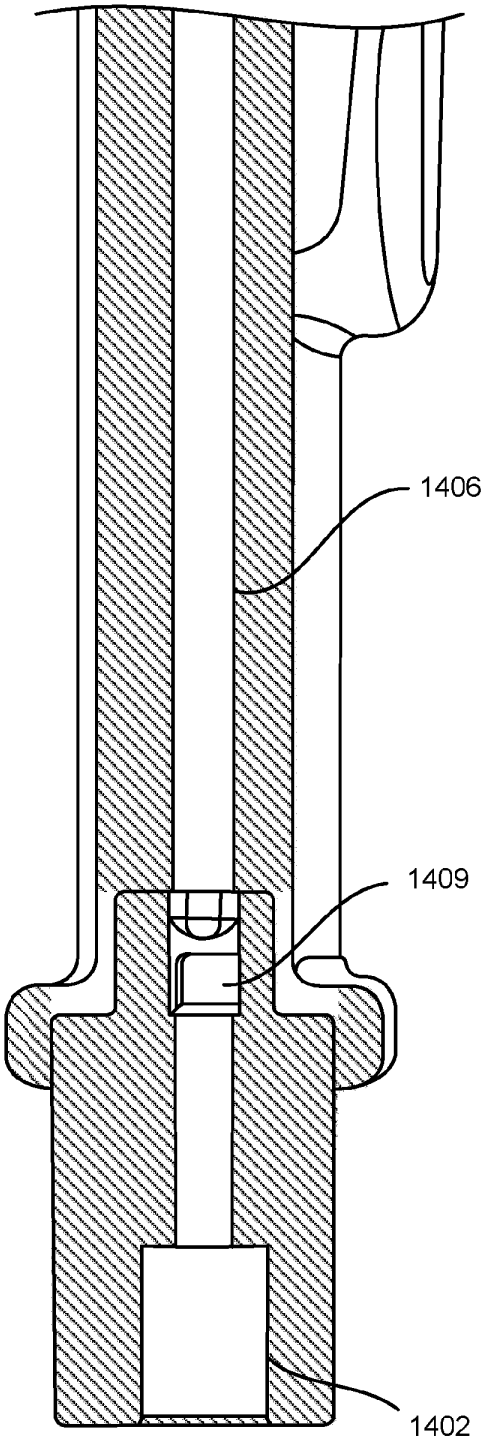


FIG. 14D

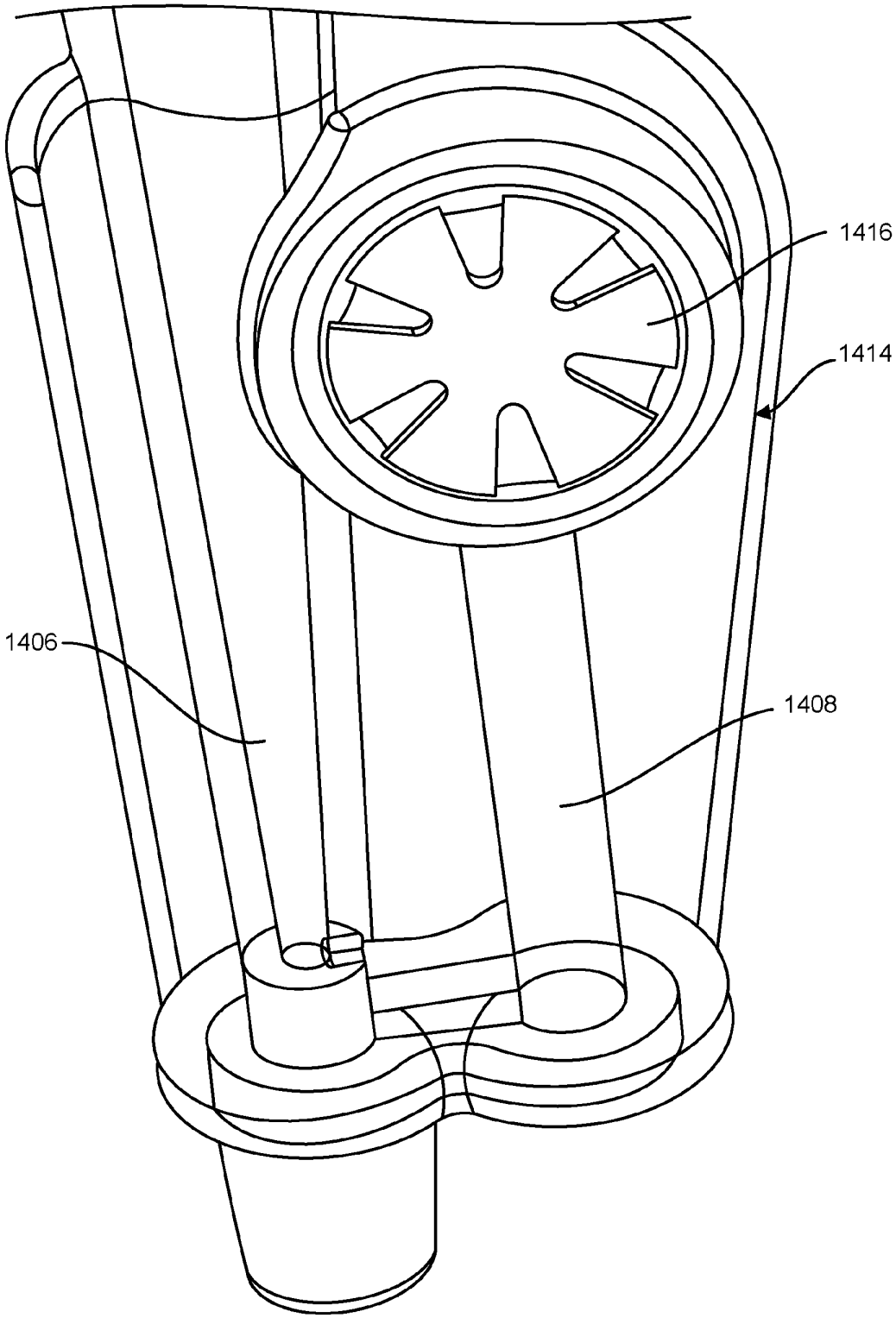


FIG. 14E

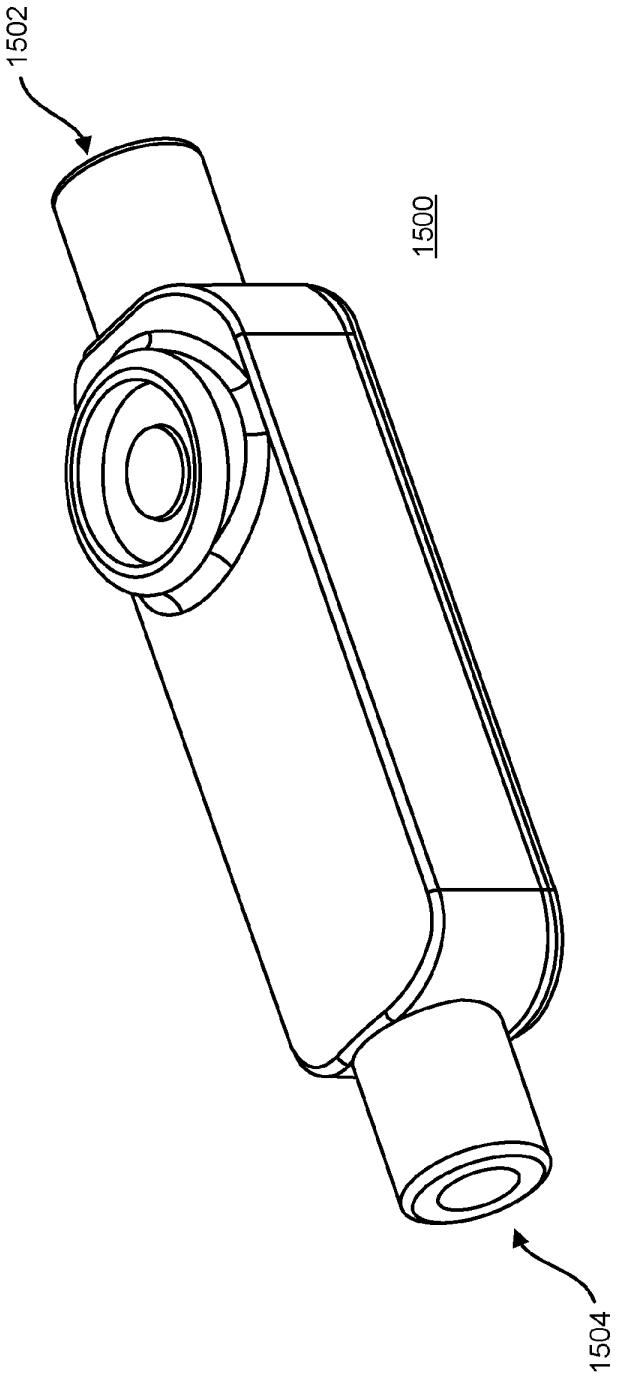


FIG. 15A

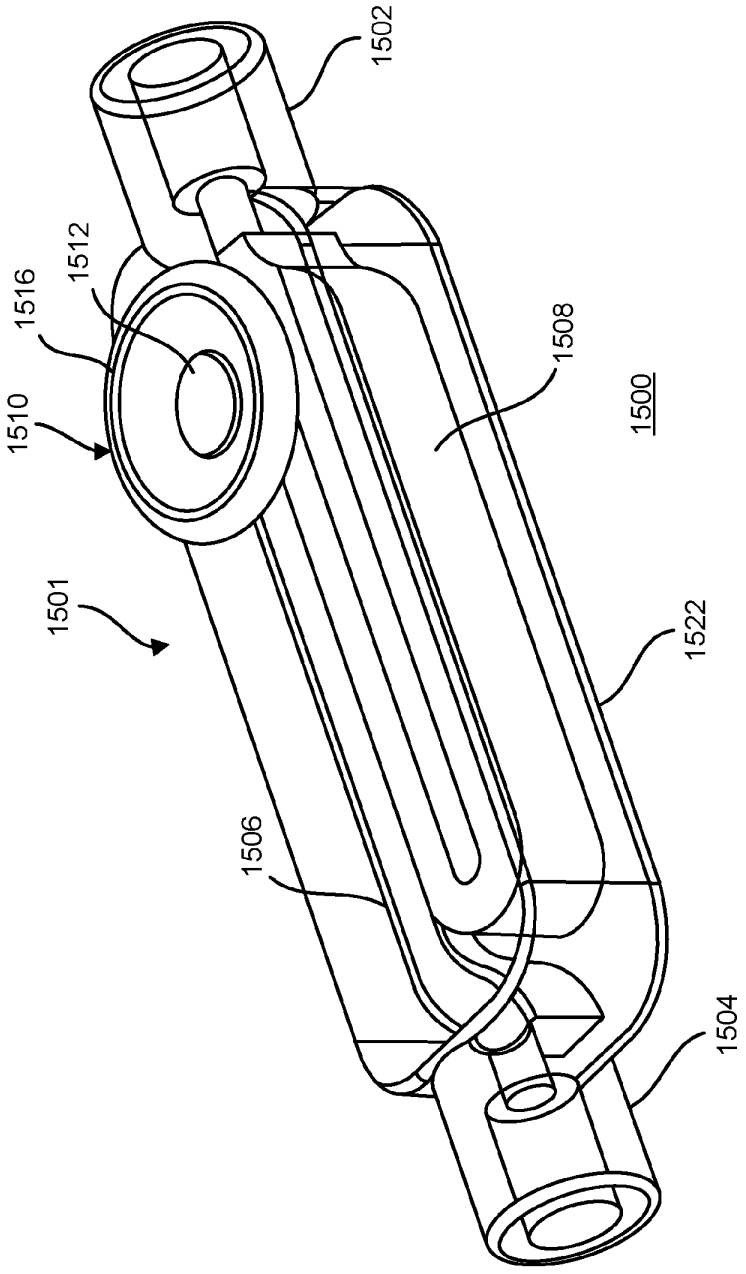


FIG. 15B

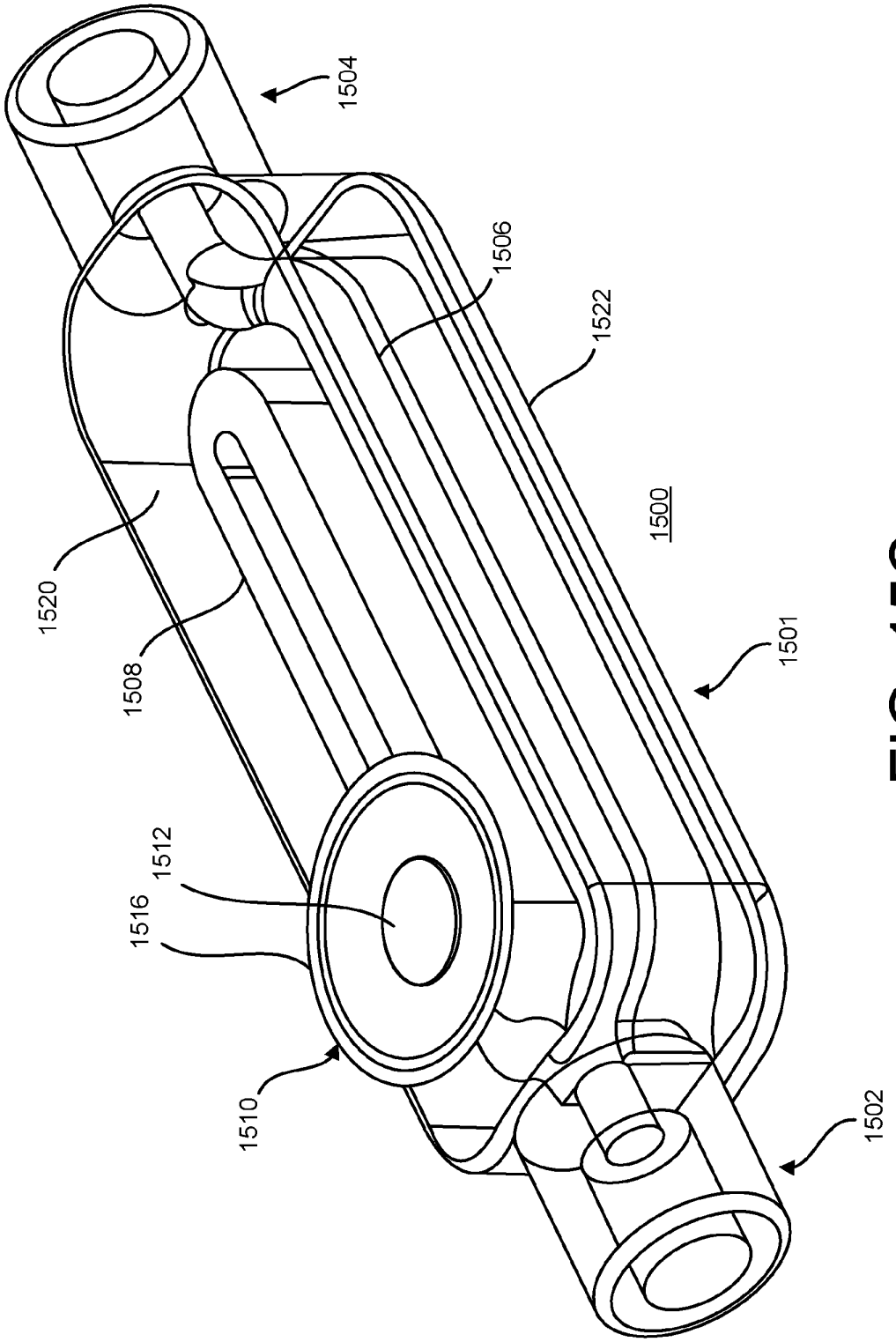


FIG. 15C

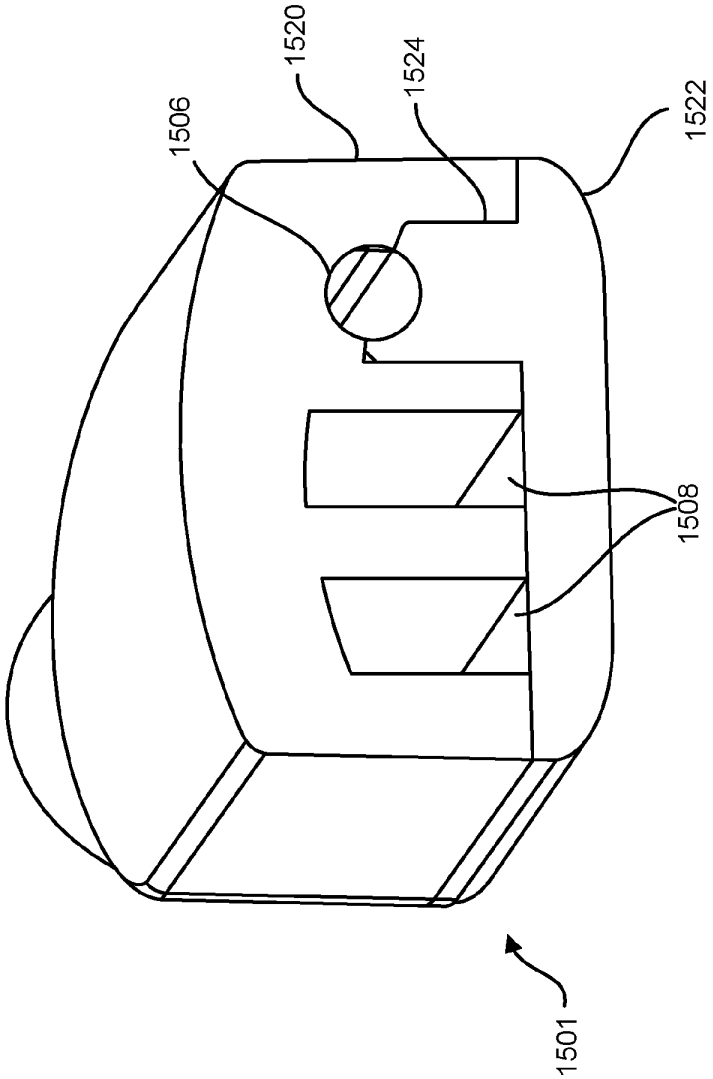


FIG. 15D

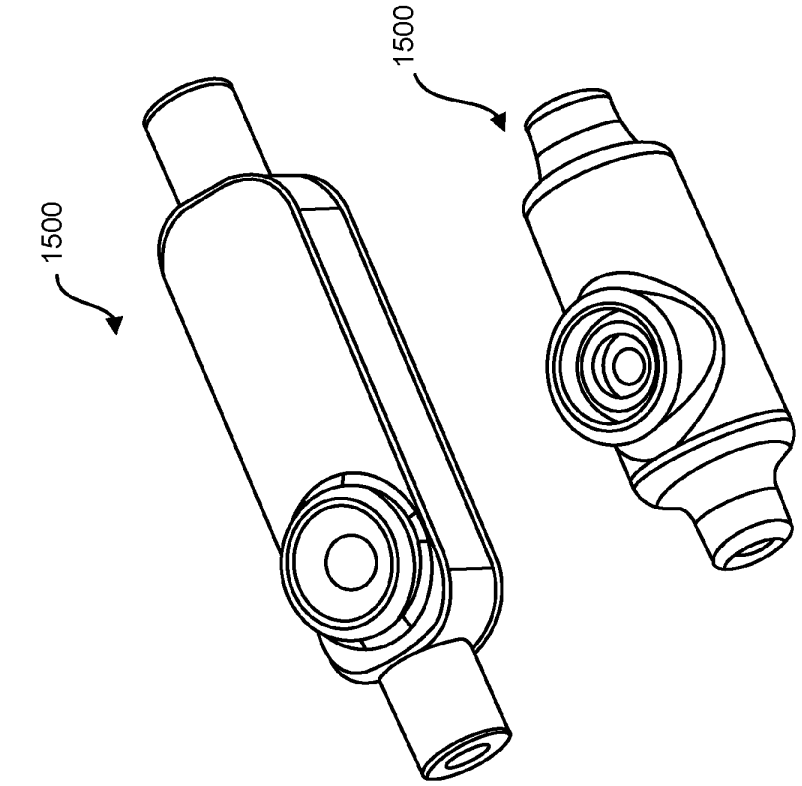


FIG. 15F

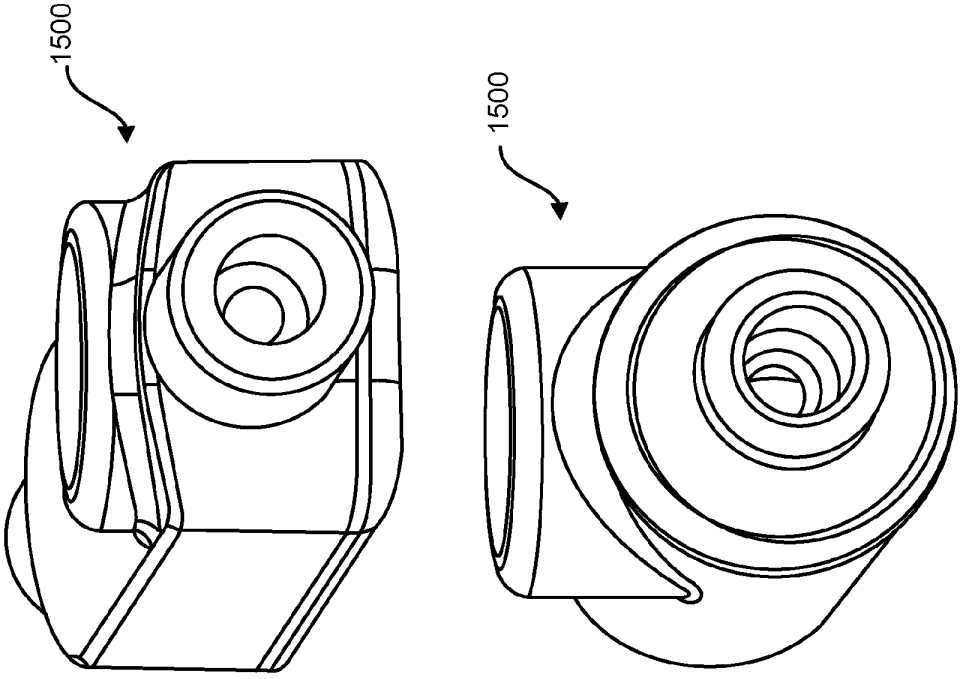


FIG. 15E

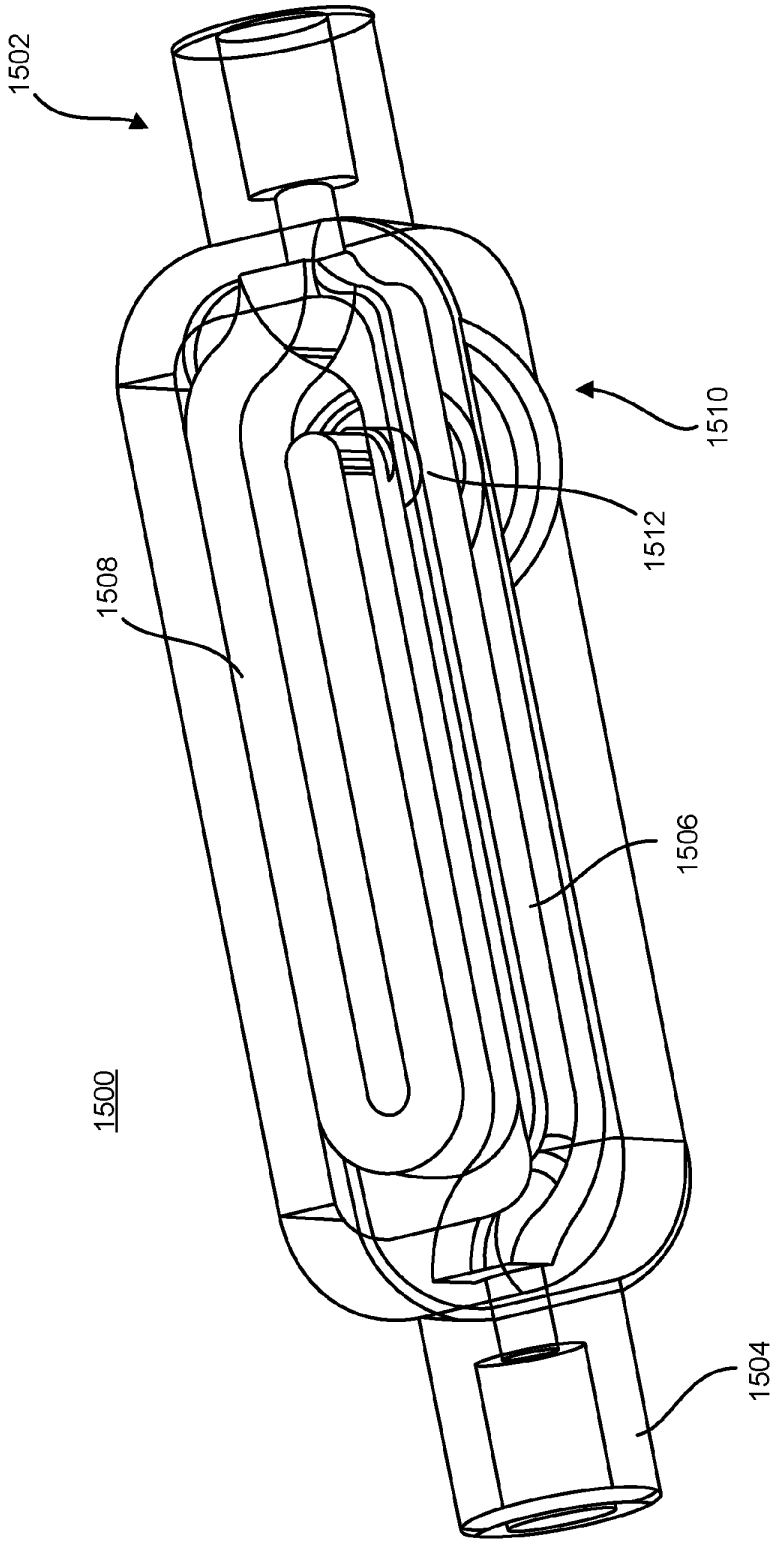


FIG. 15G

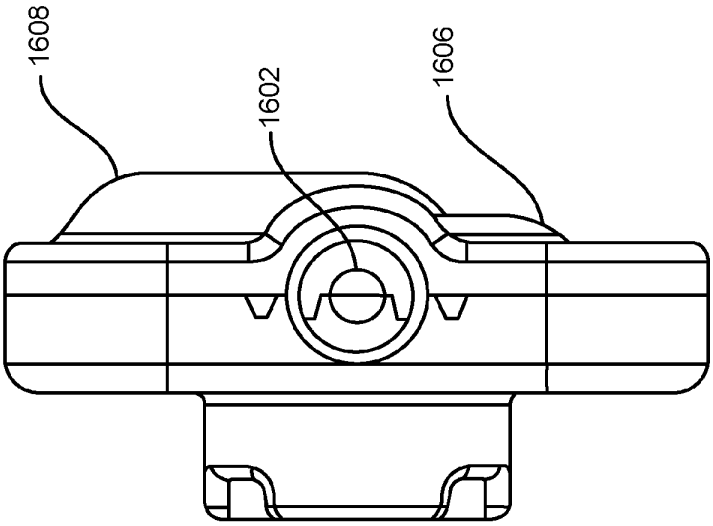


FIG. 16C

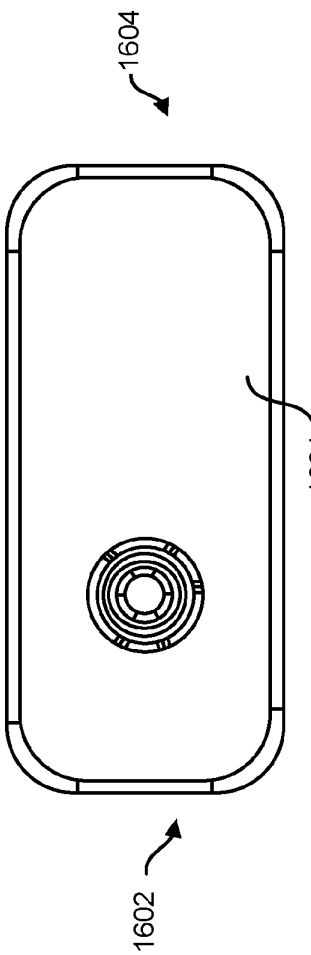


FIG. 16A

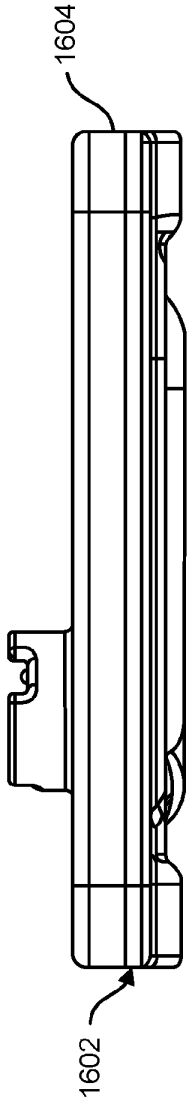


FIG. 16B

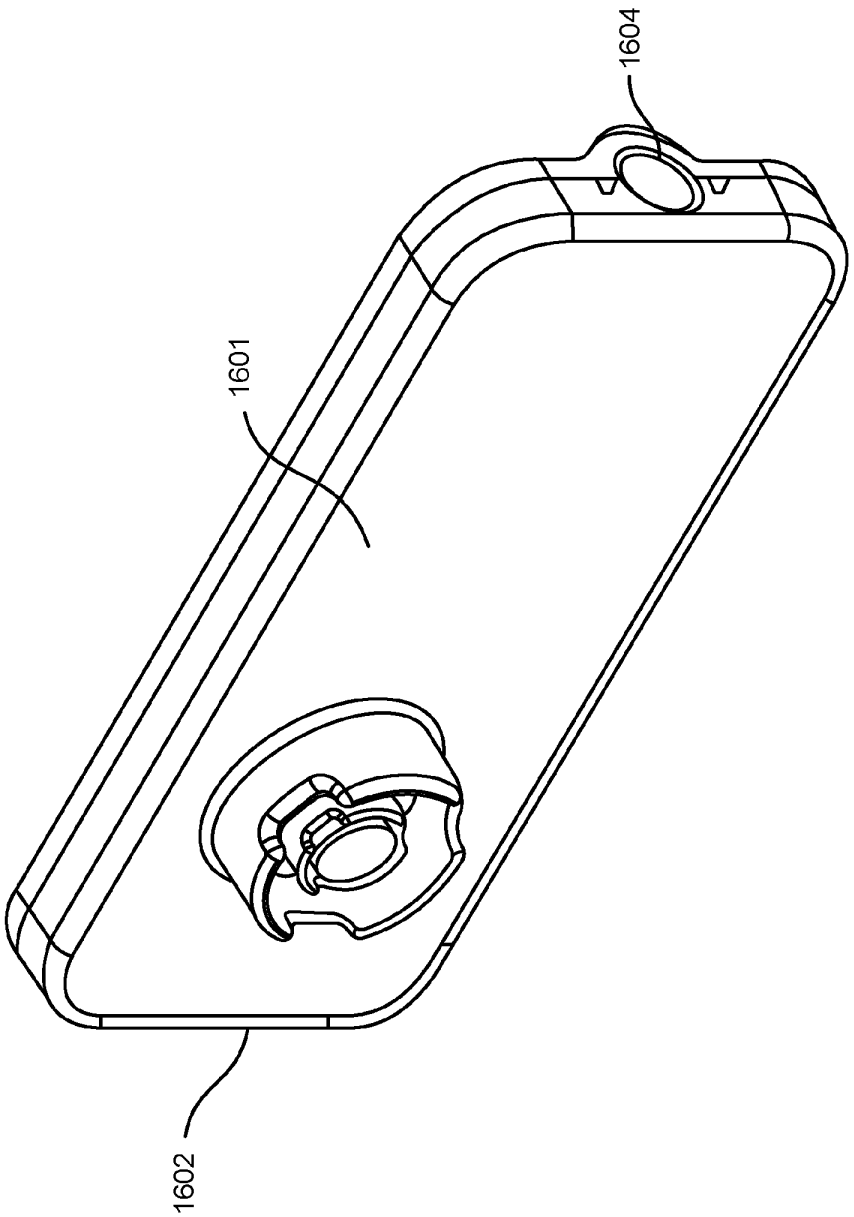


FIG. 16D

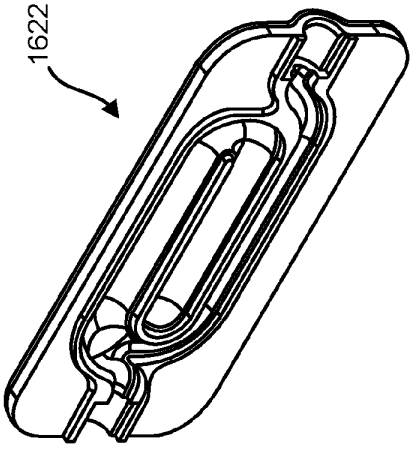


FIG. 17B



FIG. 17E

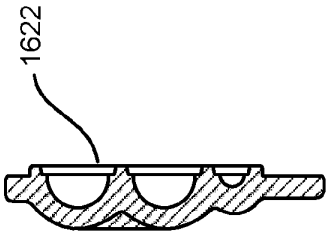


FIG. 17D

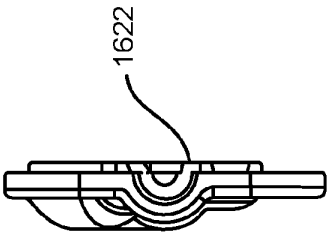


FIG. 17C

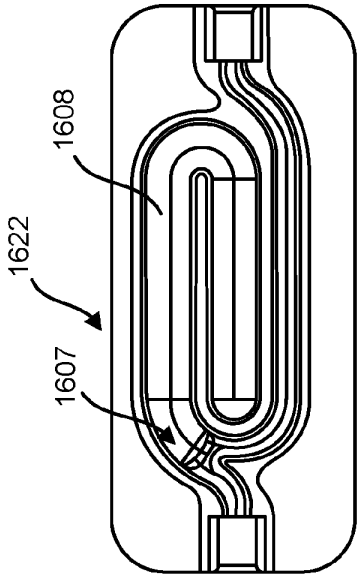


FIG. 17A

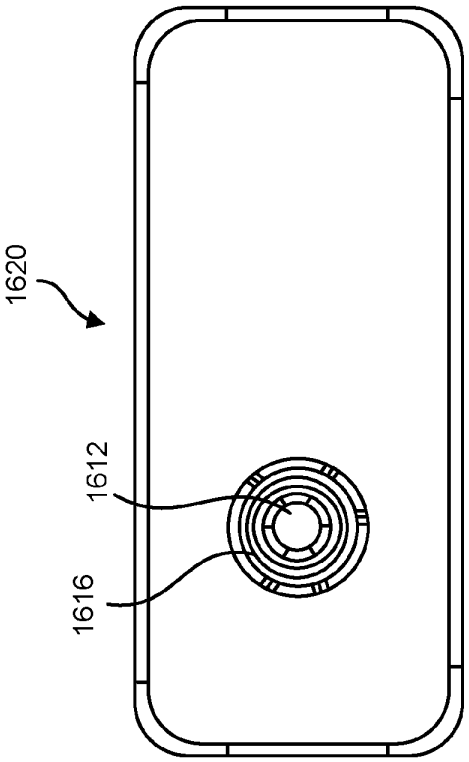


FIG. 18A

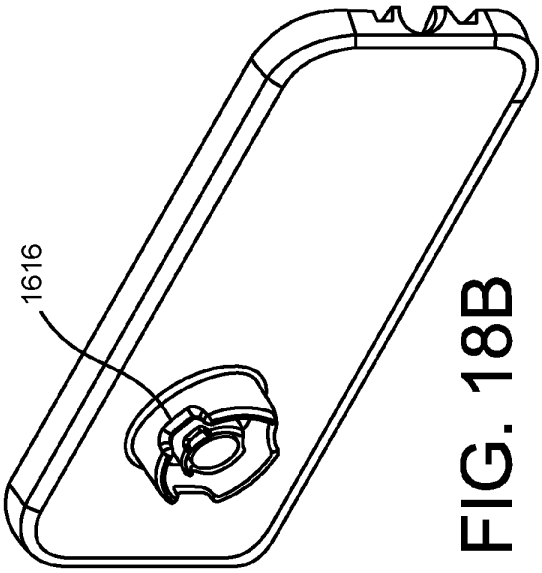


FIG. 18B



FIG. 18C

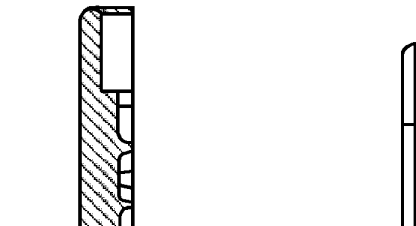


FIG. 18F

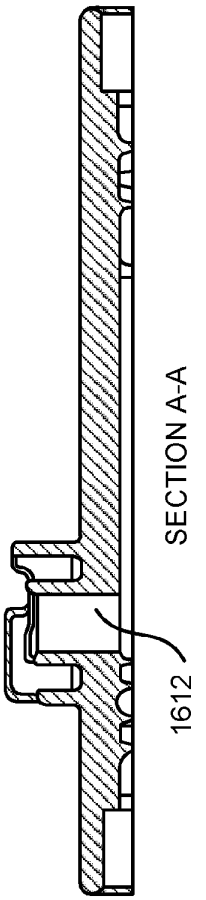


FIG. 18D

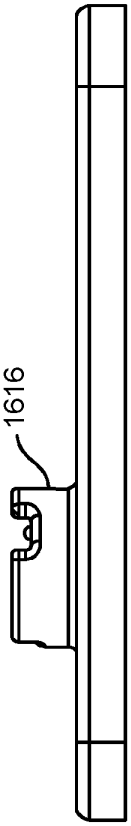


FIG. 18E

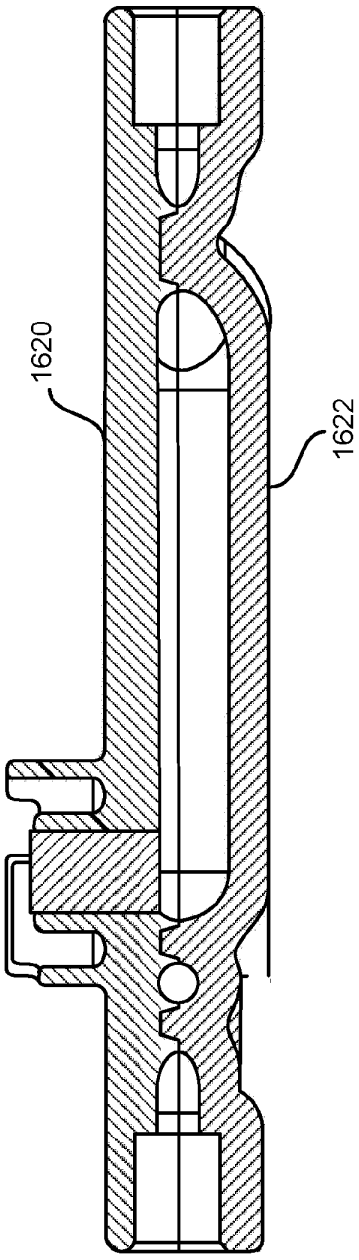


FIG. 19A

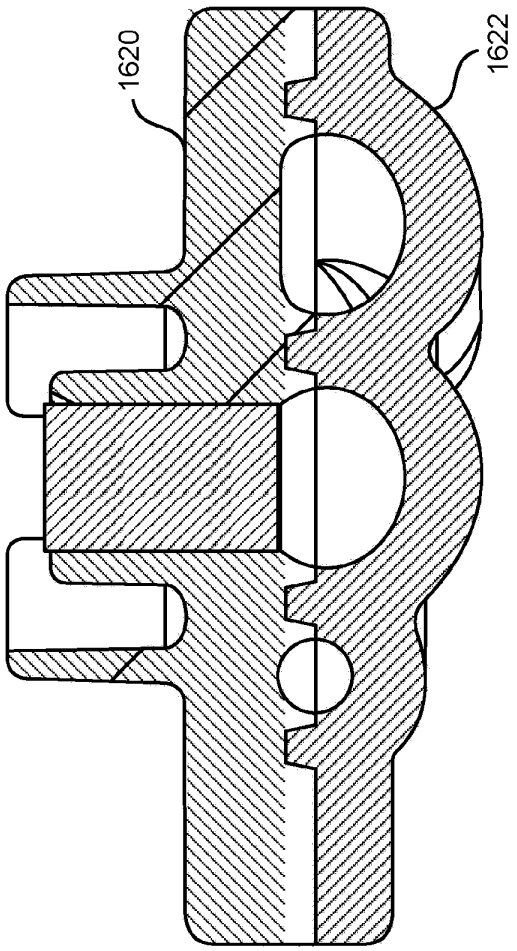


FIG. 19B

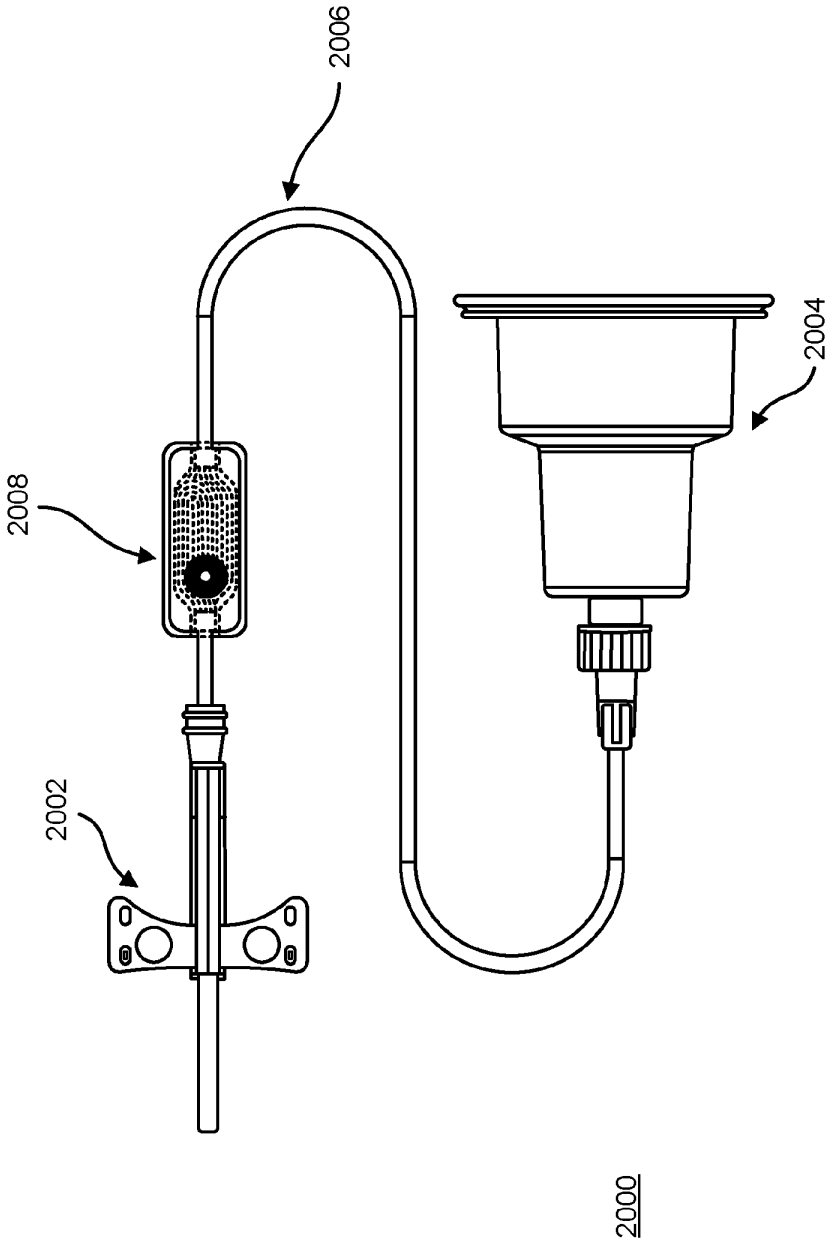


FIG. 20

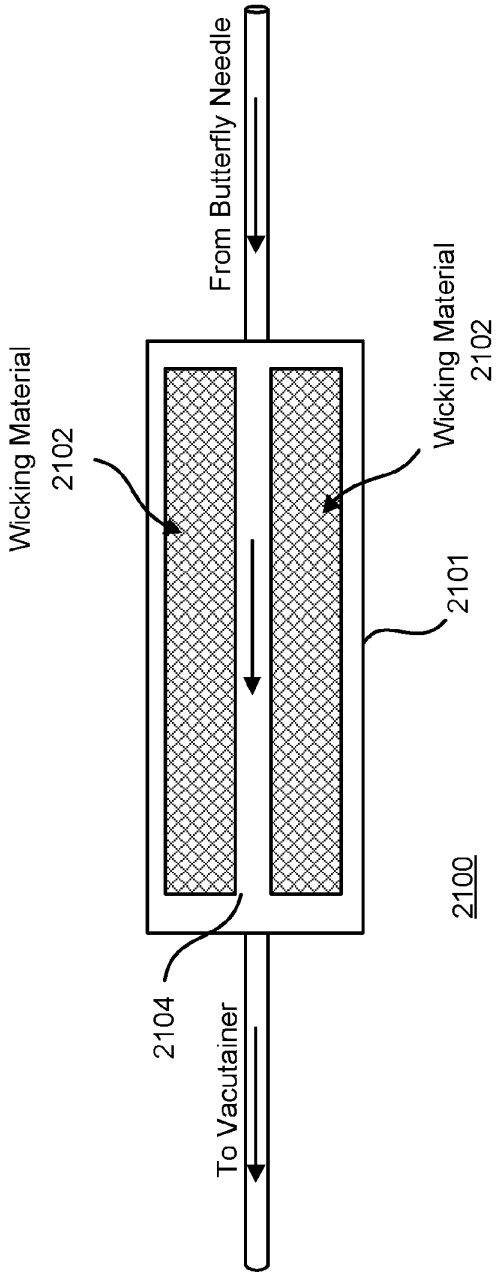

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

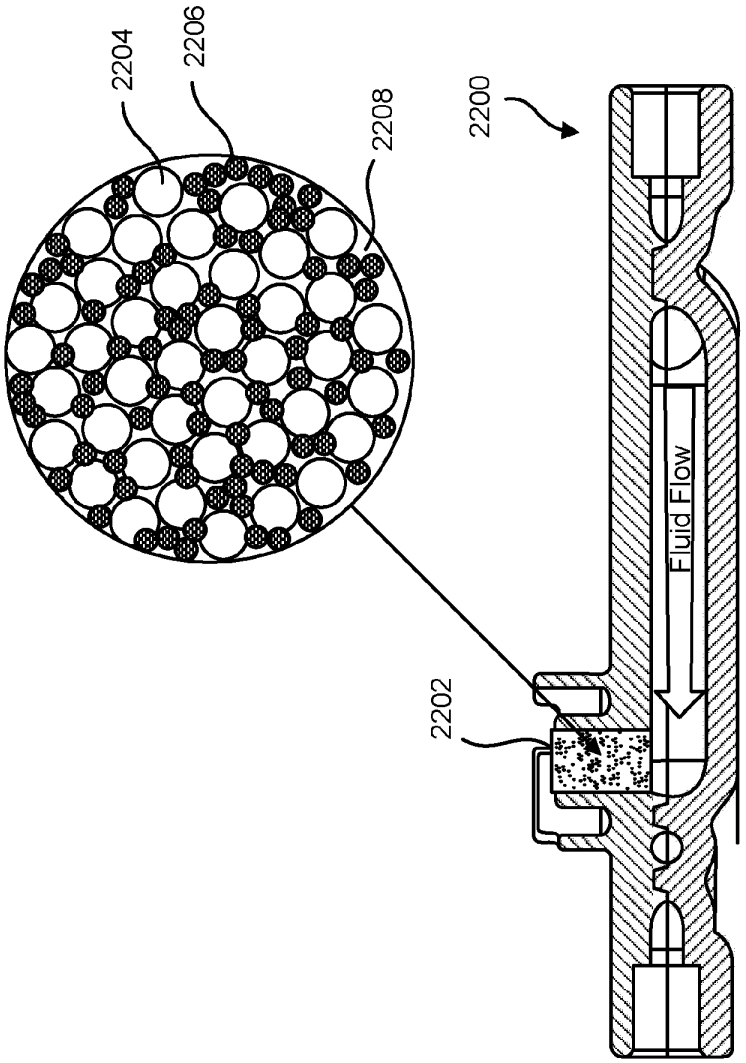


FIG. 22A

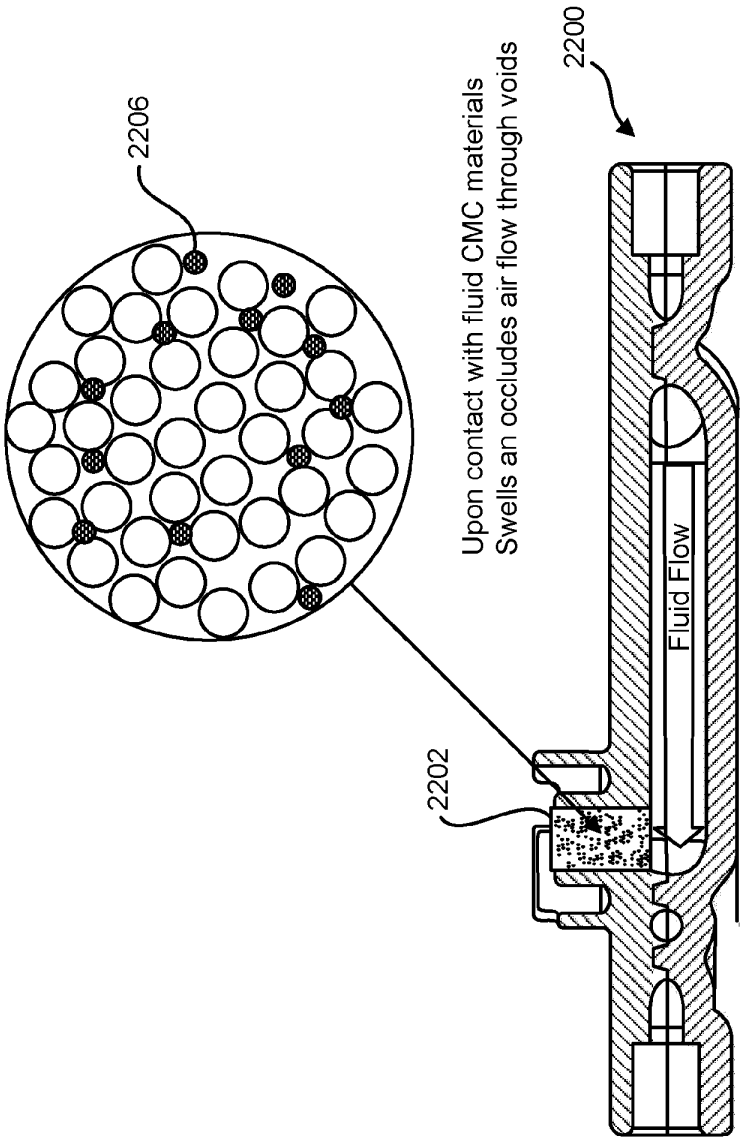

2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2200
2202
Fluid Flow

FIG. 22B

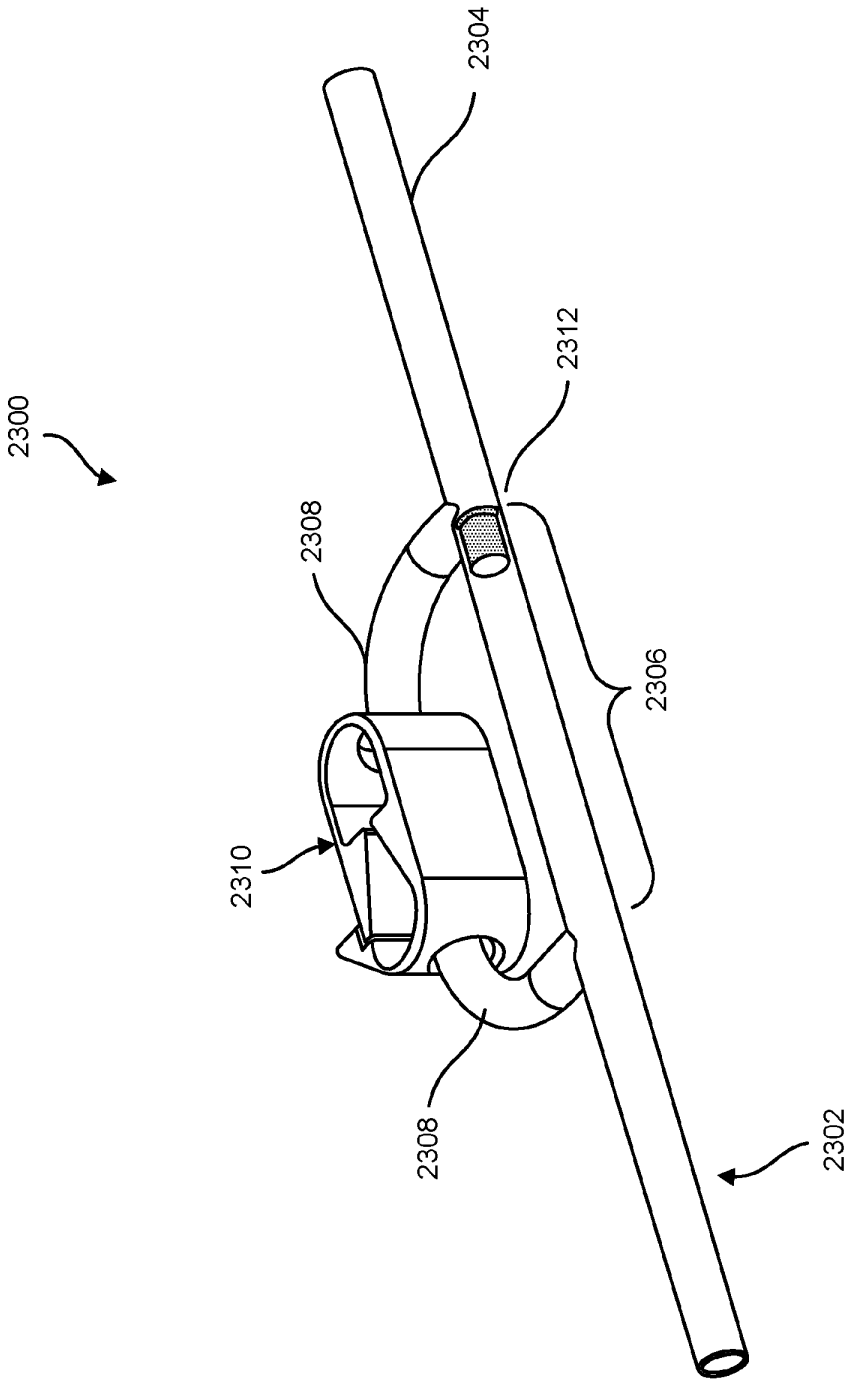


FIG. 23A

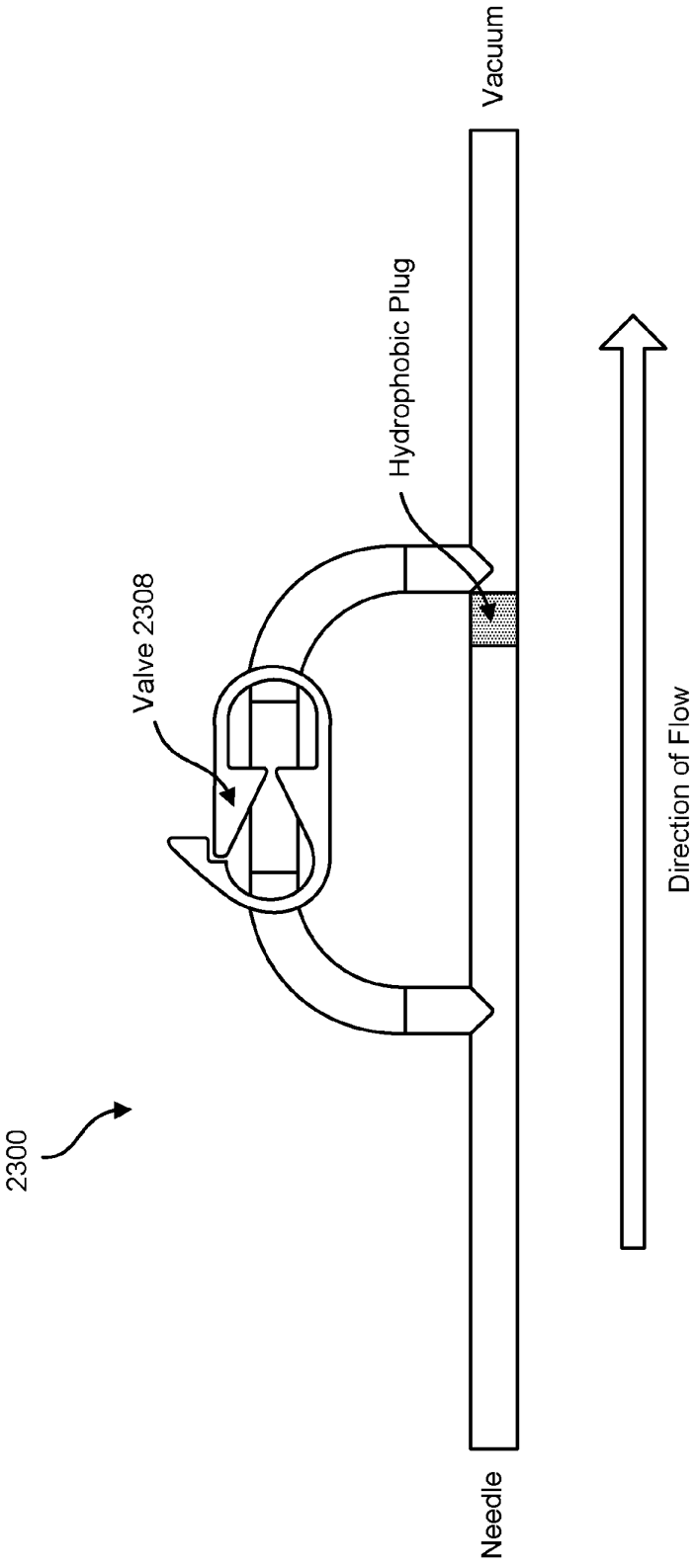

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011 (2011-12-29)	1-5, 7-13, 15-20
A	paragraph [0070] figure 15 abstract	6,14
A	US 2009/227953 A1 (TAN CHEE LEONG [SG] ET AL) 10 September 2009 (2009-09-10) the whole document	1-20
A	JP H08 257018 A (NISSHO KK) 8 October 1996 (1996-10-08) abstract; figures	1-20

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2016	19/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schultz, Ottmar

2

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 416 290 A (LUTKOWSKI LAWRENCE [US]) 22 November 1983 (1983-11-22) abstract; figures	1-20
A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) abstract; figures	1-20
A	EP 1 665 986 A1 (BECTON DICKINSON CO [US]) 7 June 2006 (2006-06-07) figures 13,14	1-20
A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) abstract; figures	1-20
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) paragraphs [0084] - [0094] figures 16-18	1-20

2

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011162772 A1	29-12-2011	NONE	
US 2009227953 A1	10-09-2009	US 2009227953 A1	10-09-2009
		US 2010262038 A1	14-10-2010
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JP H08257018 A	08-10-1996	NONE	
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EP 1665986 A1	07-06-2006	BR PI0505336 A	11-07-2006
		EP 1665986 A1	07-06-2006
		JP 4914601 B2	11-04-2012
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		US 2015099996 A1	09-04-2015
		US 2015351678 A1	10-12-2015

Form PCT/ISA/210 (patent family annex) (April 2005)

Bibliographic data: EP3324845 (A1) — 2018-05-30

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE

Inventor(s): ROGERS BOBBY [US]; KANG GINO [US]; DETLOFF JOHN [US] ± (ROGERS, Bobby, ; KANG, Gino, ; DETLOFF, John)

Applicant(s): KURIN INC [US] ± (KURIN, INC)

Classification: - international: ***A61B5/15; A61B5/153; A61B5/154; A61M39/02; A61M39/04; A61M39/06***

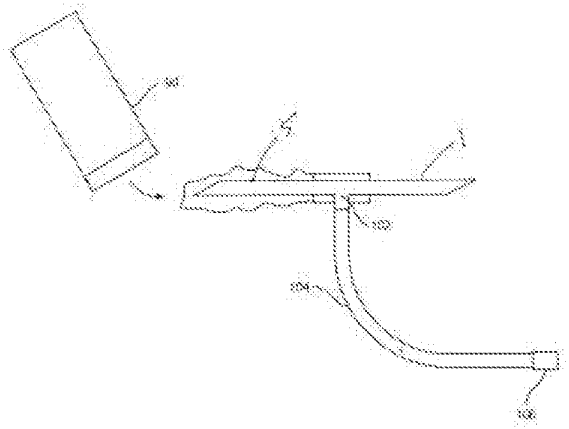
- cooperative: **A61B5/15003 (EP, IL, US); A61B5/150213 (EP, IL, US); A61B5/150221 (IL, US); A61B5/150389 (EP, IL, US); A61B5/150473 (EP, IL, US); A61B5/150572 (EP, IL, US); A61B5/150992 (IL, US); A61B5/153 (EP, IL, US); A61B5/154 (EP, IL, US); A61M39/04 (IL, US); A61M39/0693 (IL, US);** A61M2039/0202 (IL, US); A61M2039/0633 (IL, US); A61M2039/068 (IL, US)

Application number: EP20160747682 20160722 Global Dossier

Priority number(s): US201562196797P 20150724 ; US201562238636P 20151007 ; US201662318194P 20160404 ; US201615140448 20160427 ; US201615140443 20160427 ; WO2016US43709 20160722

Also published as: EP3324845 (B1) AU2016297849 (A1) AU2021202622 (A1) CA2993646 (A1) EP3622890 (A1) more

Abstract not available for EP3324845 (A1)
Abstract of corresponding document: US2017020427 (A1)



Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer:
(11) Publication number: **EP 3 324 845 A0**
(11) Numéro de publication:

Internationale Anmeldung veröffentlicht durch die Weltorganisation für geistiges Eigentum unter der Nummer:

WO 2017/019552 (Art. 153(3) EPÜ).

International application published by the World Intellectual Property Organization under number:

WO 2017/019552 (Art. 153(3) EPC).

Demande internationale publiée par l'Organisation Mondiale de la Propriété Intellectuelle sous le numéro:

WO 2017/019552 (art. 153(3) CBE).

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Patent 5789869

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(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Patent publication (B2)
(11) [Patent number] Patent No. 5789869 (P5789869)
(24) [Registration date] 2015 August 14 (2015.8.14)
(45) [Date of Issue] October 7, 2015 (2015.10.7)
(54) [Title of Invention] Auxiliary Plate for Polishing Pad and Equipped with Auxiliary Plate for Polishing Pad Polishing Apparatus
(51) [International Patent Classification]
B24B 37/12 (2012.01)
[FI]
B24B 37/04 A
[Number of Claims] 11
[Total Number of Pages] 21
(21) [Application Number] Patent Application 2011-165360 (P2011-165360)
(22) [Application date] July 28, 2011 (2011.7.28)
(65) [Publication number] JP-A-2013-27951 (P2013-27951A) (43) [Publication date] 2013 February 7, 2013 (February 7, 2013) [Date of request for examination] June 25, 2014 (June 25,

2014) [Matters to be stated regarding results of research commissioned by the government] (report by applicant) commissioned by the government Patent application related to research results (FY2010 Ministry of Economy, Trade and Industry "Strategic Fundamental Technology Advancement Support Project" commissioned research, patent application subject to Article 1 9 of the Industrial Technology Enhancement Act) (73) [Patentee] [Identification number] 599 096053

[Name] Toho Engineering Co., Ltd.
(74) [Agent]
[Identification Number] 100103252 [
Patent Attorney]
[Name] Yoshitaka Kasai
(74) [Agent]
[Identification Number] 100147717
[Patent Attorney]
[Name] Or name] Mie Nakane
(72) [Inventor]
[Name] Tatsutoshi Suzuki
(72) [Inventor]
[Name] Eiji Suzuki
[Examiner] Takashi Kameda
(56) [References] [Reference] Japanese Patent Application
Laid- Open No. 08- 118231 (JP, A) [Reference] JP-A-07-328915 (JP, A) (58) [Field investigate d] (Int.Cl., DB name) B24B 37/12 H01L 21/304

The scope of the claims open ---

(57) [Scope of Claims]
[Claim 1] A

polishing pad auxiliary plate mounted on a rotating surface plate of a polishing apparatus for detachably attaching a polishing pad to the rotating surface plate, wherein

:

a first fixing means for fixing the lower auxiliary plate to the rotating surface plate; and

a pad supporting surface on which the polishing pad is superposed and fixed. an upper auxiliary plate superimposed on the upper surface of the lower auxiliary plate;

second fixing means for fixing the upper auxiliary plate to the lower auxiliary plate;

the lower auxiliary plate and the upper side; positioning means for aligning the center axis of the auxiliary plate with respect to each other

, and the lower auxiliary plate is fixed to the rotating surface plate of the polishing apparatus by the first fixing means. By removing the upper auxiliary plate from the lower auxiliary plate held and fixed to the rotating surface plate, the polishing pad can be rotated while being fixed to the pad supporting surface of the upper auxiliary plate. The upper auxiliary plate can be removed from the surface plate, and the removed upper auxiliary plate can be fixed and attached again to the lower auxiliary plate while being aligned by the positioning means, and ,

the fixing force between the lower auxiliary plate and the upper auxiliary plate by the second fixing means is smaller than the fixing force between the rotating platen and the lower auxiliary plate by the first fixing means;

Auxiliary plate for a polishing pad, characterized in that :

[Claim 2]

2. The auxiliary plate for a polishing pad according to claim 1 , wherein said positioning means is located inside the outer peripheral surfaces of said lower auxiliary plate and said upper auxiliary plate.

3. The positioning

means

includes an engaging projection provided on one of the lower auxiliary plate and the upper auxiliary plate and protruding toward the other, and the lower auxiliary plate and the upper auxiliary plate. 3. An auxiliary plate for a polishing pad according to claim 2 , wherein said auxiliary plate for a polishing pad comprises an engaging concave portion provided on the other side thereof and with which said engaging convex portion is engaged .

4. The polishing pad according to claim 3

, wherein said engaging projections and said engaging recesses are formed with engaging portions located on the outer peripheral portions of said lower auxiliary plate and said upper auxiliary plate. Auxiliary plate. 5. An annular engagement in which the engaging portions of the engaging protrusion and the engaging recess extend continuously in the circumferential direction of the lower auxiliary plate and the upper auxiliary plate and are fitted to each other. 5. The auxiliary plate for a polishing pad according to claim 4 , comprising an outer peripheral surface and an engaging inner peripheral surface . 6. At a plurality of locations on the circumference of the outer peripheral portions of the lower auxiliary plate and the upper auxiliary plat

e, the lower auxiliary plate and the upper auxiliary plate are overlapped on one side toward th e other. The engaging concave portion that opens and the engaging convex portion that protr udes toward one side of the other of the mutual overlapping surfaces of the lower auxiliary pl ate and the upper auxiliary plate are formed at positions corresponding to each other. wherein said engaging portion is formed by fitting said engaging convex portion into said engaging con cave portion.

5. The polishing pad auxiliary plate according to 4 .

7.

The engaging protrusions projecting from a plurality of locations on the circumference of one of the lower auxiliary plate and the upper auxiliary plate toward the other are formed of an el astic material, and The engagement portion is formed by engaging the tip of the engagement projection with the engagement recess provided in the outer peripheral surface of the other of the side auxiliary plate and the upper auxiliary plate. 5. The polishing pad auxiliary plate acco rding to claim 4 .

8. A polishing pad auxiliary plate according to claim 3

, wherein said engaging projections and said engaging recesses are provided on the central axes of said lower auxiliary plate and said upper auxiliary plate. 9. An outer peripheral surfac e of said engaging projection and an inner peripheral surface of said engaging recess are form ed with screw grooves for engaging with each other, and said engaging projection and said en gaging portion constituting said positioning means are formed with thread grooves for engagi ng with each other. 9. The auxiliary plate for a polishing pad according to claim 8 , wherein sai d second fixing means is formed by screwing with said mating recess . 10. The engaging pro jection provided on one of the lower auxiliary plate and the upper auxiliary plate is formed of t he same material as one of the lower auxiliary plate and the upper auxiliary plate. The auxilia ry plate for a polishing pad according to any one of claims 3 , 4 , 5 , 6 , 8 and 9 .

11. The auxiliary plate for a polishing pad according to any one of claims 1 to 10 is mounted o n the upper surface of a rotating surface plate, and a protective member is provided on the ou ter peripheral side of the rotating surface plate with a gap

therebetween . 11. The positioning means according to any one of claims 1 to 10 , wherein t he positioning means is disposed on the inner peripheral side of the outer peripheral end faces of the rotating platen and the polishing pad auxiliary plate. 2. A polishing apparatus comprisin g the polishing pad auxiliary plate according to 1 or 2 above.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to the polishing of substrates such as silicon wafers, semiconductor substrates, glass substrates, etc., which are workpieces requiring high flatness accuracy. It relates to a related technique, and more particularly to a technique that makes it possible to reuse a polishing pad used in polishing the surface of such a substrate.

is. 2.

Description of the Related Art As is well known, in manufacturing a semiconductor, a polishing process is performed to flatten the surface of a substrate such as a silicon wafer, a semiconductor substrate, a glass substrate, or the like. Such a polishing process generally involves fixing a disc-shaped polishing pad made of a resin material or the like directly on a rotating surface plate of a polishing apparatus with a double-sided tape, and supplying a polishing liquid containing abrasive grains to the polishing pad. Polishing is performed by rotating the substrates relative to each other. [0003] Polishing pads for carrying out such a polishing process are made of foamed or non-foamed urethane or the like, as described in Japanese Patent Application Laid-Open No. 2002-11630 (Patent Document 1). A resin pad is used. Further, in many cases, the polishing surface of such a polishing pad is provided with grooves such as concentric circles, grids, or radial grooves, or the bubbles of foamed resin are opened. [0004] By the way, when performing a polishing process using a polishing pad, when changing the type of substrate to be polished, the polishing pad used for the polishing process is peeled off from the rotating platen and replaced with another polishing pad. sometimes you have to. Also, for example, when a polishing pad that has deteriorated due to polishing is to be re-processed, such as by grooving the surface, with another processing device for the purpose of reusing the polishing pad, the polishing pad is removed from the rotating platen. Needs to be pulled off. [0005]

However, since the thin disk-shaped polishing pad is firmly fixed to the rotating surface plate

of the polishing apparatus with an adhesive tape, when the polishing pad is peeled off from th e rotating surface plate, Damage such as bending, breaking, wrinkling, and tearing is likely to occur. Therefore, due to such damage, there is often a problem that such polishing pads cann ot be reused and must be discarded even though their service life has not expired.

[0006]

Moreover, the work of peeling off the polishing pad from the rotating surface plate while payi ng close attention not to damage it requires skill and caution, and there is also the problem of placing a heavy burden on the operator. In addition, since it takes a considerable amount of ti me to peel off the polishing pad from the rotating surface plate, the polishing apparatus, whic h is expensive and valuable equipment, must be stopped for a long time, which shortens the o peration time of the equipment. There was also the problem that the

[0007]

Therefore, the present inventor previously described in Japanese Patent Application Laid-Ope n No. 2010-214579 (Patent Document 2) that an auxiliary plate is attached to the back surfac e of the polishing pad, and the polishing pad is rotated by the polishing apparatus through thi s auxiliary plate. We proposed a polishing pad with an auxiliary plate that is fixed to the surfa ce plate with double-sided tape. With such a polishing pad with auxiliary plate, since the polis hing pad is attached to and detached from the rotating surface plate while being supported by the auxiliary plate, damage to the polishing pad during attachment and detachment is reinforc ed by the auxiliary plate. Therefore, it is possible to attach and detach the polishing pad to an d from the rotating platen with good workability while preventing the polishing pad from being damaged.

[0008]

However, as a result of further studies and studies by the present inventors, it has been foun d that it is difficult to say that the polishing pad with an auxiliary plate proposed in Patent Doc ument 2 is easily compatible with all polishing apparatuses. rice field.

[0009]

That is, when the polishing pad is overlaid and fixed to the rotating surface plate, it is necess ary to align the center of the polishing pad with the rotation center of the rotating surface plat e. Accuracy is required for center alignment. If the number of attachment/detachment of the polishing pad to/from the rotating platen increases by adopting the auxiliary plate as describe d above, it becomes more difficult and labor-intensive to align the center position when attach ing the polishing pad to the rotating platen. big is big

It becomes a problem. Further, in the polishing pad with auxiliary plate proposed in Patent D ocument 2, in order to detachably attach the auxiliary plate while aligning the center of the au xiliary plate with respect to the rotary surface plate, the following are provided between the a uxiliary plate and the rotary surface plate

:

For example, fixing means such as an outer peripheral ring may be provided on the outer peri

pheral surface of the rotating surface plate. On the other hand, in some polishing apparatuse s, a protective cover or the like is attached to the outer peripheral side of the rotary platen, so that the space on the outer peripheral side of the rotary platen is extremely narrow. Therefor e, if such an outer peripheral ring were to be adopted, and a polishing device with a narrow sp ace on the outer peripheral side of the rotating surface plate was used, there was a possibility that the polishing device would need to be modified. of.

[Prior Art Documents]

[Patent Documents]

[0011]

[Patent Document 1] Japanese Unexamined Patent Application Publication No. 2002-11630 [P atent Document 2] Japanese Unexamined Patent Application Publication No. 2010-214579 [Su mmary of the Invention] [Problems to be Solved by the Invention] SUMMARY OF THE INVEN TION It is an object of the present invention to provide a polishing pad which can be easily att ached to and detached from a rotating surface plate while sufficiently securing the fixing force of the polishing pad to the rotating surface plate . For a polishing pad with a novel structure, which can prevent damage to the polishing pad when the polishing pad is removed from the r otating platen, and which can be advantageous for reuse of the polishing pad, for example. To provide an auxiliary plate. [0013]

In addition, according to the present invention, the work of aligning the center when mounti ng the polishing pad on the rotating surface plate can be performed easily and accurately, and the labor burden can be reduced. Another object of the present invention is to provide an auxi liary plate for a polishing pad with an improved structure, which can be easily and advantageo usly applied to a rotating surface plate in a polishing machine without requiring any special m odification. A further object of the present invention is to provide a polishing apparatus havin g such a novel polishing pad auxiliary plate

. Means for Solving the Problems In order to solve the above problems, a first aspect of the present invention relating to an auxiliary plate for a polishing pad is: (A) mounted on a rotatin g surface plate of a polishing apparatus; A polishing pad auxiliary plate for detachably attachi ng a pad to the rotary platen, comprising: (B) a lower auxiliary plate disposed on the upper s urface of the rotary platen; and (C) the lower auxiliary plate. and (D) a pad supporting surfac e on which the polishing pad is superimposed and fixed, which is superimposed on the upper s urface of the lower auxiliary plate. (E) a second fixing means for fixing the upper auxiliary plat e to the lower auxiliary plate; The lower auxiliary plate is held in a fixed state by the first fixin

g means to the rotating surface plate of the polishing apparatus, and is fixed to the rotating s urface plate. Further, by removing the upper auxiliary plate from the lower auxiliary plate, the polishing pad can be removed from the rotating surface plate while being fixed to the pad sup porting surface of the upper auxiliary plate. At the same time, it is possible to attach the remo ved upper auxiliary plate to the lower auxiliary plate by fixing it again in a state of being align ed by the positioning means.

and the fixing force between the lower auxiliary plate and the upper auxiliary plate by the sec ond fixing means is stronger than the fixing force between the rotating platen and the lower a uxiliary plate by the first fixing means. It features a smaller auxiliary plate for the polishing pa d. In the polishing pad auxiliary plate constructed according to the present invention, the pol ishing pad is composed of the upper auxiliary plate and the upper auxiliary plate

.

It is fixedly attached to the rotating surface plate via the lower auxiliary plate. Thereby, the u pper auxiliary plate can be removed from the lower auxiliary plate while the lower auxiliary pl ate is fixed to the rotating surface plate, and the polishing pad can be removed from the rotati ng surface plate while being fixed to the upper auxiliary plate. becomes possible. Therefore, in a state in which the polishing pad is reinforced and protected by the upper auxiliary plate, t he polishing pad can be removed from the rotating surface plate while preventing damage to t he polishing pad, and the thin polishing pad can be easily handled

.

becomes. For example, when the polishing pad is repeatedly attached and detached when the object to be polished or the polishing conditions are changed, or when the worn polishing pad is detached and reattached after reprocessing, the attachment and detachment of the polishin g pad to and from the rotating platen and the polishing are difficult. It is also possible to easil y perform operations such as reproduction processing for pads. Moreover, since the lower au xiliary plate still fixed to the rotating surface plate and the upper auxiliary plate removed toge ther with the polishing pad are aligned with each other by the positioning means, the position on the rotating surface plate can be easily adjusted

.

The attachment and detachment work of the polishing pad, which requires alignment, can be performed more easily. In particular, since the positioning means is provided between the low er auxiliary plate and the upper auxiliary plate, there is no need to apply special processing or the like to the rotating surface plate. In addition, it is possible to prevent such positioning me ans from protruding to the outer peripheral side of the rotating surface plate. applicable witho ut In the polishing pad auxiliary plate according to the first aspect of the present invention

,

, the fixing force between the lower auxiliary plate and the upper auxiliary plate by the seco nd fixing means is smaller than the fixing force between the rotating platen and the lower aux iliary plate by the first fixing means; A certain aspect is employed . According to the first aspe ct , the fixing forces of the first and second fixing means are mutually adjusted, so that the up per auxiliary plate to which the polishing pad is fixed can be rotated

. This makes it easier to remove the lower auxiliary plate that is still fixed to the surface plate. In short, there is no need for a special operation or the like to keep the lower auxiliary plate fi xed to the rotating platen, and the polishing pad can be attached to the upper supporting plat e while the lower auxiliary plate remains fixed to the rotating platen. It becomes possible to e asily remove the plate from the rotating surface plate while it is fixed to the plate. According t o a second aspect of the present invention , in the polishing pad auxiliary plate according to the first aspect, the positioning means is arranged on the inner peripheral side of the outer pe ripheral surfaces of the lower auxiliary plate and the upper auxiliary plate . It is located and pr ovided. [0022] In the polishing pad auxiliary plate of this aspect, the projection of the upper and lower auxiliary plates to the outer peripheral side of the positioning means is completely a voided. Therefore, for example, even when the outer diameter of the upper and lower auxiliar y plates is set to be the same as or slightly smaller than the outer diameter of the rotating sur face plate, the supporting surface of the polishing pad can be secured sufficiently large and th e It is possible to prevent the positioning means from protruding to the outer peripheral side, and even if a protective cover or the like is installed on the outer peripheral side of the rotatin g surface plate, it will not become an obstacle when applying the polishing pad auxiliary plate according to the present invention. Avoided.

A third

aspect of the present invention is the polishing pad auxiliary plate according to the second a spect, wherein the positioning means is provided on one of the lower auxiliary plate and the u pper auxiliary plate and on the other . It is composed of an engaging projection projecting to ward and an engaging recess provided in the other of the lower auxiliary plate and the upper auxiliary plate with which the engaging projection is engaged. In the polishing pad auxiliary pl ate of this aspect, it is possible to easily obtain a mechanically large positioning force based on the mutual engagement between the engaging projections and the engaging recesses. Furt her, by adjusting the shape, size, number, etc. of the engaging projections and engaging rece sses, it is possible to easily set the direction and acting force of the positioning action with a l arge degree of freedom.

A fourth aspect

of the present invention is the auxiliary plate for a polishing pad according to the third aspec t, wherein the engaging projections and the engaging recesses are located on the outer perip heries of the lower auxiliary plate and the upper auxiliary plate . It is formed with an engagin g portion located in the portion. In the polishing pad auxiliary plate of this aspect, the engag ement outer peripheral surface of the engagement projection and the engagement recess are positioned in the outer peripheral portion away from the center of the polishing pad auxiliary plate and are engaged with each other in a concave-convex manner . By forming the engage ment inner peripheral surface of the upper and lower auxiliary plates, the relative positioning accuracy, particularly the radial positioning accuracy, can be improved. As shown in the sixth and seventh aspects below, the engaging outer peripheral surface of the engaging convex por tion and the engaging inner peripheral surface of the engaging concave portion are arranged around the center of the polishing pad auxiliary plate. It may extend in the circumferential dir ection along the outer peripheral edge of the polishing pad auxiliary plate, or it may extend on the circumference like the engaging protrusions and engaging recesses formed on the outer p eripheral portion of the polishing pad auxiliary plate. It may be in a partially positioned form. A fifth aspect of the present invention is the auxiliary plate for a polishing pad according to t he fourth aspect, wherein the engaging portions of the engaging projections and the engaging recesses correspond to the lower auxiliary plate and the It is composed of an annular engagin g outer peripheral surface and an engaging inner peripheral surface that extend continuously i n the circumferential direction of the upper auxiliary plate and are fitted to each other. [0028]

In the polishing pad auxiliary plate of this aspect, more preferably, the engaging concave por tion and the engaging convex portion are formed with an annular inner and outer peripheral e ngaging surface that spreads around the central axis of the polishing pad auxiliary plate. Ther efore, when the upper auxiliary plate is attached to the lower auxiliary plate, it is not necessar y to align the upper auxiliary plate with each other in the circumferential direction, and the wo rk can be performed easily and quickly. A sixth aspect of the present invention is a polishing pad auxiliary plate according to the fourth aspect, wherein the lower auxiliary plate and the u pper auxiliary plate are provided at a plurality of locations on the periphery of the outer perip heral portions of the lower auxiliary plate and the upper auxiliary plate

. The engaging recess opening toward the other on one of the overlapping surfaces of the low er auxiliary plate and the upper auxiliary plate, and the other of the mutually overlapping surf

aces of the lower auxiliary plate and the upper auxiliary plate and the engaging projection pro jecting toward one side are formed at positions corresponding to each other, and the engaging portion is formed by fitting the engaging projection into the engaging recess. is. In the polishi ng pad auxiliary plate of this mode, the mutual positioning of the upper and lower auxiliary p lates can be easily realized not only in the direction perpendicular to the axis but also in the ci rcumferential direction around the central axis. In a seventh aspect of the present invention , in the polishing pad auxiliary plate according to the fourth aspect, the outer peripheral portio n of one of the lower auxiliary plate and the upper auxiliary plate has a plurality of points on t he circumference of the other . The engaging convex portion protruding toward the upper auxi liary plate is formed of an elastic material, and engages with the engaging concave portion pr ovided in an opening on the outer peripheral surface of the other of the lower auxiliary plate a nd the upper auxiliary plate. The engaging portion is configured by engaging the tip of the en gaging projection.

In the polishing pad auxiliary plate of this aspect, it is possible to form the engaging portions so as to be exposed on the outer peripheral surfaces of the upper and lower auxiliary plates . can be confirmed. In addition, in this aspect, the engagement state of the engagement portio n can be stably maintained by utilizing the elasticity of the engagement convex portion. An ei ghth
aspect of
the present invention is the polishing pad auxiliary plate according to the third aspect, where in the engaging projections and the engaging recesses are located at the centers of the lower auxiliary plate and the upper auxiliary plate . It is provided on the shaft. In the polishing pad auxiliary plate of this aspect, the engaging projections and the engaging recesses are formed on the central axis of the upper and lower auxiliary plates .

By providing this, it becomes possible to align the central axes of the upper and lower auxiliar y plates with one engaging portion. Further, when the engaging projections and the engaging recesses provided on the central axis are aligned with each other, it is not necessary to align t he upper and lower auxiliary plates with each other in the circumferential direction. can be ea sily brought into engagement. According to a ninth aspect of the present invention , in the p olishing pad auxiliary plate according to the eighth aspect, the outer peripheral surface of the engaging projection and the inner peripheral surface of the engaging recess are screwed toget

her

. A groove is formed, and the second fixing means is formed by screwing the engaging project ion and the engaging recess that constitute the positioning means. [0036] In the polishing p ad auxiliary plate of this mode, the fixing force between the upper auxiliary plate and the low er auxiliary plate can be obtained by the positioning means. Therefore, it is possible to config ure the second fixing means only by such positioning means, or to configure the fixing force b etween the upper and lower auxiliary plates by the second fixing means as an auxiliary means by the positioning means. A tenth aspect of the present invention is the third , fourth , fifth , sixth , eighth and ninth

2. In the polishing pad auxiliary plate according to any one of the above aspects, the engagin g projection provided on one of the lower auxiliary plate and the upper auxiliary plate is arran ged between the lower auxiliary plate and the upper auxiliary plate. It is made of the same m aterial as the one. In the polishing pad auxiliary plate of this aspect, it is possible to prevent the support characteristics of the polishing pad of the auxiliary plates superimposed one on to p of the other from greatly differing locally at the portions where the engaging projections are formed

.

. Therefore, when a pressing force acts on the surface of the polishing pad during pad polishin g, the pressure reaction force and the elasticity of the polishing pad are reduced at the format ion portions of the engaging convex portions and the engaging concave portions of the upper and lower auxiliary plates that support the polishing pad. It is possible to reduce or avoid defe cts such as polishing accuracy caused by local differences in such characteristics. Further, ac cording to the present invention, the auxiliary plate for a polishing pad according to any one o f the first to tenth aspects of the present invention is mounted on the upper surface of a rotati ng platen, and is attached to the outer peripheral side of the rotating platen

. A polishing apparatus in which a protective member is arranged with a gap in between, and the positioning means is provided on the inner peripheral side of the outer peripheral end surf aces of the rotating platen and the polishing pad auxiliary plate, Characterized by EFFECTS OF THE INVENTION By adopting the polishing pad auxiliary plate structured according to the pre sent invention or using the polishing apparatus structured according to the present invention, the polishing pad can be prevented from being damaged and polished. can be easily removed from and attached to the rotating surface plate, and positioning of the polishing pad on the ro tating surface plate can be performed easily and accurately. [Brief Description of the Drawings]

FIG. 1 is a vertical cross-sectional view showing the essential parts of a polishing apparatus e quipped with a polishing pad auxiliary plate according to a first embodiment of the present inv ention;

2 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 1; FIG.

FIG. 3 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a second embodiment of the present inventio n;

4 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 3; FIG.

FIG. 5 is a vertical cross-sectional view showing the essential parts of a polishing apparatus e quipped with a polishing pad auxiliary plate according to a third embodiment of the present in vention;

6 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 5; FIG.

FIG. 7 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a fourth embodiment of the present inventio n;

8 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 7; FIG.

FIG. 9 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a fifth embodiment of the present invention;

10 is a side view of a lower auxiliary plate that constitutes the polishing pad auxiliary plate sh own in FIG. 9; FIG.

11 is a plan view of the lower auxiliary plate shown in FIG. 10; FIG.

FIG. 12 is a longitudinal sectional view showing the essential parts of a polishing apparatus eq uipped with a polishing pad auxiliary plate according to a sixth embodiment of the present inv ention;

FIG. 13 is a vertical cross-sectional view showing the essential parts of a polishing apparatus equipped with a polishing pad auxiliary plate according to a seventh embodiment of the prese nt invention;

FIG. 14 is a vertical cross-sectional view showing a main part of a polishing apparatus equipp ed with a polishing pad auxiliary plate according to an eighth embodiment of the present inve ntion;

FIG. 15 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a ninth embodiment of the present invention is removed;
FIG. 16 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate is removed according to a tenth embodiment of the present invention;
FIG. 17 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to an eleventh embodiment of the present invention is removed;
FIG. 18 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a twelfth embodiment of the present invention is removed;
FIG. 19 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a thirteenth embodiment of the present invention is removed;
FIG. 20 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a fourteenth embodiment of the present invention is positione d;
FIG. 21 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a fifteenth embodiment of the present invention is positioned;
FIG. 22 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a sixteenth embodiment of the present invention is removed;
DETAILED DESCRIPTION OF THE INVENTION Embodiments of the present invention will be de scribed
below

with reference to the drawings. First, FIGS. 1 and 2 show a polishing pad auxiliary plate 10 a s a first embodiment of the present invention. This polishing pad auxiliary plate 10 is used by being attached to a rotary surface plate 14 of a polishing apparatus 12, and a polishing pad 1 6 is detachably attached to the rotary surface plate 14. As shown in FIG.
The polishing apparatus is used ,

for example, as a CMP apparatus as described in Japanese Patent Application Laid-Open No. 2010-141155, for example. A rotating shaft extending vertically is rotatably supported by the main body of the apparatus fixedly installed above, and a disk-shaped rotating platen 14 is fix ed to the upper end of the rotating shaft. The rotating surface plate 14 has a flat upper surfac e 18 extending horizontally, and the upper surface 18 serves as a support surface for the polis hing pad 16 . The rotating shaft is connected to the rotating output shaft of an electric motor, and the driving force of the electric motor is transmitted so that the rotating shaft and thus th e rotating surface plate 14 are rotated about the central axis. there is A nozzle for supplying p olishing slurry is arranged above the upper surface 18 supporting the polishing pad 16, and a wafer or the like to be polished (an object to be polished) is held and rotated while being mov ed to the polishing pad 16. A polishing head is provided for polishing by pressing. In such a polishing apparatus, the polishing pad auxiliary plate 10 mounted on the rotating platen 14
is

includes a lower auxiliary plate 20 and an upper auxiliary plate 22 . A lower auxiliary plate 20 is fixed to the upper surface 18 of the rotating platen 14 by first fixing means 24 , and an upp er auxiliary plate 22 is attached to the upper surface of the lower auxiliary plate 20 . It is fixe d by two fixing means 26 . That is, the lower auxiliary plate 20 and the upper auxiliary plate 2 2 are overlapped and fixed to each other via the second fixing means 26, thereby forming the polishing pad auxiliary plate 10 having a two-layer structure as a whole. , and is attached to t he upper surface 18 of the rotating surface plate 14 by the first fixing means 24 .

Each of the lower auxiliary plate 20 and the upper

auxiliary plate 22 has a thin, substantially circular flat plate shape, and has a flat front surfa ce (upper surface) and a rear surface (lower surface). These upper and lower auxiliary plates 22 and 20 are desirably made of a harder material than the polishing pad 16 to which it is att ached, or having a higher member rigidity than the polishing pad 16 . Although it depends on the method of use, as will be described later, the lower auxiliary plate 20 can be used without being repeatedly attached and detached after being attached to the rotary surface plate 14, w hile the upper auxiliary plate 22 can be attached and detached after being attached to the rot ary surface plate 14. is expected to be repeated, it is desirable that at least the upper auxiliar y plate 22 should have higher member rigidity than the polishing pad 16 .

[0046]

Of course, the upper auxiliary plate 22 supports the polishing pad 16 and provides the stren gth, rigidity, and rigidity required for various treatments such as polishing, cleaning, and re-gr ooving of the polishing pad surface, in addition to polishing by the polishing device 12 . Any m aterial that satisfies shape stability and accuracy may be used, and its material and thickness are not limited. In particular, not only the lower auxiliary plate 20 but also the upper auxiliary plate 22 alone bears the supporting strength and rigidity of the polishing pad 16. Since the lo wer surface is supported by the rotating surface plate 14 by being superimposed on each othe r and used, the strength and rigidity of the single unit are not required so much. Therefore, in addition to metals such as stainless steel, synthetic resins, fiber-reinforced resins, and the like can be employed as materials for forming the lower auxiliary plate 20 and the upper auxiliary plate 22 . In particular, synthetic resin materials are lighter than metal materials and easier to process and handle. . In order to obtain a stable supporting force over the entire polishing p ad 16, it is desirable to set the outer diameter dimension of the upper auxiliary plate 22 to be equal to or larger than the outer diameter dimension of the polishing pad 16,

and

It is desirable to set the outer diameter of the lower auxiliary plate 20 to be equal to or larger than the outer diameter of the upper auxiliary plate 22, and set the outer diameter of the low er auxiliary plate 20 to be equal to or smaller than the outer diameter of the rotating surface plate 12. should be set to In particular, as shown in FIGS. 1 and 2, the outer diameters of the lower auxiliary plate 20 and the upper auxiliary plate 22 are made substantially the same, and the outer diameter of the rotating surface plate 14 to be mounted is also substantially the sa

me. By doing so, it becomes possible to ensure a sufficiently large support area for the polishi ng pad 16 . As a result, the polishing pad 16 having approximately the same size as the rotati ng surface plate 14 can be attached to the rotating surface plate 14 with approximately the sa me supporting force over the entirety thereof.

[0048]

Furthermore, as the first fixing means 24 and the second fixing means 26, the lower auxiliar y plate 20 and the upper auxiliary plate 22 are fixed to the upper surface 18 of the rotating pl aten 14 against the external force exerted during polishing. It is not particularly limited as lon g as it can be held at. Specifically, an adhesive, a pressure-sensitive adhesive, or a double-sid ed tape having an adhesive or a pressure-sensitive adhesive attached to both sides of a base sheet may be employed as the first and second fixing means 24, 26. In addition, negative pre ssure suction using negative pressure air or the like, or magnetic suction using a permanent magnet or an electromagnet can be employed. In addition, it is desirable that the fixing mean s made of adhesive or the like apply substantially uniform fixing force over substantially the e ntire surface of the flat overlapping surfaces of the lower auxiliary plate 20 and the upper auxi liary plate 22. Adhesive strength can be obtained, and problems such as locally different supp ort characteristics of the polishing pad 16 on the surface of the polishing pad auxiliary plate 1 0 can be avoided.

For example ,

the fixing force can be turned ON/OFF by negative pressure suction or an electromagnet. au xiliary

It is desirable to set the fixing force of the upper auxiliary plate 22 to the lower auxiliary plate 20 by the second fixing means 26 to be smaller than the fixing force of the plate 20 . As a res ult, when the upper auxiliary plate 22 is peeled off from the lower auxiliary plate 20 and remo ved, the lower auxiliary plate 20 can be easily left fixed on the rotating surface plate 14.例文帳 に追加 The specific realization of such a difference in adhesion force is achieved by differentiati ng the adhesion means itself such as the material of the adhesive and pressure-sensitive adh esive, as well as the adhesion area and the condition of the adhesion surface (surface roughn ess, presence or absence of plasma treatment, etc.) can also be realized by making the .

Further, the surface (upper surface) of the upper auxiliary plate 22 serves as a

polishing pad supporting surface, and the polishing pad 16 is superimposed and mounted th ereon. As such a polishing pad 16, conventionally known various types of polishing pads can b e employed. The back surface of the polishing pad 16 is fixed to the surface of the upper auxil iary plate 22 using a conventionally known adhesive tape or suitable adhesive for attaching th e polishing pad.

It is desirable that the fixing means for fixing

the polishing pad 16 to the upper auxiliary plate 22 has a larger fixing force than the second fixing means 26 described above. As a result, when the upper auxiliary plate 22 is removed fr om the lower auxiliary plate 20 with the polishing pad 16 still fixed, the polishing pad 16 does

not move from the upper auxiliary plate 22 even if the upper auxiliary plate 22 is bent or the l ike. It is possible to effectively prevent the peeling off. The outer diameter of the polishing p ad 16 is generally a standard value, but in many cases it is set equal to or smaller than the ou ter diameter of the upper surface 18 of the rotating surface plate 14 to which it is attached . [0053]

Further, for example, at least one of between the upper surface 18 of the rotating surface pl ate 14 and the lower auxiliary plate 20, between the lower auxiliary plate 20 and the upper au xiliary plate 22, and between the upper auxiliary plate 22 and the polishing pad 16 A suitable cushioning layer may be provided. By providing such a cushion layer, it becomes possible to a chieve uniform polishing efficiency over the entire surface of the workpiece when polishing wit h the polishing pad 16 .

[0054]

As such a cushion layer, for example, a resin sheet, an elastomer sheet, a rubber sheet, or t he like to which a certain degree of compressibility is imparted by foaming can be suitably em ployed. A cushion layer can also be configured by the first fixing means 24 , the second fixing means 26 , and the means for fixing the polishing pad 16 to the upper auxiliary plate 22 . In o rder to prevent local distortion on the support surface of the polishing pad 16, the cushion lay er is formed so as to have a size and a constant thickness over substantially the entire suppor t area of the polishing pad 16. is desirable. Positioning means 28 are provided between the l ower auxiliary plate 20 and the upper auxiliary plate 22 that constitute the polishing pad auxil iary plate 10 to align the centers of the plates with each other

.

In the present embodiment, a circular stepped surface 30 is formed on the outer peripheral p ortion of the lower auxiliary plate 20 and extends around the central axis of the lower auxiliar y plate 20 over the entire circumference. By reducing the thickness of the lower auxiliary plat e 20 on the outer peripheral side of the stepped surface 30, the notch cross-sectional shape t hat opens to the outer peripheral surface of the lower auxiliary plate 20 continues to the entir e circumference in the circumferential direction. An annular engaging recess 32 that extends i nward is formed integrally with the lower auxiliary plate 20 so as to protrude therefrom.

[0056]

On the other hand, in the present embodiment, a circular stepped surface 34 is formed on th e outer peripheral portion of the upper auxiliary plate 22 so as to extend around the central a xis of the upper auxiliary plate 22 over the entire circumference. Since the thickness of the up per auxiliary plate 22 is increased on the outer peripheral side of the stepped surface 34, an a nnular engagement continuously extends along the outer peripheral edge of the upper auxiliar y plate 22 along the entire circumference in the circumferential direction. A mating projection 36 is integrally formed so as to protrude from the upper auxiliary plate 22 . Incidentally, the e

ngaging convex portion 36 and the engaging concave portion 32 may be formed on either of t he upper and lower auxiliary plates 22 and 20 .

The stepped surface 30 and the engaging recess 32 of the lower auxiliary plate 20 are aligne d with the stepped surface 34 and the engaging projection 36 of the upper auxiliary plate 22 . It constitutes an engagement outer peripheral surface and an engagement inner peripheral su rface. When the upper auxiliary plate 22 is superimposed on the lower auxiliary plate 20, the engaging convex portion 36 is fitted into the engaging concave portion 32, and the stepped su rface 34 is superimposed on the stepped surface 30 in the radial direction. is formed. As a res ult, the engaging concave portion 32 and the engaging convex portion 36 constitute the positi oning means 28, and the lower auxiliary plate 20 and the upper side support plate 20 are alig ned in the radial direction with their central axes aligned with each other. Auxiliary plates 22 a re superimposed. In addition, the positioning means 28 is positioned on the inner peripheral si de of the outer peripheral surfaces of the upper and lower auxiliary plates 22 and 20, thereby preventing the upper and lower auxiliary plates 22 and 20 and the polishing apparatus 12 fro m becoming large. . In the polishing apparatus 12 provided with the polishing pad auxiliary plate 10 having such a structure, the upper and lower auxiliary plates 22 are mounted on the upper surface 18 of the rotating platen 14 as shown in FIG

.

, 20 is fixedly attached, and the polishing pad 16 is fixedly supported on the upper surface of the upper auxiliary plate 22. Then, the rotating platen 14 is driven to rotate, and the substrat e or the like is processed. CMP (Chemical Mechanical Polishing) is applied to objects. The polis hing apparatus 12 can exhibit the following special technical effects by being provided with th e polishing pad auxiliary plate 10 having a specific structure.

[0059]

First, as shown in FIG. 2, while the polishing pad 16 is fixed to the upper surface of the uppe r auxiliary plate 22, the upper auxiliary plate 22 is fixed to the rotating surface plate 14 by th e first fixing means 24. By removing the side auxiliary plate 20, the polishing pad 16 can be r emoved from the rotating surface plate 14. - 特許庁 Even when the surface (polishing surface) of the polishing pad 16 is removed from the rotating platen 14 and cleaned or reprocessed, th e polishing pad 16 can be kept fixed to the upper surface of the upper auxiliary plate 22 . As a result, the upper auxiliary plate 22 provides reinforcement not only when the polishing pad 16 is attached to and detached from the rotating surface plate 14, when the polishing pad 16 is c leaned and reprocessed, but also when the polishing pad 16 is transported or stored. By this a ction, the polishing pad 16 can be prevented from being bent or damaged, and the polishing p ad 16 can be kept in good condition.

Further

, even when the polishing pad 16 is removed from the rotating surface plate 14 together wit h the upper auxiliary plate 22 , the lower auxiliary plate 20 remains on the upper surface 18 o

f the rotating surface plate 14 . When the polishing pad 16 is again mounted on the rotating p laten 14, the positioning means 28 provided between the upper auxiliary plate 22 and the low er auxiliary plate 20 moves the upper auxiliary plate 22 and thus the polishing pad 16 to the l ower auxiliary plate. The center axis of the plate 20 and thus the rotating platen 14 can be ali gned with high accuracy and easily.

[0061]

Here, since the engaging concave portion 32 and the engaging convex portion 36 constitutin g the positioning means 28 are overlapped with almost no gap in a mutually fitted state, the s upport characteristics of the polishing pad 16 are improved. can be prevented from adversely affecting Of the outer peripheral portions of the upper and lower auxiliary plates 22 and 20, p articularly in the present embodiment, an engaging portion, in other words, a positioning mea ns 28, is formed on the outer peripheral edge portion, and the diameter of the polishing pad 1 6 that serves as the main region for polishing is formed. Since it is out of the middle part in th e direction, even if there is a slight gap between the engaging concave portion 32 and the eng aging convex portion 36, the supporting characteristics of the polishing pad 16 are such that a serious problem occurs in the polishing characteristics. can be avoided. Moreover, the engagi ng concave portion 32 and the engaging convex portion 36 constituting the positioning means 28 are formed on the superimposed surfaces of the upper and lower auxiliary plates 22 and 2 0, in other words, on the outer circumferences of the rotating surface plate 14 and the polishi ng pad auxiliary plate 10

.

Since it is formed on the inner peripheral side of the end face, the upper and lower auxiliary pl ates 22 and 20 can be prevented from projecting onto the outer peripheral surface. Therefore, as shown in FIGS. 1 and 2, for example, even when the protective member 38 is installed clos e to the outer peripheral side of the rotating surface plate 14 in the polishing apparatus 12, th e protective member 38 cannot be protected. Polishing provided with upper and lower auxiliar y plates 22, 20 provided with positioning means 28 while avoiding interference

A device 12 is made possible. Furthermore, as described above, while preventing damage to the polishing pad 16, the polishing pad 16 can be quickly attached to and detached from the r otating platen 14 with accurate positioning accuracy

.

The operating time of the expensive polishing equipment is not unnecessarily limited for such work, and the operating efficiency of the polishing equipment can be improved, and thus the production efficiency of substrates and the like (polishing work efficiency) can be improved. In addition, since the polishing pad 16 can be easily attached to and detached from the rotati ng surface

plate 14, the reuse of the polishing pad 16 can be realized on a practical level without specia l skill or knowledge. That is, for example, the polishing pad 16 once removed from the rotatin g platen 14 can be reused when changing the type of the object to be polished such as a subs

trate, or the polishing pad 16 can be re-processed by another processing device such as surfa ce grooving as a countermeasure against deterioration. It is also possible to consider reusing t he polishing pad 16 once removed from the rotating surface plate 14 after reprocessing at a p ractical level. Although the first embodiment of the present invention has been described ab ove, the specific structure of the present invention should not be construed as limited by the fi rst embodiment

.

A plurality of other embodiments of the present invention having different positioning means between the upper and lower auxiliary plates 22 and 20 are illustrated below, but these embo diments are not intended to limit the configuration of the present invention. In the following e mbodiments, members and parts having the same structure as in the first embodiment are de noted by the same reference numerals as those in the first embodiment in the corresponding parts in each figure. , their detailed description is omitted. 3 and 4 show a polishing apparat us 42 provided with a polishing pad auxiliary plate 40 as a second embodiment of the present invention

.

In this polishing pad auxiliary plate 40, an engaging recess 44 is formed by an annular groov e continuously extending in the circumferential direction on the outer peripheral portion of the upper surface of the lower auxiliary plate 20. As shown in FIG . On the other hand, on the out er peripheral portion of the lower surface of the upper auxiliary plate 22, an engagement conv ex portion 46 is formed by an annular protrusion extending continuously in the circumferential direction. The engaging projection 46 may be formed integrally with the upper auxiliary plate 22, or may be formed separately as illustrated. That is, in this embodiment, an annular circu mferential groove 48 that opens in the lower surface of the upper auxiliary plate 22 and exten ds in the circumferential direction is formed. block is fitted and fixed at one end in the axial di rection to form an engagement convex portion 46 . The engaging concave portion 44 of the l ower auxiliary plate 20 and the engaging convex portion 46 of the upper auxiliary plate 22 are both formed at corresponding radial positions around the central axis

.

are overlapped, the engagement projections 46 are fitted into the engagement recesses 44, t hereby aligning the upper and lower auxiliary plates 22 and 20 with each other in the radial di rection. In the present embodiment, two side walls of the engaging recess 44 of the lower aux iliary plate 20 and the inner and outer peripheral surfaces of the engaging protrusion 46 of th e upper auxiliary plate 20 are superimposed on each other in the corresponding radial directio n. A pair of inner and outer engagement surfaces are provided. 5 and 6 show a polishing ap paratus 52 provided with a polishing pad auxiliary plate 50 as a third embodiment of the pres ent invention

. [0070]

In this polishing pad auxiliary plate 50, the lower auxiliary plate 20 has a stepped surface 54 as a circular engagement inner peripheral surface extending all around the central axis on the outer peripheral portion thereof. By increasing the thickness of the lower auxiliary plate 20 on the outer peripheral side of the stepped surface 54, an annular shape continuously extends al ong the outer peripheral edge of the lower auxiliary plate 20 along the entire circumference in the circumferential direction. The engaging convex portion 56 of
It is formed integrally with the side auxiliary plate 20 . On the other hand, on the outer perip heral portion of the upper auxiliary plate 22, there is formed a stepped surface 58 as a circula r engagement outer peripheral surface extending all around the central axis
.
Since the thickness of the upper auxiliary plate 22 is reduced on the outer peripheral side of t he step surface 58, the upper auxiliary plate 22 has a notched cross-sectional shape that ope ns to the outer peripheral surface and extends continuously along the entire circumference in the circumferential direction. An annular engaging recess 60 is formed integrally with the upp er auxiliary plate 22 .
Further, the step surface 54 of the lower auxiliary plate 20 is formed with
female threads, while the step surface 58 of the upper auxiliary plate 22 is formed with male threads. Then, the female thread of the stepped surface 54 of the lower auxiliary plate 20 is s crewed with the male thread of the stepped surface 58 of the upper auxiliary plate 22 so that the stepped surface 54 of the lower auxiliary plate 20 and the stepped surface 58 of the upper auxiliary plate 22 are screwed together. are superimposed on each other in the radial directio n, the upper auxiliary plate 22 is superimposed on the upper surface of the lower auxiliary pla te 20 . Further, in such a superimposed state, the screwing structure of the stepped surfaces 58, 54 of the upper and lower auxiliary plates 22, 20 constitutes a second fixing means 62 for detachably fixing the upper and lower auxiliary plates 22, 20. . The direction of the male and female threads in such a threaded structure is set in consideration of the rotational reaction fo rce exerted on the rotating surface plate 14 of the polishing device 12 during polishing so that the screws do not loosen
.
It is desirable that
FIGS.
7 and 8 show a polishing apparatus 66 having a polishing pad auxiliary plate 64 as a fourth embodiment of the present invention.
[0075]
In this polishing pad auxiliary plate 64 , a cylindrical engaging convex portion 68 projecting upward is formed at the central portion of the upper surface of the lower auxiliary plate 20 . T

he engaging projection 68 may be formed integrally with the lower auxiliary plate 20, or may be formed separately as shown in the drawing. That is, in this embodiment, a circular fitting r ecess 70 is formed on the central axis of the lower auxiliary plate 20, and a cylindrical block f ormed separately from the fitting recess 70 is provided. An engaging convex portion 68 is for med by being fitted and fixed at one end in the axial direction. On the other hand, in the centr al portion of the lower surface of the upper auxiliary plate 22, there is formed a bottomed circ ular engaging recess 72 that opens to the lower surface on the central axis. Incidentally, the e ngaging convex portion 68 and the engaging concave portion 72 may be formed on either of t he upper and lower auxiliary plates 22 and 20. As shown in FIG. When the upper and lower auxiliary plates 22 and 20 are superimposed, the engaging convex portion 68 is fitted into the engaging concave portion 72, thereby aligning the upper and lower auxiliary plates 22 and 20 with each other in the radial direction

.

It is designed to be In this embodiment, the engagement outer peripheral surface and the eng agement inner peripheral surface are formed by the outer peripheral surface of the engaging protrusion 68 of the lower auxiliary plate 20 and the inner peripheral surface of the engaging recess 72 of the upper auxiliary plate 22. It is configured.

FIG.

9 shows a polishing apparatus 76 provided with a polishing pad auxiliary plate 74 as a fifth e mbodiment of the present invention.

[0078]

In this polishing pad auxiliary plate 74 , a cylindrical engaging convex portion 78 projecting upward is formed on the outer peripheral portion of the upper surface of the lower auxiliary pl ate 20 . This engaging projection 78 may be formed integrally with the lower auxiliary plate 2 0, or may form a fitting recess in the lower auxiliary plate 20 like the engaging projection in t he fourth embodiment. Alternatively, a separate pin or the like may be fixed by press-fitting o r the like. Also, as shown in FIGS. 10 and 11, a plurality of such engaging projections 78 are f ormed independently of each other at the outer peripheral portion of the lower auxiliary plate 20 at predetermined intervals in the circumferential direction. Particularly preferably, the plura lity of engaging protrusions 78 are formed at regular intervals in the circumferential direction and positioned on the same circle on the central axis.

On the other hand, on the outer peripheral portion of the lower surface of the upper auxiliar y plate 22, bottomed circular engagement grooves are provided at positions corresponding to the formation positions of the plurality of engaging projections 78 on the lower auxiliary plate 20, respectively . A concave portion 80 is formed to open downward. Incidentally, the engagin g convex portion 78 and the engaging concave portion 80 may be formed on either of the upp er and lower auxiliary plates 22 and 20. As shown in FIG. When the upper and lower auxiliar y plates 22 and 20 are superimposed, the engaging convex portions 78 are fitted into the eng

aging concave portions 80, respectively, so that the upper and lower auxiliary plates 22 and 20 are positioned radially relative to each other

.

are designed to be matched. In the present embodiment, the outer circumferences of the lower auxiliary plate 20 and the upper auxiliary plate 22 are formed by the outer circumference of the engagement projection 78 of the lower auxiliary plate 20 and the inner circumference of the engagement recess 80 of the upper auxiliary plate 22 . An engaging outer peripheral surface and an engaging inner peripheral surface located in a portion are configured. In particular, as in this embodiment, by adopting positioning means consisting of a plurality of engaging projections 78 and engaging recesses 80 independent in the circumferential direction, the superimposed upper and lower auxiliary plates 22, 20 can be diametrically aligned

.

Mutual positioning is possible not only in the direction but also in the circumferential direction. Instead of the plurality of independent engaging recesses 80 formed in the upper auxiliary plate 22 ,

a circumferential groove continuously extending circularly in the circumferential direction around the central axis of the upper auxiliary plate 22 may be employed. Alternatively, as shown in the sixth embodiment of the present invention in FIG. 12, a circular stepped surface 82 is formed around the central axis of the outer peripheral portion of the upper auxiliary plate 22 and extends over the entire circumference. By making the thickness dimension of the outer peripheral side smaller than 82, it is also possible to form an annular engagement concave portion 83 that has a notched cross-sectional shape that opens to the outer peripheral surface of the upper auxiliary plate 22 and that extends continuously all around in the circumferential direction. It is possible.

[0083]

In this way, in the upper auxiliary plate 22, the engaging surfaces of the engaging projections 78 of the lower auxiliary plate 20 are formed continuously over the entire circumference, so that when the upper and lower auxiliary plates 20 and 22 are superimposed, the upper and lower auxiliary plates 20 and 22 can be overlapped. Since it is no longer necessary to align the auxiliary plates 20 and 22 with each other in the circumferential direction, the mounting work can be easily performed.

FIG.

13 shows a polishing pad auxiliary plate 84 as a seventh embodiment of the present invention.

In this polishing pad auxiliary plate 84, the upper portion of the outer peripheral surface of the lower auxiliary plate 20 and the lower portion of the outer peripheral surface of the upper

auxiliary plate 22 are each provided with a small diameter portion. By superimposing the upper and lower auxiliary plates 22 and 20, the small diameter portions of the upper and lower auxiliary plates 22 and 20 form an annular ring that extends across the entire circumference i

n the circumferential direction by widening a predetermined width across the upper and lower auxiliary plates 22 and 20. A shaped receiving recess 86 is formed. A groove-shaped engagi ng recess 88 is formed at the lower end of the small diameter portion of the lower auxiliary pl ate 20

.

The engagement recess 88 opens to the outer peripheral surface of the lower auxiliary plate 2 0 at the bottom surface of the accommodation recess 86 . Here, the bottom surface of the acc ommodation recess 86 refers to an annular surface extending over the upper and lower auxili ary plates 22 and 20 and extending in the vertical direction in FIG. On the other hand, a plate -shaped engaging projection 90 made of an elastic material is attached to the small-diameter portion of the upper auxiliary plate 22 that constitutes the accommodation recess 86 so that it s proximal end is fixed by a fixing pin 92 . The engaging protrusions 90 are accommodated in accommodation recesses 86 formed on the outer peripheral surfaces of the upper and lower a uxiliary plates 22 , 20 and extend from the upper auxiliary plate 22 onto the outer peripheral surface of the lower auxiliary plate 20 . there is An engaging claw portion 94 formed at the tip portion of the engaging projection portion 90 is engaged with an engaging recess portion 88 f ormed in the small diameter portion of the lower auxiliary plate 20, and the engaging projecti on portion 90 is locked. It is held in a locked state based on elasticity.

Furthermore, a plurality of such engaging projections 90 are provided on the outer periphera l surfaces of the upper and lower auxiliary plates 22 and 20 at predetermined intervals in the circumferential direction . And attached to the outer peripheral surface of the upper auxiliary plate 22

Each of the engaging projections 90 is elastically pressed against the outer peripheral surface of the lower auxiliary plate 20, thereby forming positioning means for positioning the upper a nd lower auxiliary plates 22, 20 relative to each other on the central axis. Further, by engagin g the engaging claw portion 94 of the engaging convex portion 90 with the engaging concave portion 88, a fixing means is also configured to hold the upper and lower auxiliary plates 22 a nd 20 in a superimposed state and apply a fixing force. there is Instead of the engaging prot rusions 90 having the engaging claws 94 that engage with the engaging recesses 88 as descri bed above, for example, an eighth embodiment of the present invention shown in FIG

.

In addition, a connecting plate 100 extending across the upper and lower auxiliary plates 22 a nd 20 and superimposed on the bottom surface of the housing recess 86 is adopted, and both ends of the connecting plate 100 are connected to one of the upper and lower auxiliary plates 22 and 20. It is also possible to fix to the outer peripheral surface of the by connecting pins 1 02 , 102 . At least one of the connecting pins 102, 102 is detachable from the lower auxiliary plate 20 or the upper auxiliary plate 22, so that the connection of the upper and lower auxiliar y plates 22, 20 by the connecting plate 100 can be released. , the attachment and detachmen

t of the upper auxiliary plate 22 to which the polishing pad 16 is fixed with respect to the lowe r auxiliary plate 20 is permitted. The first fixing means 24 and the second fixing means 26 m ade of double-faced tape or the like shown in the first to eighth embodiments are used when r emoving the upper and lower auxiliary plates 22 and 20 and the rotating surface plate 14

.

In addition, it is desirable to be held on the fixing surface on the side of a specific member. Th is facilitates handling of the upper and lower auxiliary plates 22, 20 and the first and second fi xing means 24, 26 in a detached state. In addition, the fixing surfaces on which the first and second fixing means 24 and 26 remain are determined by making the fixing force of both surf aces of the first fixing means and the second fixing means 24 and 26 themselves different fro m each other. It is possible to set by differentiating the surface roughness, material, etc. of th e fixed upper and lower auxiliary plates 22 and 20 and the rotating platen 14 from each other. In particular, it

is desirable that the first fixing means 24 is held on the fixing surface on the side of the lowe r auxiliary plate 20 when the lower auxiliary plate 20 is removed. becomes easier. On the othe r hand, as shown in FIG. 2 in the first embodiment, the second fixing means 26 is held on the fixing surface on the side of the upper auxiliary plate 22 when the upper auxiliary plate 22 is r emoved. Alternatively, it may remain on the upper surface of the lower auxiliary plate 20 as in the ninth embodiment of the present invention shown in FIG. By holding the second fixing me ans 26 on the fixing surface on the side of the upper auxiliary plate 22, the removed upper au xiliary plate 22 can be attached to the rotating surface plate of the device for reprocessing suc h as grooving of the polishing pad 16. At the time of mounting, it is also possible to use the se cond fixing means 26 held by the upper auxiliary plate 22 for mounting. On the other hand, b y holding the second fixing means 26 on the fixing surface of the lower auxiliary plate 20, whe n mounting another upper auxiliary plate 22 with another polishing pad 16 mounted thereon t o the lower auxiliary plate 20, It is also possible to attach using the second fixing means 26 h eld by the lower auxiliary plate 20 .

Further, the engaging recesses 32, 44, 60, 72, 80, (83), 88 and the engaging projections 36, 46, 56,

70, 78, 90 shown in the first to seventh embodiments may be provided on opposite sides of the lower auxiliary plate 20 side and the upper auxiliary plate 22 side. For example, as the te nth embodiment of the present invention is shown in FIG. The stepped surface 30 and the eng aging recess 32 may be formed on the upper auxiliary plate 22 , while the stepped surface 34 and the engaging convex portion 36 forming the inner peripheral surface of the engagement may be formed on the lower auxiliary plate 20 . It is possible.

[0092]

Furthermore, the engaging recesses 32, 44, 60, 72, 80, (83) and the engaging protrusions 3 6, 46, 56, 70, 78 shown in the first to sixth embodiments are overlapped with each other. It is also possible to form an inclination angle with respect to the outer peripheral surface of the en

gaging projection and the inner peripheral surface of the engaging recess for positioning the u pper and lower auxiliary plates 22 and 20 by using the upper and lower auxiliary plates 22 an d 20 as shown in FIG. For example, as an eleventh embodiment of the present invention is sh own in FIG. On the other hand, while the engaging convex portion 36 is tapered in the incline d direction in which it gradually tapers in the projecting direction,

A stepped surface 30 serving as an engaging outer peripheral surface of an engaging recess 3 2 formed in the outer peripheral portion of the upper auxiliary plate 22 can be tapered at an i nclination direction and an inclination angle corresponding to the stepped surface 34 . As a re sult, the operation of fitting the engaging convex portion 36 into the engaging concave portio n 32 and overlapping the upper and lower auxiliary plates 22, 20 can be further facilitated by using the tapers provided on both the stepped surfaces 34, 30 as guide surfaces. It becomes possible to do it easily. Incidentally, as shown in the twelfth embodiment of the invention sh own in FIG. 18 and the thirteenth embodiment of the invention shown in FIG

.

Even when adopting a plurality of projection-shaped engaging projections 78 formed independ ently in the direction and a plurality of hole-shaped engaging recesses 80 formed at respectiv e corresponding positions of the upper auxiliary plate 22, the engagement A tapered portion 1 04 having a tapered shape can be formed by giving an inclination angle to the outer periphera l surface of the projecting tip portion of the convex portion 78 . In FIG. 19, an engagement pi n 106 formed separately is press-fitted into a fitting hole 105 formed in the lower auxiliary pla te 20 to form the engagement convex portion 78. The lower end of the locking pin 106 also h as a tapered portion 104 similar to the upper end. As a result, the locking pin 106 has no dire ctivity and is easy to handle, and the operation of press-fitting it into the fitting hole 105 is als o facilitated.

[0094]

Further, in the fourteenth embodiment of the present invention shown in FIG. 20, a straddle between the upper and lower auxiliary plates 22, 20 is used as a kind of positioning means for aligning the central axis of the upper and lower auxiliary plates 22, 20 in a superimposed stat e. A locating sleeve 108 is thus shown fitted over. The positioning sleeve 108 has an inner dia meter that is the same as or slightly larger than the outer diameter of the upper and lower au xiliary plates 22 and 20, which are disk-shaped and have substantially the same outer diamet er. formed. Such a positioning sleeve 108 is used when superimposing the upper and lower au xiliary plates 22 and 20, and by superimposing the upper and lower auxiliary plates 22 and 20 within the positioning sleeve 108, the central axes of the upper and lower auxiliary plates 22 and 20 are aligned. They can be axially superimposed and secured to each other with a secon d securing means 26 . Therefore, the positioning sleeve 108 can be removed after the upper a nd lower auxiliary plates 22 and 20 are superimposed and fixed to each other, thereby positio ning the upper and lower auxiliary plates 22 and 20 so as to protrude on the outer peripheral surface. It is possible to attach them to each other without means and in precise alignment.

[0095]

Furthermore, in the fifteenth embodiment of the present invention shown in FIG. 21, a slit-shaped engagement groove 110 is formed extending across the overlapping direction when the upper and lower auxiliary plates 22 and 20 are overlapped. ing. The engaging grooves 110 are open to the outer peripheral surfaces of the upper and lower auxiliary plates 22 and 20 and have a predetermined depth radially inward. It is A plate-shaped engaging plate 112 is fitted into the engaging groove 110 from the opening of the outer peripheral surface, so that the upper and lower auxiliary plates 22 and 20 are positioned by the engaging plate 112 and is in a connected state. Although the engaging plate 112 is formed separately from the upper and lower auxiliary plates 22 and 20, it may be formed integrally with one of the upper and lower auxiliary plates 22 and 20 so as to protrude toward the other. . In that case, the engagement groove 110 is formed only in the other auxiliary plate.

Furthermore, in the sixteenth embodiment of the present invention shown in FIG. 22 ,

a fitting recess 114 is formed as an engaging recess opening in the lower surface of the upper auxiliary plate 22 . In particular, in this embodiment, the fitting recess 114 is formed as an annular groove extending continuously in the circumferential direction around the central axis of the upper auxiliary plate 22 . On the other hand, the lower auxiliary plate 20 has a fitting convex portion 116 as an engaging convex portion that protrudes upward on the upper surface that overlaps with the upper auxiliary plate 22 . In addition, in this embodiment, the fitting protrusion 116 is formed as an annular protrusion corresponding to the fitting recess 114 . When the upper and lower auxiliary plates 22 and 20 are superimposed, the fitting convex portion 116 is positioned so as to enter the fitting concave portion 114 .

[0097]

The fitting projection 116 has a hollow structure, and the inside of the fitting projection 116 is provided with an external space.

A fluid reservoir 118 is formed which is sealed between them. Further, at least the inner peripheral wall and the outer peripheral wall of the wall portion of the fitting convex portion 116 that defines the fluid reservoir 118 are bulged and deformable in the radial direction. Specifically, for example, by forming the fitting convex portion 116 with a rubber elastic material or the like, it is possible to realize an inner peripheral wall that can bulge radially inward and an outer peripheral wall that can bulge radially outward. be. Further, the lower auxiliary plate 22 is formed with a fluid passage 120 that communicates with the fluid reservoir 118 and extends radially outward and opens to the outer peripheral surface

.

A pressure screw 122 is screwed into the end opening. In addition, a sealed area composed of the fluid passage 120 and the fluid reservoir 118 sealed by the pressurizing screw 122 is filled with an incompressible fluid such as oil.

Thus

, by screwing the pressure screw 122, the internal pressure of the fluid reservoir 118 can be

increased through the fluid passage 120, and the inner and outer peripheral walls of the fluid reservoir 118 can be expanded outward. As a result, the fitting convex portion 116 is expande d and pressed against the inner surface of the fitting concave portion 114, so that the upper a nd lower auxiliary plates 22 and 20 can be positioned by mutual frictional force and the like, a nd can also exert a fixing force. there is

When removing the upper auxiliary plate 22 from the lower auxiliary plate 20 ,

the pressure screw 122 is rotated in the direction of loosening and moved to the outer perip heral side of the lower auxiliary plate 20, whereby the fluid reservoir 118 is removed. , the pr essing force of the fitting protrusion 116 against the fitting recess 114 can be released.

[0101]

In addition, although not listed individually, the present invention can be implemented with v arious changes, modifications, improvements, etc. based on the knowledge of those skilled in the art. It is also possible to attach an O-ring or a sealing material to the portion to prevent fo reign matter from entering the overlapping surfaces of the upper and lower auxiliary plates.

In addition to the auxiliary plates 20 and 22 having the two-layer structure described above, i t

is also possible to add additional auxiliary plates in a laminated state and fixed by fixing mea ns. By adopting the auxiliary plate of the third layer in this way, it becomes possible to realize an elastic support state or to dispose of the intermediate layer.

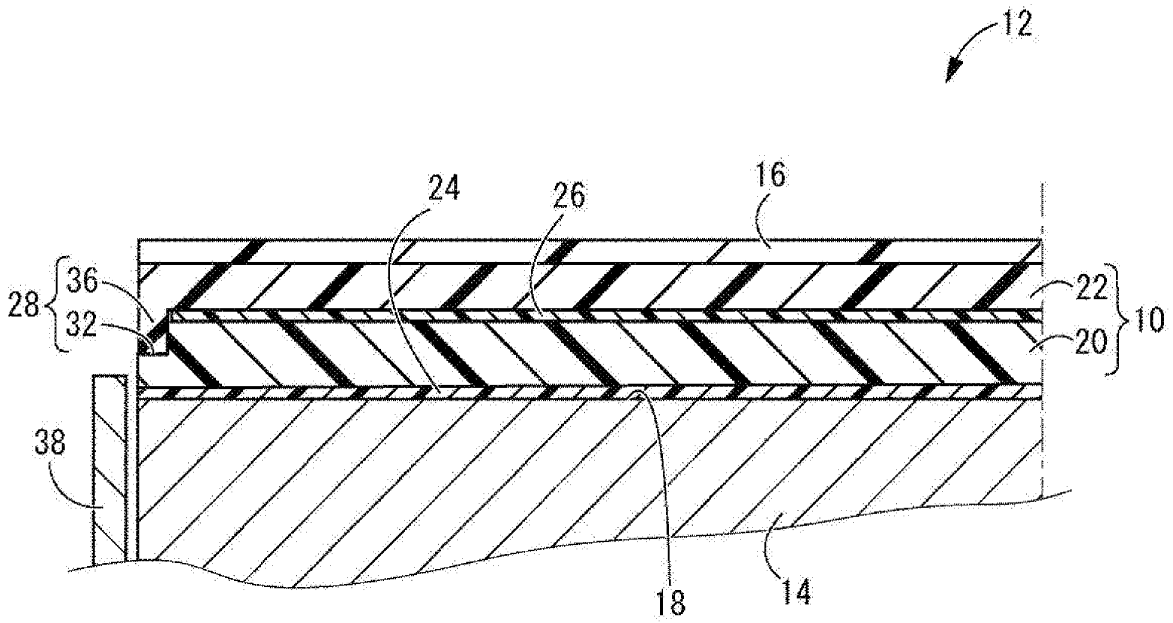
[Description of Reference Symbols]

10

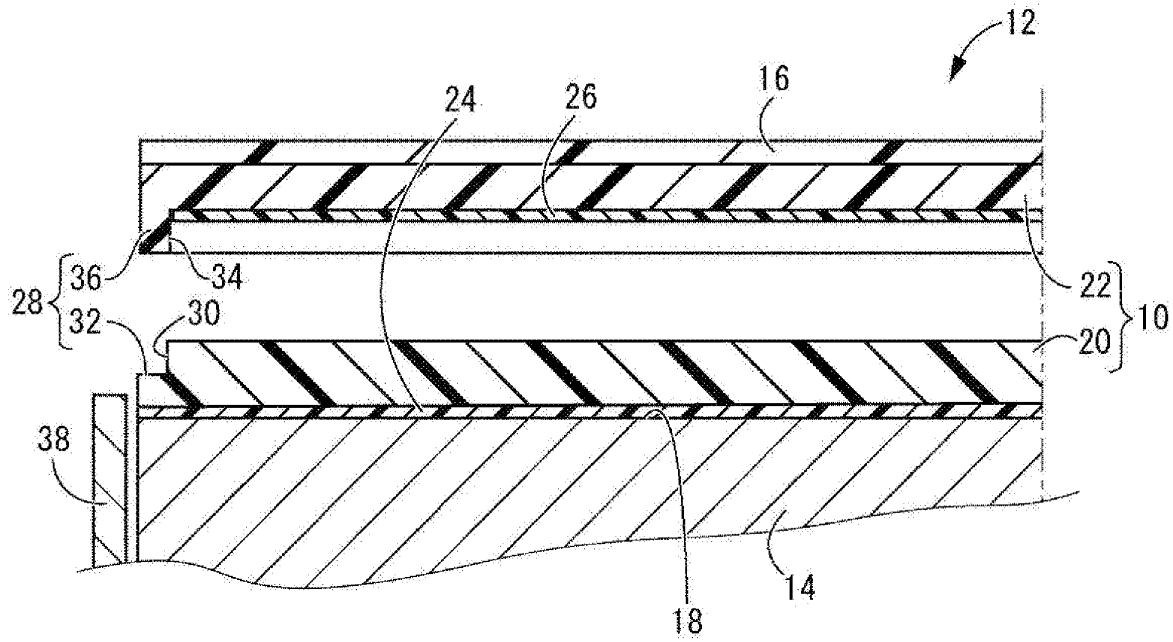
, 40, 50, 64, 74, 84: polishing pad auxiliary plate, 12, 42, 52, 66, 76: polishing device, 14: ro tating platen, 16: polishing pad, 18: upper surface, 20: lower auxiliary plate, 22: upper auxili ary plate, 24: first fixing means, 26, 62: second fixing means, 28: positioning means, 30, 58: step surface (engagement outer circumference surface), 32, 44, 60, 72, 80, 88: engagement concave portion, 34, 54: step surface (engagement inner peripheral surface), 36, 46, 56, 68, 78, 90: engagement convex portion, 38: Protective member

drawing open —

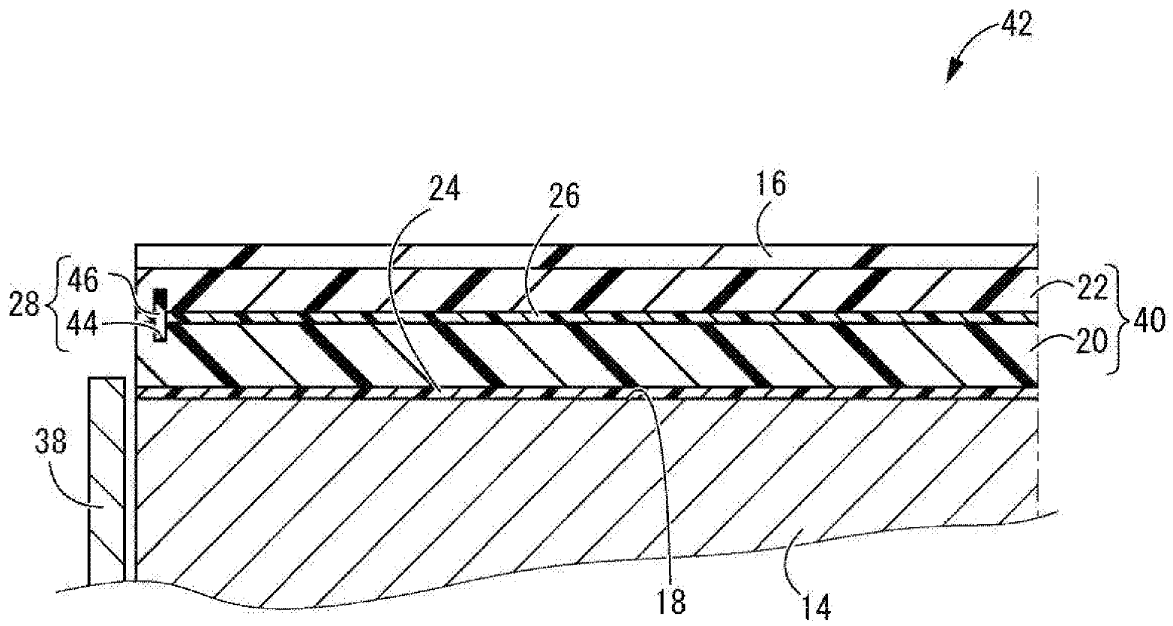
[Fig. 1]



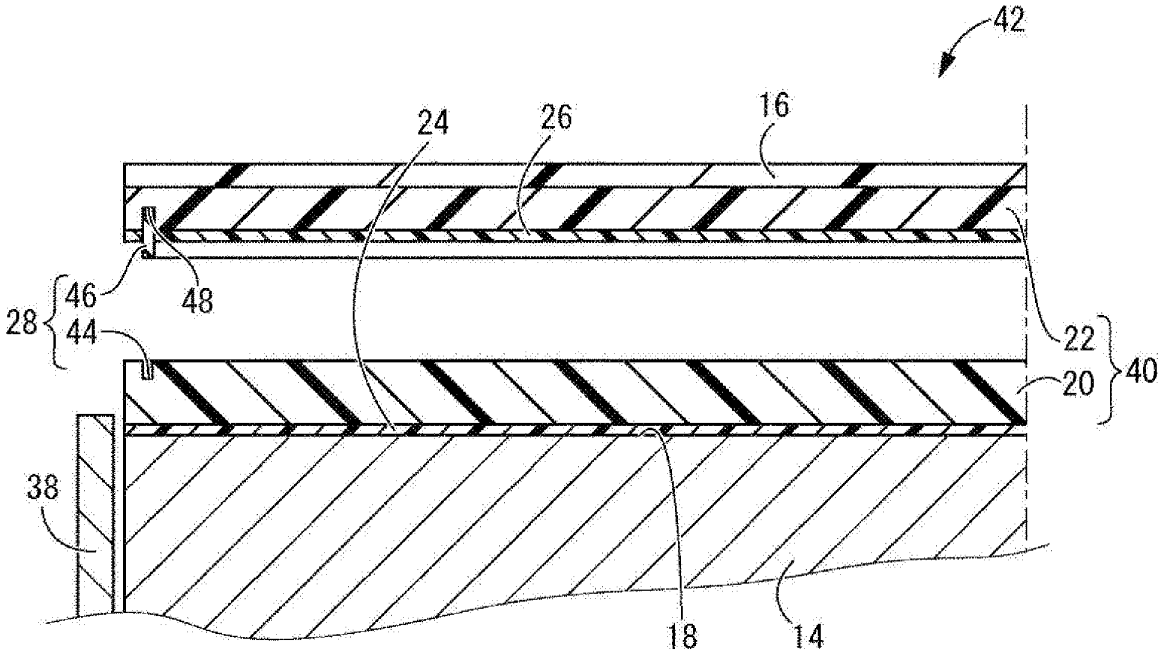
[Figure 2]



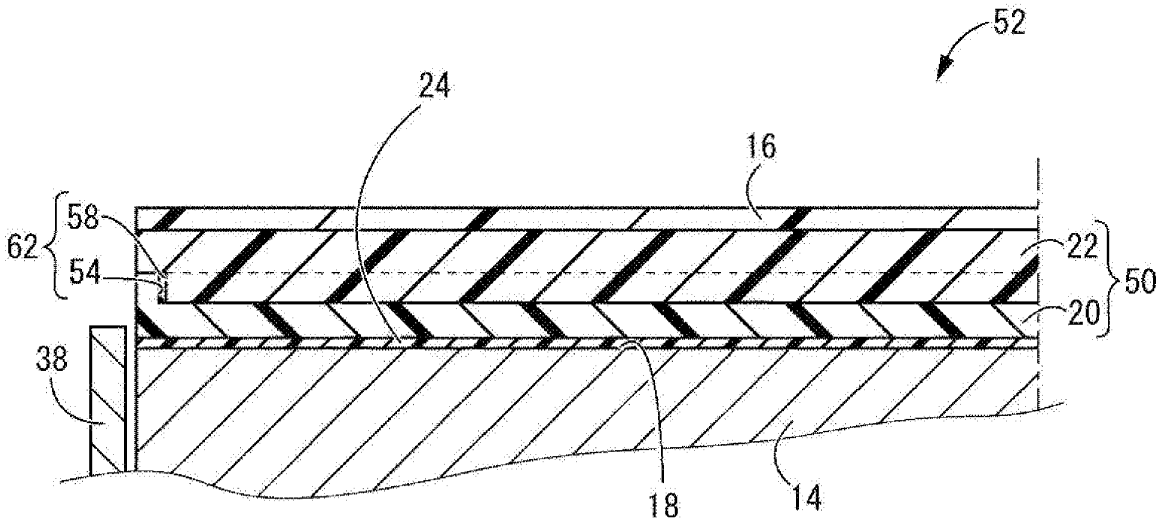
[Figure 3]



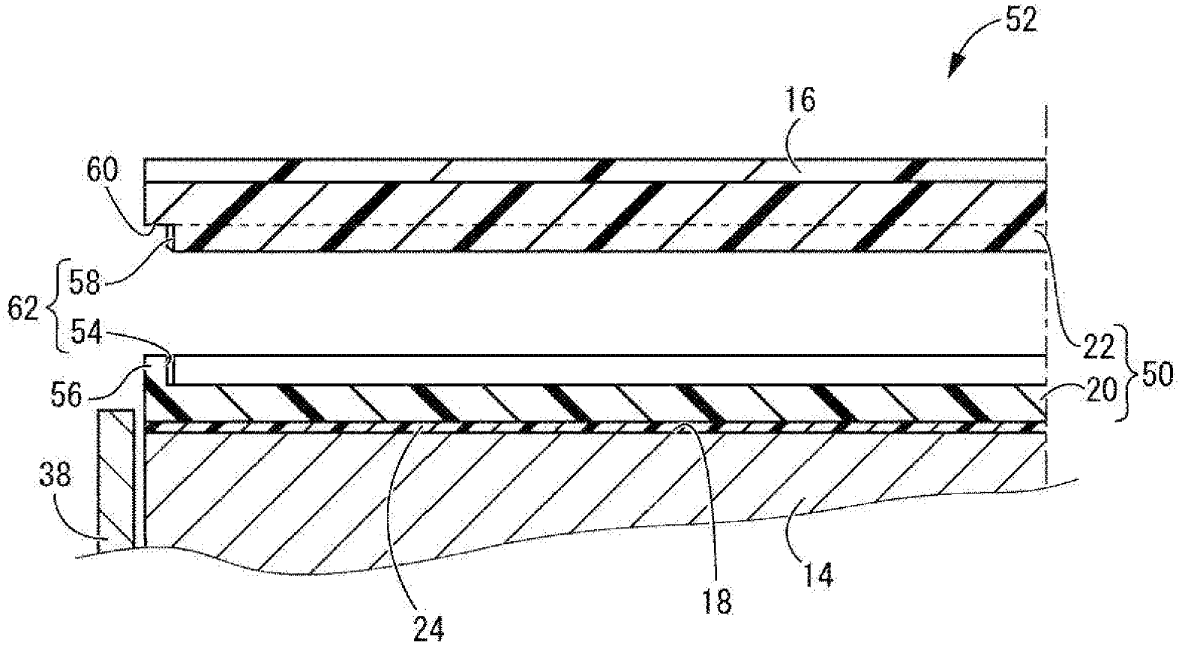
[Figure 4]



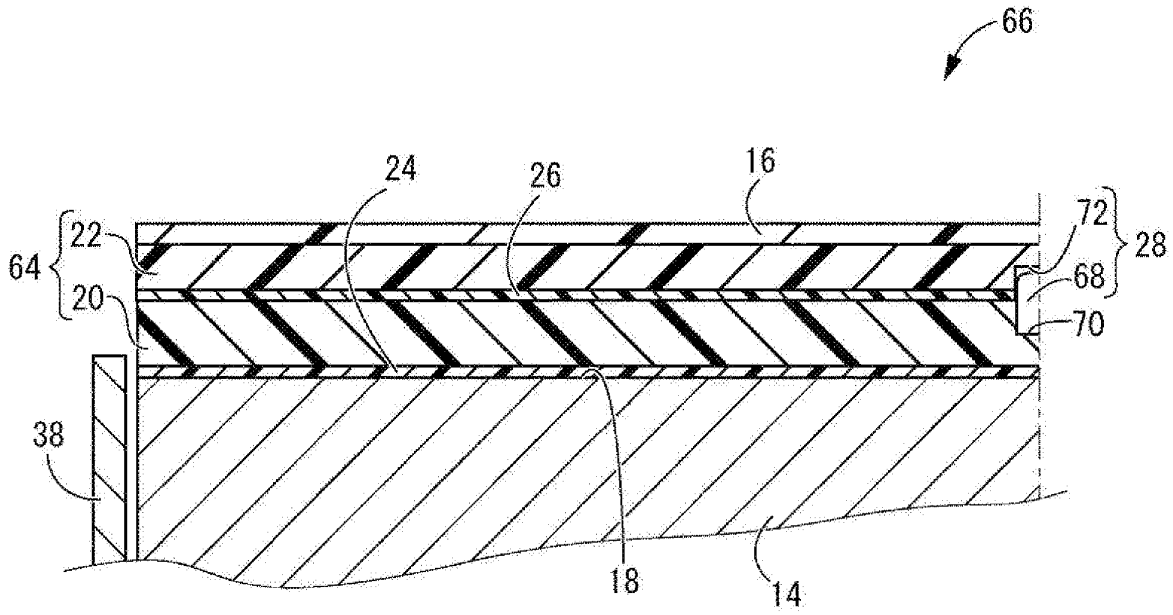
[Figure 5]


52
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16
58
62
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38
18
14

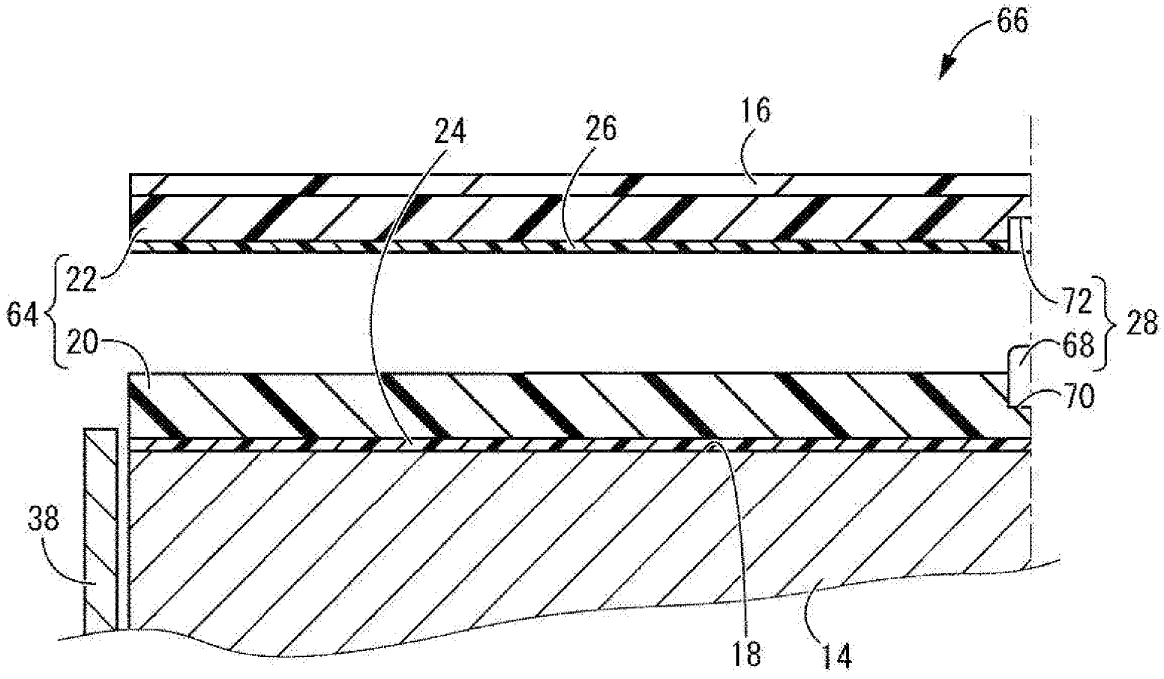
[Fig. 6]


52
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60
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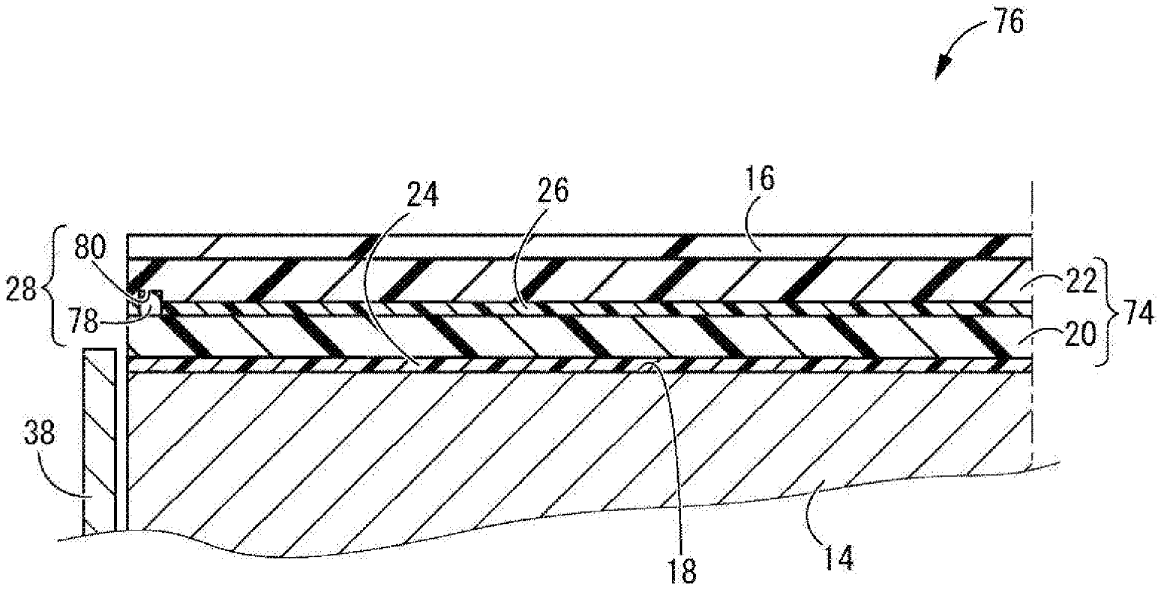
[Fig. 7]


66
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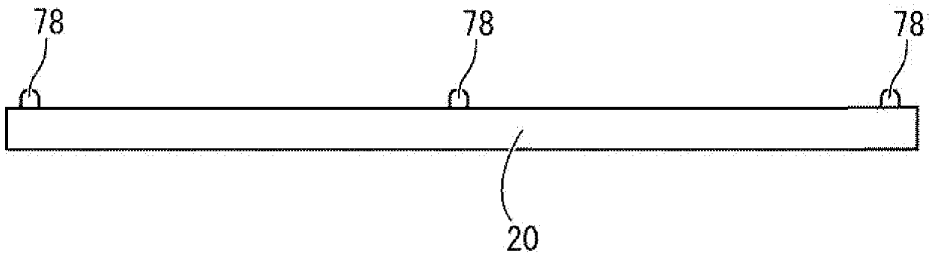
[Fig. 8]


66
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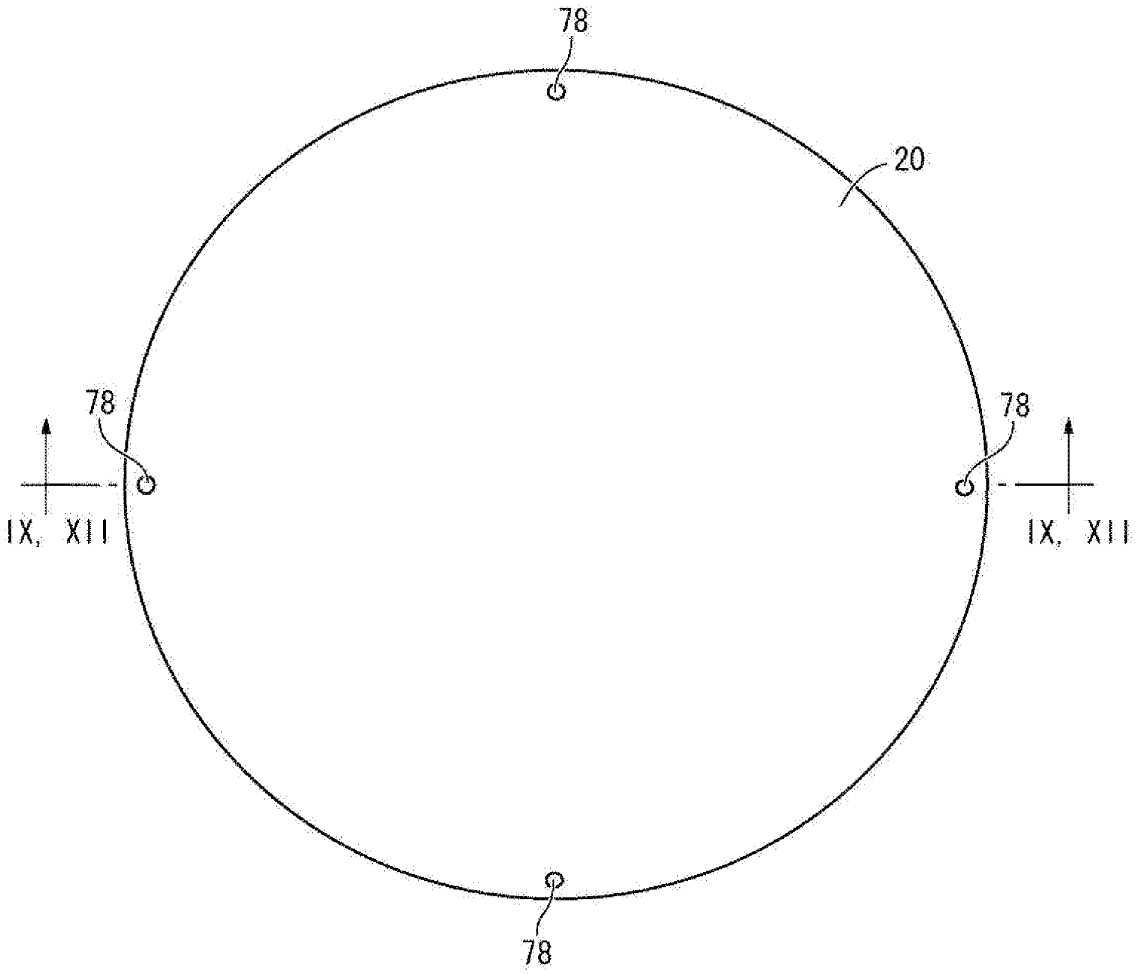
[Fig. 9]



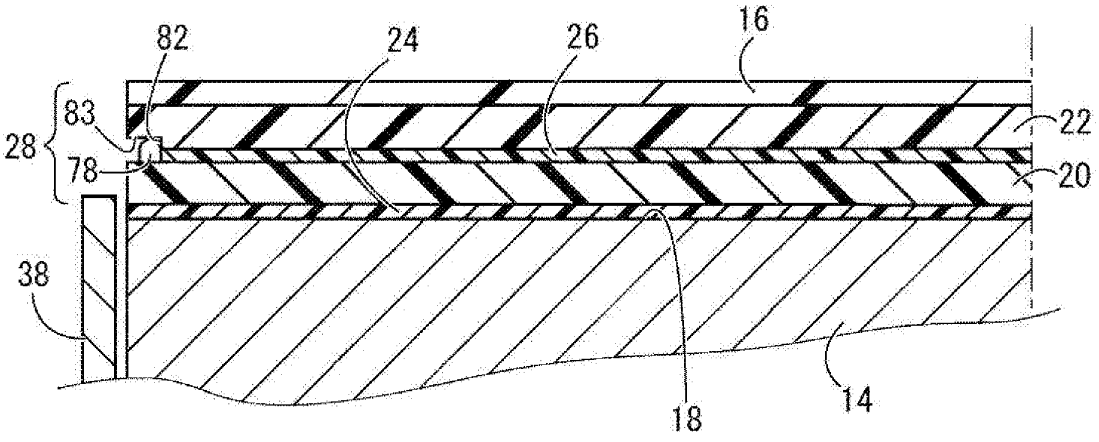
[Fig. 10]



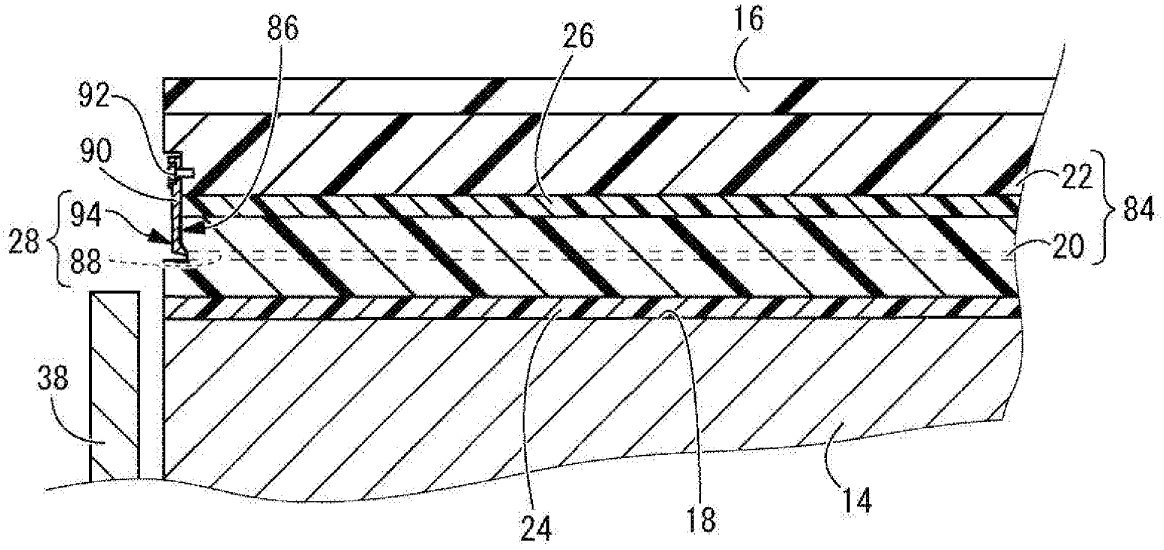
[Fig. 11]



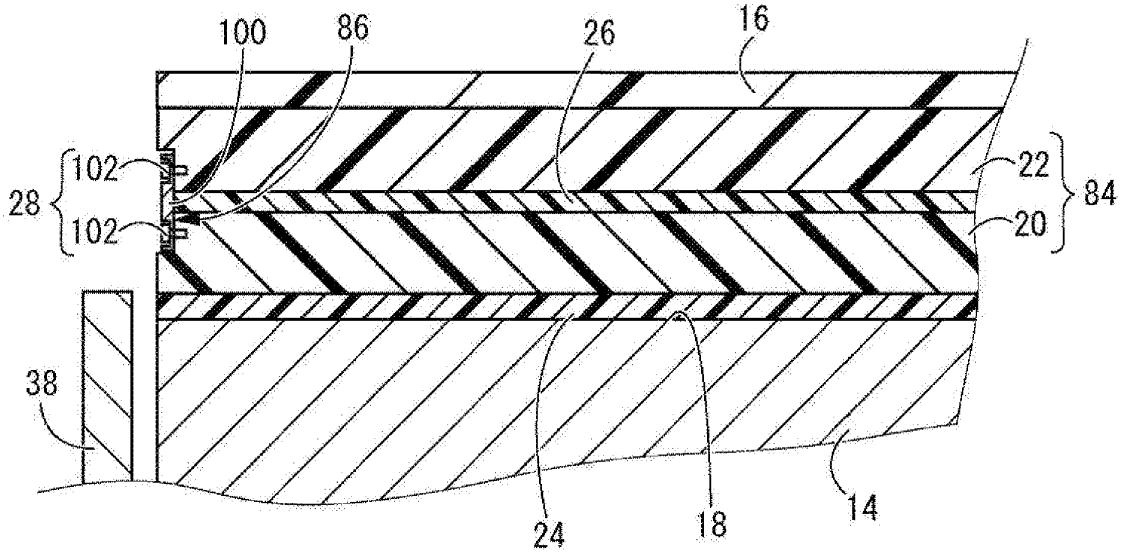
[Fig. 12]



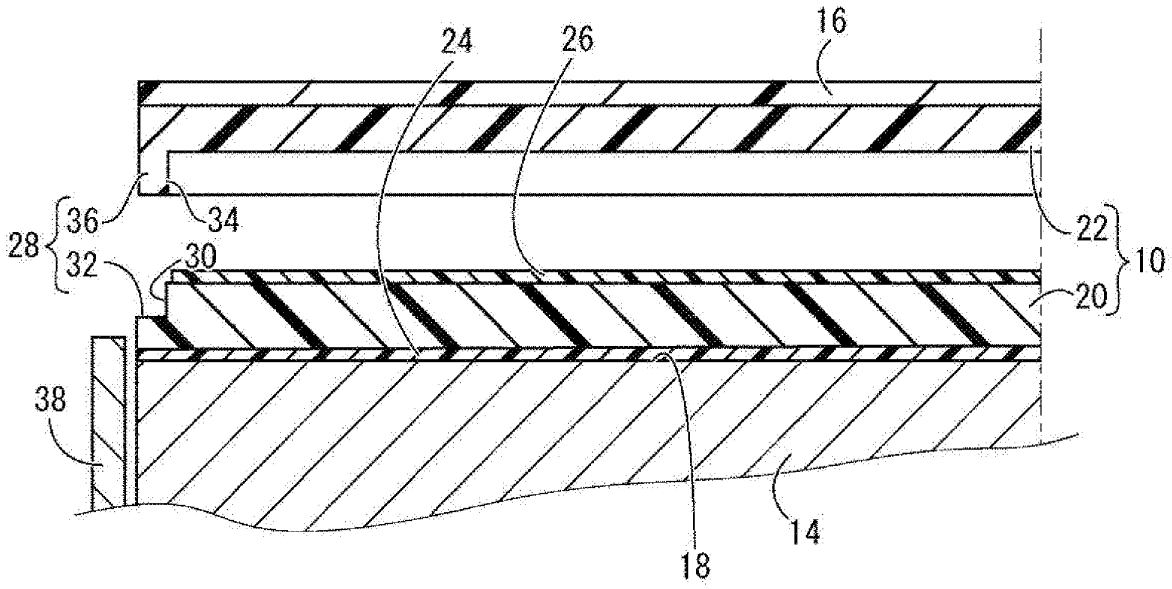
[Fig. 13]


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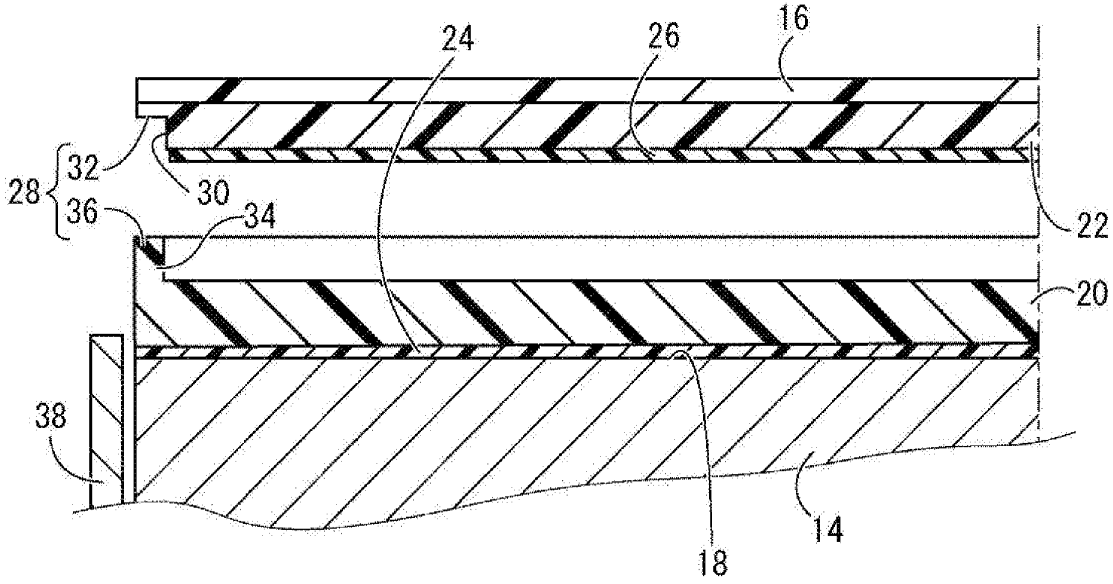
[Fig. 14]


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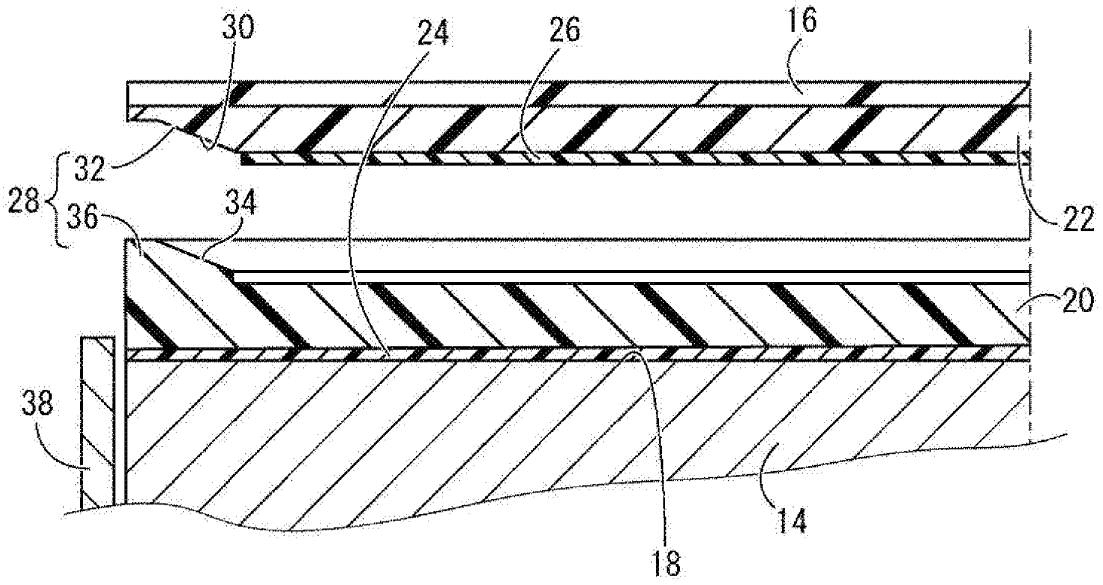
[Fig. 15]


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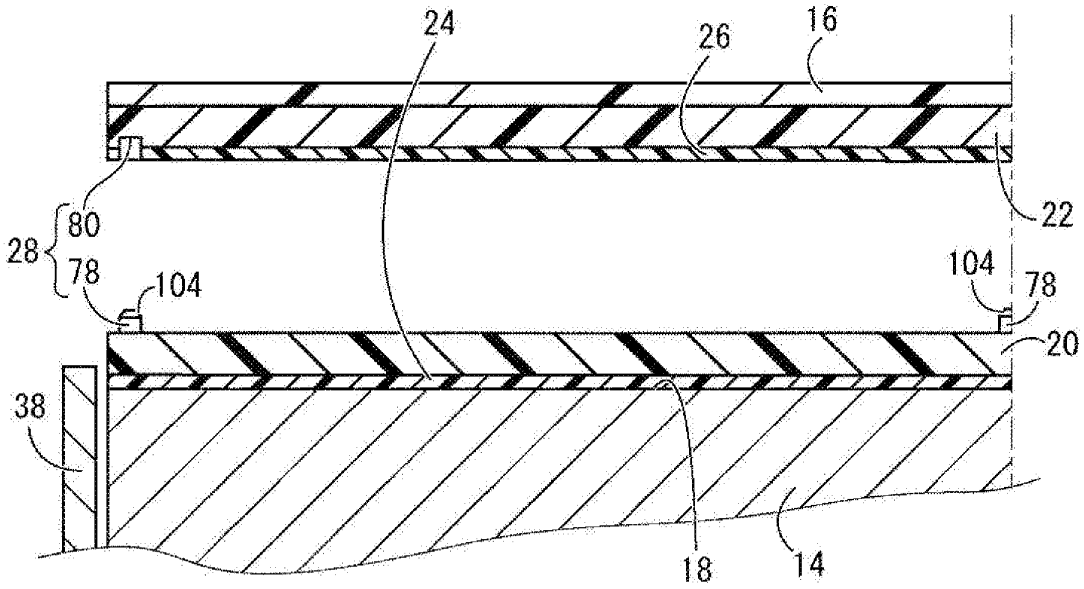
[Fig. 16]


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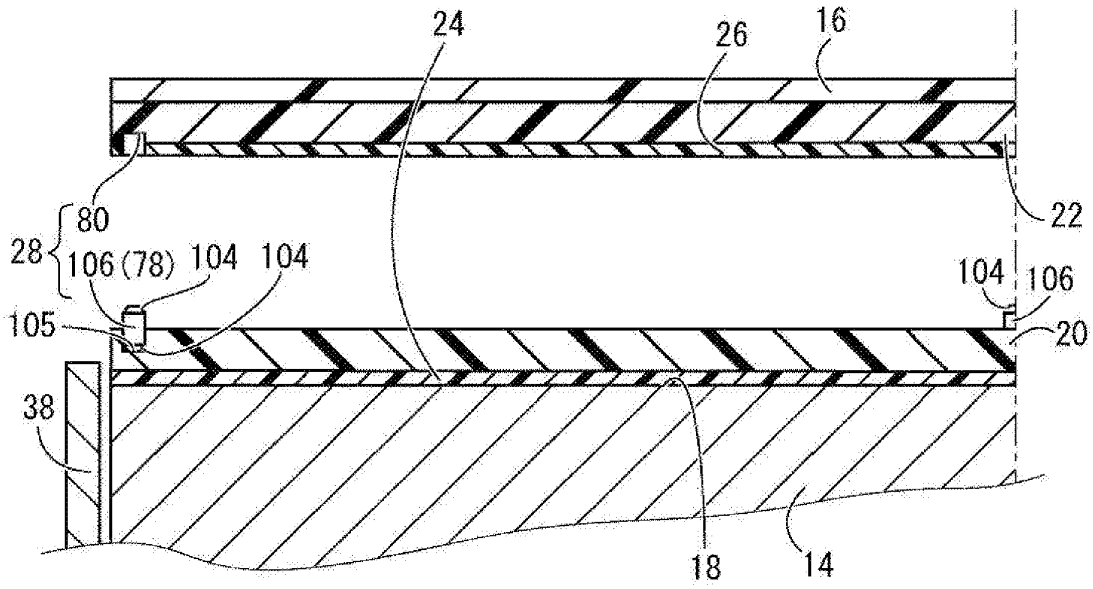
[Fig. 17]


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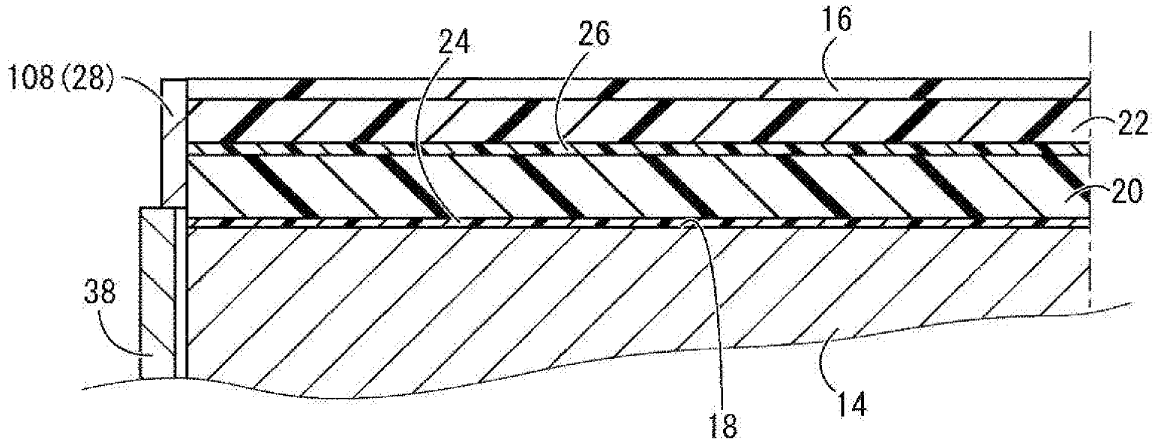
[Fig. 18]


24
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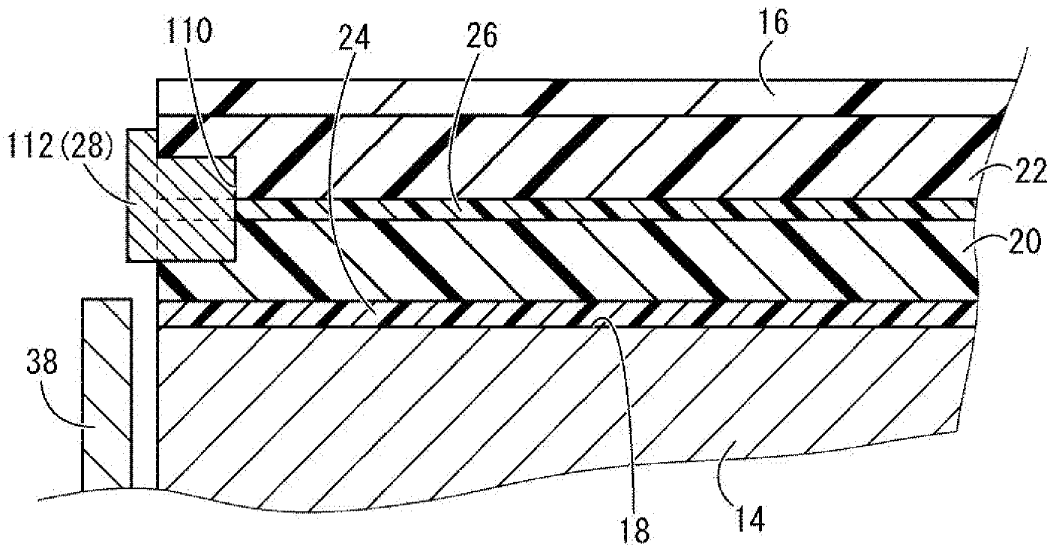
[Fig. 19]


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106 (78)
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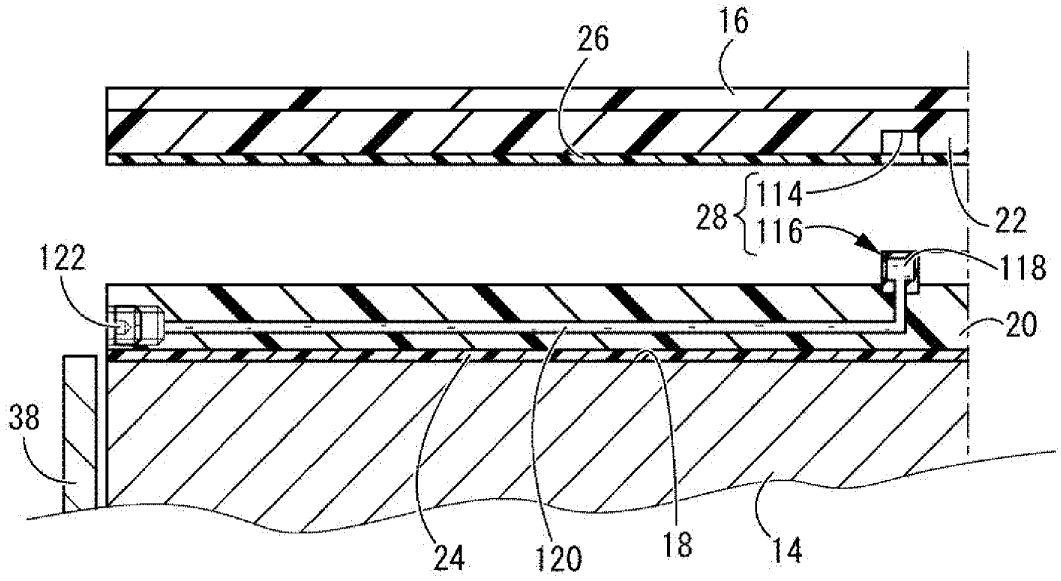
[Fig. 20]


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108 (28)
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[Fig. 21]



[Fig. 22]



drawing open —

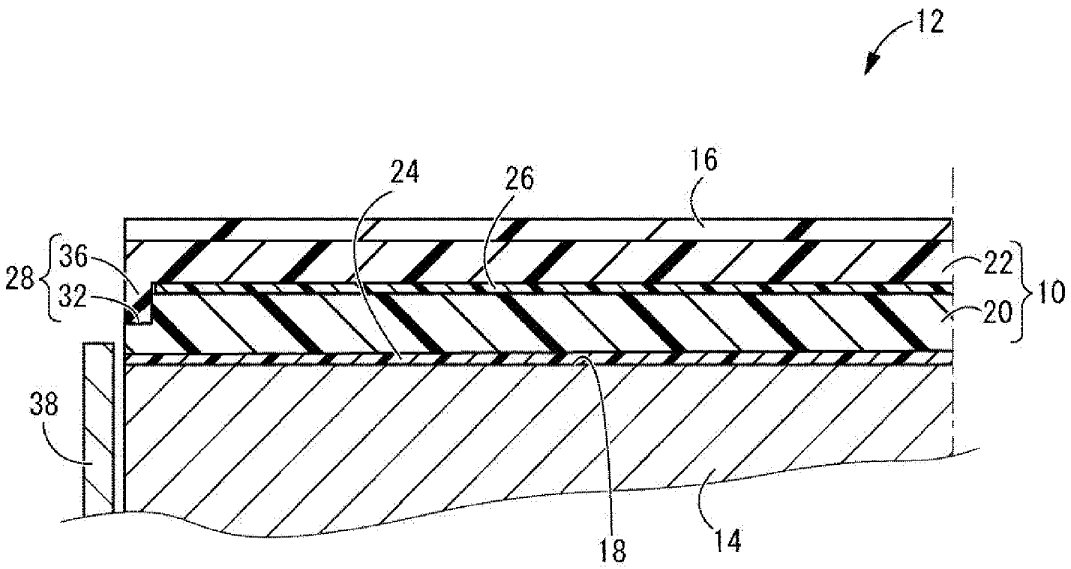


Figure 1

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[FI]
B24B 37/04 A
[Number of Claims] 11
[Total Number of Pages] 21
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(22) [Application date] July 28, 2011 (2011.7.28)
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2014) [Matters to be stated regarding results of research commissioned by the government] (report by applicant) commissioned by the government Patent application related to research results (FY2010 Ministry of Economy, Trade and Industry "Strategic Fundamental Technology Advancement Support Project" commissioned research, patent application subject to Article 1 9 of the Industrial Technology Enhancement Act) (73) [Patentee] [Identification number] 599 096053

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(72) [Inventor]
[Name] Eiji Suzuki
[Examiner] Takashi Kameda
(56) [References] [Reference] Japanese Patent Application
Laid- Open No. 08- 118231 (JP, A) [Reference] JP-A-07-328915 (JP, A) (58) [Field investigate d] (Int.Cl., DB name) B24B 37/12 H01L 21/304

The scope of the claims open ----

(57) [Scope of Claims]
[Claim 1] A

polishing pad auxiliary plate mounted on a rotating surface plate of a polishing apparatus for detachably attaching a polishing pad to the rotating surface plate, wherein

:

a first fixing means for fixing the lower auxiliary plate to the rotating surface plate; and

a pad supporting surface on which the polishing pad is superposed and fixed. an upper auxiliary plate superimposed on the upper surface of the lower auxiliary plate;

second fixing means for fixing the upper auxiliary plate to the lower auxiliary plate;

the lower auxiliary plate and the upper side; positioning means for aligning the center axis of the auxiliary plate with respect to each other

, and the lower auxiliary plate is fixed to the rotating surface plate of the polishing apparatus by the first fixing means. By removing the upper auxiliary plate from the lower auxiliary plate held and fixed to the rotating surface plate, the polishing pad can be rotated while being fixed to the pad supporting surface of the upper auxiliary plate. The upper auxiliary plate can be removed from the surface plate, and the removed upper auxiliary plate can be fixed and attached again to the lower auxiliary plate while being aligned by the positioning means, and ,

the fixing force between the lower auxiliary plate and the upper auxiliary plate by the second fixing means is smaller than the fixing force between the rotating platen and the lower auxiliary plate by the first fixing means;

Auxiliary plate for a polishing pad, characterized in that :

[Claim 2]

2. The auxiliary plate for a polishing pad according to claim 1 , wherein said positioning means is located inside the outer peripheral surfaces of said lower auxiliary plate and said upper auxiliary plate.

3. The positioning

means

includes an engaging projection provided on one of the lower auxiliary plate and the upper auxiliary plate and protruding toward the other, and the lower auxiliary plate and the upper auxiliary plate. 3. An auxiliary plate for a polishing pad according to claim 2 , wherein said auxiliary plate for a polishing pad comprises an engaging concave portion provided on the other side thereof and with which said engaging convex portion is engaged .

4. The polishing pad according to claim 3

, wherein said engaging projections and said engaging recesses are formed with engaging portions located on the outer peripheral portions of said lower auxiliary plate and said upper auxiliary plate. Auxiliary plate. 5. An annular engagement in which the engaging portions of the engaging protrusion and the engaging recess extend continuously in the circumferential direction of the lower auxiliary plate and the upper auxiliary plate and are fitted to each other. 5. The auxiliary plate for a polishing pad according to claim 4 , comprising an outer peripheral surface and an engaging inner peripheral surface . 6. At a plurality of locations on the circumference of the outer peripheral portions of the lower auxiliary plate and the upper auxiliary plat

e, the lower auxiliary plate and the upper auxiliary plate are overlapped on one side toward th e other. The engaging concave portion that opens and the engaging convex portion that protr udes toward one side of the other of the mutual overlapping surfaces of the lower auxiliary pl ate and the upper auxiliary plate are formed at positions corresponding to each other. wherein said engaging portion is formed by fitting said engaging convex portion into said engaging con cave portion.

5. The polishing pad auxiliary plate according to 4 .

7.

The engaging protrusions projecting from a plurality of locations on the circumference of one of the lower auxiliary plate and the upper auxiliary plate toward the other are formed of an el astic material, and The engagement portion is formed by engaging the tip of the engagement projection with the engagement recess provided in the outer peripheral surface of the other of the side auxiliary plate and the upper auxiliary plate. 5. The polishing pad auxiliary plate acco rding to claim 4 .

8. A polishing pad auxiliary plate according to claim 3

, wherein said engaging projections and said engaging recesses are provided on the central axes of said lower auxiliary plate and said upper auxiliary plate. 9. An outer peripheral surfac e of said engaging projection and an inner peripheral surface of said engaging recess are form ed with screw grooves for engaging with each other, and said engaging projection and said en gaging portion constituting said positioning means are formed with thread grooves for engagi ng with each other. 9. The auxiliary plate for a polishing pad according to claim 8 , wherein sai d second fixing means is formed by screwing with said mating recess . 10. The engaging pro jection provided on one of the lower auxiliary plate and the upper auxiliary plate is formed of t he same material as one of the lower auxiliary plate and the upper auxiliary plate. The auxilia ry plate for a polishing pad according to any one of claims 3 , 4 , 5 , 6 , 8 and 9 .

11. The auxiliary plate for a polishing pad according to any one of claims 1 to 10 is mounted o n the upper surface of a rotating surface plate, and a protective member is provided on the ou ter peripheral side of the rotating surface plate with a gap

therebetween . 11. The positioning means according to any one of claims 1 to 10 , wherein t he positioning means is disposed on the inner peripheral side of the outer peripheral end faces of the rotating platen and the polishing pad auxiliary plate. 2. A polishing apparatus comprisin g the polishing pad auxiliary plate according to 1 or 2 above.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to the polishing of substrates such as silicon wafers, semiconductor substrates, glass substrates, etc., which are workpieces requiring high flatness accuracy. It relates to a related technique, and more particularly to a technique that makes it possible to reuse a polishing pad used in polishing the surface of such a substrate.

is. 2.

Description of the Related Art As is well known, in manufacturing a semiconductor, a polishing process is performed to flatten the surface of a substrate such as a silicon wafer, a semiconductor substrate, a glass substrate, or the like. Such a polishing process generally involves fixing a disc-shaped polishing pad made of a resin material or the like directly on a rotating surface plate of a polishing apparatus with a double-sided tape, and supplying a polishing liquid containing abrasive grains to the polishing pad. Polishing is performed by rotating the substrates relative to each other. [0003] Polishing pads for carrying out such a polishing process are made of foamed or non-foamed urethane or the like, as described in Japanese Patent Application Laid-Open No. 2002-11630 (Patent Document 1). A resin pad is used. Further, in many cases, the polishing surface of such a polishing pad is provided with grooves such as concentric circles, grids, or radial grooves, or the bubbles of foamed resin are opened. [0004] By the way, when performing a polishing process using a polishing pad, when changing the type of substrate to be polished, the polishing pad used for the polishing process is peeled off from the rotating platen and replaced with another polishing pad. sometimes you have to. Also, for example, when a polishing pad that has deteriorated due to polishing is to be re-processed, such as by grooving the surface, with another processing device for the purpose of reusing the polishing pad, the polishing pad is removed from the rotating platen. Needs to be pulled off. [0005]

However, since the thin disk-shaped polishing pad is firmly fixed to the rotating surface plate

of the polishing apparatus with an adhesive tape, when the polishing pad is peeled off from th e rotating surface plate, Damage such as bending, breaking, wrinkling, and tearing is likely to occur. Therefore, due to such damage, there is often a problem that such polishing pads cann ot be reused and must be discarded even though their service life has not expired.

[0006]

Moreover, the work of peeling off the polishing pad from the rotating surface plate while payi ng close attention not to damage it requires skill and caution, and there is also the problem of placing a heavy burden on the operator. In addition, since it takes a considerable amount of ti me to peel off the polishing pad from the rotating surface plate, the polishing apparatus, whic h is expensive and valuable equipment, must be stopped for a long time, which shortens the o peration time of the equipment. There was also the problem that the

[0007]

Therefore, the present inventor previously described in Japanese Patent Application Laid-Ope n No. 2010-214579 (Patent Document 2) that an auxiliary plate is attached to the back surfac e of the polishing pad, and the polishing pad is rotated by the polishing apparatus through thi s auxiliary plate. We proposed a polishing pad with an auxiliary plate that is fixed to the surfa ce plate with double-sided tape. With such a polishing pad with auxiliary plate, since the polis hing pad is attached to and detached from the rotating surface plate while being supported by the auxiliary plate, damage to the polishing pad during attachment and detachment is reinforc ed by the auxiliary plate. Therefore, it is possible to attach and detach the polishing pad to an d from the rotating platen with good workability while preventing the polishing pad from being damaged.

[0008]

However, as a result of further studies and studies by the present inventors, it has been foun d that it is difficult to say that the polishing pad with an auxiliary plate proposed in Patent Doc ument 2 is easily compatible with all polishing apparatuses. rice field.

[0009]

That is, when the polishing pad is overlaid and fixed to the rotating surface plate, it is necess ary to align the center of the polishing pad with the rotation center of the rotating surface plat e. Accuracy is required for center alignment. If the number of attachment/detachment of the polishing pad to/from the rotating platen increases by adopting the auxiliary plate as describe d above, it becomes more difficult and labor-intensive to align the center position when attach ing the polishing pad to the rotating platen. big is big

It becomes a problem. Further, in the polishing pad with auxiliary plate proposed in Patent D ocument 2, in order to detachably attach the auxiliary plate while aligning the center of the au xiliary plate with respect to the rotary surface plate, the following are provided between the a uxiliary plate and the rotary surface plate

:

For example, fixing means such as an outer peripheral ring may be provided on the outer peri

pheral surface of the rotating surface plate. On the other hand, in some polishing apparatuse s, a protective cover or the like is attached to the outer peripheral side of the rotary platen, so that the space on the outer peripheral side of the rotary platen is extremely narrow. Therefor e, if such an outer peripheral ring were to be adopted, and a polishing device with a narrow sp ace on the outer peripheral side of the rotating surface plate was used, there was a possibility that the polishing device would need to be modified. of.

[Prior Art Documents]

[Patent Documents]

[0011]

[Patent Document 1] Japanese Unexamined Patent Application Publication No. 2002-11630 [P atent Document 2] Japanese Unexamined Patent Application Publication No. 2010-214579 [Su mmary of the Invention] [Problems to be Solved by the Invention] SUMMARY OF THE INVEN TION It is an object of the present invention to provide a polishing pad which can be easily att ached to and detached from a rotating surface plate while sufficiently securing the fixing force of the polishing pad to the rotating surface plate . For a polishing pad with a novel structure, which can prevent damage to the polishing pad when the polishing pad is removed from the r otating platen, and which can be advantageous for reuse of the polishing pad, for example. To provide an auxiliary plate. [0013]

In addition, according to the present invention, the work of aligning the center when mounti ng the polishing pad on the rotating surface plate can be performed easily and accurately, and the labor burden can be reduced. Another object of the present invention is to provide an auxi liary plate for a polishing pad with an improved structure, which can be easily and advantageo usly applied to a rotating surface plate in a polishing machine without requiring any special m odification. A further object of the present invention is to provide a polishing apparatus havin g such a novel polishing pad auxiliary plate

. Means for Solving the Problems In order to solve the above problems, a first aspect of the present invention relating to an auxiliary plate for a polishing pad is: (A) mounted on a rotatin g surface plate of a polishing apparatus; A polishing pad auxiliary plate for detachably attachi ng a pad to the rotary platen, comprising: (B) a lower auxiliary plate disposed on the upper s urface of the rotary platen; and (C) the lower auxiliary plate. and (D) a pad supporting surfac e on which the polishing pad is superimposed and fixed, which is superimposed on the upper s urface of the lower auxiliary plate. (E) a second fixing means for fixing the upper auxiliary plat e to the lower auxiliary plate; The lower auxiliary plate is held in a fixed state by the first fixin

g means to the rotating surface plate of the polishing apparatus, and is fixed to the rotating s urface plate. Further, by removing the upper auxiliary plate from the lower auxiliary plate, the polishing pad can be removed from the rotating surface plate while being fixed to the pad sup porting surface of the upper auxiliary plate. At the same time, it is possible to attach the remo ved upper auxiliary plate to the lower auxiliary plate by fixing it again in a state of being align ed by the positioning means.

and the fixing force between the lower auxiliary plate and the upper auxiliary plate by the sec ond fixing means is stronger than the fixing force between the rotating platen and the lower a uxiliary plate by the first fixing means. It features a smaller auxiliary plate for the polishing pa d. In the polishing pad auxiliary plate constructed according to the present invention, the pol ishing pad is composed of the upper auxiliary plate and the upper auxiliary plate

.

It is fixedly attached to the rotating surface plate via the lower auxiliary plate. Thereby, the u pper auxiliary plate can be removed from the lower auxiliary plate while the lower auxiliary pl ate is fixed to the rotating surface plate, and the polishing pad can be removed from the rotati ng surface plate while being fixed to the upper auxiliary plate. becomes possible. Therefore, in a state in which the polishing pad is reinforced and protected by the upper auxiliary plate, t he polishing pad can be removed from the rotating surface plate while preventing damage to t he polishing pad, and the thin polishing pad can be easily handled

.

becomes. For example, when the polishing pad is repeatedly attached and detached when the object to be polished or the polishing conditions are changed, or when the worn polishing pad is detached and reattached after reprocessing, the attachment and detachment of the polishin g pad to and from the rotating platen and the polishing are difficult. It is also possible to easil y perform operations such as reproduction processing for pads. Moreover, since the lower au xiliary plate still fixed to the rotating surface plate and the upper auxiliary plate removed toge ther with the polishing pad are aligned with each other by the positioning means, the position on the rotating surface plate can be easily adjusted

.

The attachment and detachment work of the polishing pad, which requires alignment, can be performed more easily. In particular, since the positioning means is provided between the low er auxiliary plate and the upper auxiliary plate, there is no need to apply special processing or the like to the rotating surface plate. In addition, it is possible to prevent such positioning me ans from protruding to the outer peripheral side of the rotating surface plate. applicable witho ut In the polishing pad auxiliary plate according to the first aspect of the present invention

,

, the fixing force between the lower auxiliary plate and the upper auxiliary plate by the seco nd fixing means is smaller than the fixing force between the rotating platen and the lower aux iliary plate by the first fixing means; A certain aspect is employed . According to the first aspe ct , the fixing forces of the first and second fixing means are mutually adjusted, so that the up per auxiliary plate to which the polishing pad is fixed can be rotated

. This makes it easier to remove the lower auxiliary plate that is still fixed to the surface plate. In short, there is no need for a special operation or the like to keep the lower auxiliary plate fi xed to the rotating platen, and the polishing pad can be attached to the upper supporting plat e while the lower auxiliary plate remains fixed to the rotating platen. It becomes possible to e asily remove the plate from the rotating surface plate while it is fixed to the plate. According t o a second aspect of the present invention , in the polishing pad auxiliary plate according to the first aspect, the positioning means is arranged on the inner peripheral side of the outer pe ripheral surfaces of the lower auxiliary plate and the upper auxiliary plate . It is located and pr ovided. [0022] In the polishing pad auxiliary plate of this aspect, the projection of the upper and lower auxiliary plates to the outer peripheral side of the positioning means is completely a voided. Therefore, for example, even when the outer diameter of the upper and lower auxiliar y plates is set to be the same as or slightly smaller than the outer diameter of the rotating sur face plate, the supporting surface of the polishing pad can be secured sufficiently large and th e It is possible to prevent the positioning means from protruding to the outer peripheral side, and even if a protective cover or the like is installed on the outer peripheral side of the rotatin g surface plate, it will not become an obstacle when applying the polishing pad auxiliary plate according to the present invention. Avoided.

A third

aspect of the present invention is the polishing pad auxiliary plate according to the second a spect, wherein the positioning means is provided on one of the lower auxiliary plate and the u pper auxiliary plate and on the other . It is composed of an engaging projection projecting to ward and an engaging recess provided in the other of the lower auxiliary plate and the upper auxiliary plate with which the engaging projection is engaged. In the polishing pad auxiliary pl ate of this aspect, it is possible to easily obtain a mechanically large positioning force based on the mutual engagement between the engaging projections and the engaging recesses. Furt her, by adjusting the shape, size, number, etc. of the engaging projections and engaging rece sses, it is possible to easily set the direction and acting force of the positioning action with a l arge degree of freedom.

A fourth aspect

of the present invention is the auxiliary plate for a polishing pad according to the third aspec t, wherein the engaging projections and the engaging recesses are located on the outer perip heries of the lower auxiliary plate and the upper auxiliary plate . It is formed with an engagin g portion located in the portion. In the polishing pad auxiliary plate of this aspect, the engag ement outer peripheral surface of the engagement projection and the engagement recess are positioned in the outer peripheral portion away from the center of the polishing pad auxiliary plate and are engaged with each other in a concave-convex manner . By forming the engage ment inner peripheral surface of the upper and lower auxiliary plates, the relative positioning accuracy, particularly the radial positioning accuracy, can be improved. As shown in the sixth and seventh aspects below, the engaging outer peripheral surface of the engaging convex por tion and the engaging inner peripheral surface of the engaging concave portion are arranged around the center of the polishing pad auxiliary plate. It may extend in the circumferential dir ection along the outer peripheral edge of the polishing pad auxiliary plate, or it may extend on the circumference like the engaging protrusions and engaging recesses formed on the outer p eripheral portion of the polishing pad auxiliary plate. It may be in a partially positioned form. A fifth aspect of the present invention is the auxiliary plate for a polishing pad according to t he fourth aspect, wherein the engaging portions of the engaging projections and the engaging recesses correspond to the lower auxiliary plate and the It is composed of an annular engagin g outer peripheral surface and an engaging inner peripheral surface that extend continuously i n the circumferential direction of the upper auxiliary plate and are fitted to each other. [0028]

In the polishing pad auxiliary plate of this aspect, more preferably, the engaging concave por tion and the engaging convex portion are formed with an annular inner and outer peripheral e ngaging surface that spreads around the central axis of the polishing pad auxiliary plate. Ther efore, when the upper auxiliary plate is attached to the lower auxiliary plate, it is not necessar y to align the upper auxiliary plate with each other in the circumferential direction, and the wo rk can be performed easily and quickly. A sixth aspect of the present invention is a polishing pad auxiliary plate according to the fourth aspect, wherein the lower auxiliary plate and the u pper auxiliary plate are provided at a plurality of locations on the periphery of the outer perip heral portions of the lower auxiliary plate and the upper auxiliary plate

. The engaging recess opening toward the other on one of the overlapping surfaces of the low er auxiliary plate and the upper auxiliary plate, and the other of the mutually overlapping surf

aces of the lower auxiliary plate and the upper auxiliary plate and the engaging projection pro jecting toward one side are formed at positions corresponding to each other, and the engaging portion is formed by fitting the engaging projection into the engaging recess. is. In the polishi ng pad auxiliary plate of this mode, the mutual positioning of the upper and lower auxiliary p lates can be easily realized not only in the direction perpendicular to the axis but also in the ci rcumferential direction around the central axis. In a seventh aspect of the present invention , in the polishing pad auxiliary plate according to the fourth aspect, the outer peripheral portio n of one of the lower auxiliary plate and the upper auxiliary plate has a plurality of points on t he circumference of the other . The engaging convex portion protruding toward the upper auxi liary plate is formed of an elastic material, and engages with the engaging concave portion pr ovided in an opening on the outer peripheral surface of the other of the lower auxiliary plate a nd the upper auxiliary plate. The engaging portion is configured by engaging the tip of the en gaging projection.

In the polishing pad auxiliary plate of this aspect, it is possible to form the engaging portions so as to be exposed on the outer peripheral surfaces of the upper and lower auxiliary plates . can be confirmed. In addition, in this aspect, the engagement state of the engagement portio n can be stably maintained by utilizing the elasticity of the engagement convex portion. An ei ghth
aspect of
the present invention is the polishing pad auxiliary plate according to the third aspect, where in the engaging projections and the engaging recesses are located at the centers of the lower auxiliary plate and the upper auxiliary plate . It is provided on the shaft. In the polishing pad auxiliary plate of this aspect, the engaging projections and the engaging recesses are formed on the central axis of the upper and lower auxiliary plates .

By providing this, it becomes possible to align the central axes of the upper and lower auxiliar y plates with one engaging portion. Further, when the engaging projections and the engaging recesses provided on the central axis are aligned with each other, it is not necessary to align t he upper and lower auxiliary plates with each other in the circumferential direction. can be ea sily brought into engagement. According to a ninth aspect of the present invention , in the p olishing pad auxiliary plate according to the eighth aspect, the outer peripheral surface of the engaging projection and the inner peripheral surface of the engaging recess are screwed toget

her

. A groove is formed, and the second fixing means is formed by screwing the engaging project ion and the engaging recess that constitute the positioning means. [0036] In the polishing p ad auxiliary plate of this mode, the fixing force between the upper auxiliary plate and the low er auxiliary plate can be obtained by the positioning means. Therefore, it is possible to config ure the second fixing means only by such positioning means, or to configure the fixing force b etween the upper and lower auxiliary plates by the second fixing means as an auxiliary means by the positioning means. A tenth aspect of the present invention is the third , fourth , fifth , sixth , eighth and ninth

2. In the polishing pad auxiliary plate according to any one of the above aspects, the engagin g projection provided on one of the lower auxiliary plate and the upper auxiliary plate is arran ged between the lower auxiliary plate and the upper auxiliary plate. It is made of the same m aterial as the one. In the polishing pad auxiliary plate of this aspect, it is possible to prevent the support characteristics of the polishing pad of the auxiliary plates superimposed one on to p of the other from greatly differing locally at the portions where the engaging projections are formed

.

. Therefore, when a pressing force acts on the surface of the polishing pad during pad polishin g, the pressure reaction force and the elasticity of the polishing pad are reduced at the format ion portions of the engaging convex portions and the engaging concave portions of the upper and lower auxiliary plates that support the polishing pad. It is possible to reduce or avoid defe cts such as polishing accuracy caused by local differences in such characteristics. Further, ac cording to the present invention, the auxiliary plate for a polishing pad according to any one o f the first to tenth aspects of the present invention is mounted on the upper surface of a rotati ng platen, and is attached to the outer peripheral side of the rotating platen

. A polishing apparatus in which a protective member is arranged with a gap in between, and the positioning means is provided on the inner peripheral side of the outer peripheral end surf aces of the rotating platen and the polishing pad auxiliary plate, Characterized by EFFECTS OF THE INVENTION By adopting the polishing pad auxiliary plate structured according to the pre sent invention or using the polishing apparatus structured according to the present invention, the polishing pad can be prevented from being damaged and polished. can be easily removed from and attached to the rotating surface plate, and positioning of the polishing pad on the ro tating surface plate can be performed easily and accurately. [Brief Description of the Drawings]

FIG. 1 is a vertical cross-sectional view showing the essential parts of a polishing apparatus e quipped with a polishing pad auxiliary plate according to a first embodiment of the present inv ention;

2 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 1; FIG.

FIG. 3 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a second embodiment of the present inventio n;

4 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 3; FIG.

FIG. 5 is a vertical cross-sectional view showing the essential parts of a polishing apparatus e quipped with a polishing pad auxiliary plate according to a third embodiment of the present in vention;

6 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 5; FIG.

FIG. 7 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a fourth embodiment of the present inventio n;

8 is an explanatory view of a longitudinal section showing a state in which the polishing pad is removed in the polishing apparatus shown in FIG. 7; FIG.

FIG. 9 is a vertical cross-sectional view showing a main part of a polishing apparatus equipped with a polishing pad auxiliary plate according to a fifth embodiment of the present invention;

10 is a side view of a lower auxiliary plate that constitutes the polishing pad auxiliary plate sh own in FIG. 9; FIG.

11 is a plan view of the lower auxiliary plate shown in FIG. 10; FIG.

FIG. 12 is a longitudinal sectional view showing the essential parts of a polishing apparatus eq uipped with a polishing pad auxiliary plate according to a sixth embodiment of the present inv ention;

FIG. 13 is a vertical cross-sectional view showing the essential parts of a polishing apparatus equipped with a polishing pad auxiliary plate according to a seventh embodiment of the prese nt invention;

FIG. 14 is a vertical cross-sectional view showing a main part of a polishing apparatus equipp ed with a polishing pad auxiliary plate according to an eighth embodiment of the present inve ntion;

FIG. 15 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a ninth embodiment of the present invention is removed;
FIG. 16 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate is removed according to a tenth embodiment of the present invention;
FIG. 17 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to an eleventh embodiment of the present invention is removed;
FIG. 18 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a twelfth embodiment of the present invention is removed;
FIG. 19 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a thirteenth embodiment of the present invention is removed;
FIG. 20 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a fourteenth embodiment of the present invention is positione d;
FIG. 21 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a fifteenth embodiment of the present invention is positioned;
FIG. 22 is an explanatory view of a longitudinal section showing a state in which a polishing p ad auxiliary plate according to a sixteenth embodiment of the present invention is removed;
DETAILED DESCRIPTION OF THE INVENTION Embodiments of the present invention will be de scribed
below

with reference to the drawings. First, FIGS. 1 and 2 show a polishing pad auxiliary plate 10 a s a first embodiment of the present invention. This polishing pad auxiliary plate 10 is used by being attached to a rotary surface plate 14 of a polishing apparatus 12, and a polishing pad 1 6 is detachably attached to the rotary surface plate 14. As shown in FIG.
The polishing apparatus is used ,

for example, as a CMP apparatus as described in Japanese Patent Application Laid-Open No. 2010-141155, for example. A rotating shaft extending vertically is rotatably supported by the main body of the apparatus fixedly installed above, and a disk-shaped rotating platen 14 is fix ed to the upper end of the rotating shaft. The rotating surface plate 14 has a flat upper surfac e 18 extending horizontally, and the upper surface 18 serves as a support surface for the polis hing pad 16 . The rotating shaft is connected to the rotating output shaft of an electric motor, and the driving force of the electric motor is transmitted so that the rotating shaft and thus th e rotating surface plate 14 are rotated about the central axis. there is A nozzle for supplying p olishing slurry is arranged above the upper surface 18 supporting the polishing pad 16, and a wafer or the like to be polished (an object to be polished) is held and rotated while being mov ed to the polishing pad 16. A polishing head is provided for polishing by pressing. In such a polishing apparatus, the polishing pad auxiliary plate 10 mounted on the rotating platen 14
is

includes a lower auxiliary plate 20 and an upper auxiliary plate 22 . A lower auxiliary plate 20 is fixed to the upper surface 18 of the rotating platen 14 by first fixing means 24 , and an upp er auxiliary plate 22 is attached to the upper surface of the lower auxiliary plate 20 . It is fixe d by two fixing means 26 . That is, the lower auxiliary plate 20 and the upper auxiliary plate 2 2 are overlapped and fixed to each other via the second fixing means 26, thereby forming the polishing pad auxiliary plate 10 having a two-layer structure as a whole. , and is attached to t he upper surface 18 of the rotating surface plate 14 by the first fixing means 24 .

Each of the lower auxiliary plate 20 and the upper

auxiliary plate 22 has a thin, substantially circular flat plate shape, and has a flat front surfa ce (upper surface) and a rear surface (lower surface). These upper and lower auxiliary plates 22 and 20 are desirably made of a harder material than the polishing pad 16 to which it is att ached, or having a higher member rigidity than the polishing pad 16 . Although it depends on the method of use, as will be described later, the lower auxiliary plate 20 can be used without being repeatedly attached and detached after being attached to the rotary surface plate 14, w hile the upper auxiliary plate 22 can be attached and detached after being attached to the rot ary surface plate 14. is expected to be repeated, it is desirable that at least the upper auxiliar y plate 22 should have higher member rigidity than the polishing pad 16 .

[0046]

Of course, the upper auxiliary plate 22 supports the polishing pad 16 and provides the stren gth, rigidity, and rigidity required for various treatments such as polishing, cleaning, and re-gr ooving of the polishing pad surface, in addition to polishing by the polishing device 12 . Any m aterial that satisfies shape stability and accuracy may be used, and its material and thickness are not limited. In particular, not only the lower auxiliary plate 20 but also the upper auxiliary plate 22 alone bears the supporting strength and rigidity of the polishing pad 16. Since the lo wer surface is supported by the rotating surface plate 14 by being superimposed on each othe r and used, the strength and rigidity of the single unit are not required so much. Therefore, in addition to metals such as stainless steel, synthetic resins, fiber-reinforced resins, and the like can be employed as materials for forming the lower auxiliary plate 20 and the upper auxiliary plate 22 . In particular, synthetic resin materials are lighter than metal materials and easier to process and handle. . In order to obtain a stable supporting force over the entire polishing p ad 16, it is desirable to set the outer diameter dimension of the upper auxiliary plate 22 to be equal to or larger than the outer diameter dimension of the polishing pad 16,

and

It is desirable to set the outer diameter of the lower auxiliary plate 20 to be equal to or larger than the outer diameter of the upper auxiliary plate 22, and set the outer diameter of the low er auxiliary plate 20 to be equal to or smaller than the outer diameter of the rotating surface plate 12. should be set to In particular, as shown in FIGS. 1 and 2, the outer diameters of the lower auxiliary plate 20 and the upper auxiliary plate 22 are made substantially the same, and the outer diameter of the rotating surface plate 14 to be mounted is also substantially the sa

me. By doing so, it becomes possible to ensure a sufficiently large support area for the polishi ng pad 16 . As a result, the polishing pad 16 having approximately the same size as the rotati ng surface plate 14 can be attached to the rotating surface plate 14 with approximately the sa me supporting force over the entirety thereof.

[0048]

Furthermore, as the first fixing means 24 and the second fixing means 26, the lower auxiliar y plate 20 and the upper auxiliary plate 22 are fixed to the upper surface 18 of the rotating pl aten 14 against the external force exerted during polishing. It is not particularly limited as lon g as it can be held at. Specifically, an adhesive, a pressure-sensitive adhesive, or a double-sid ed tape having an adhesive or a pressure-sensitive adhesive attached to both sides of a base sheet may be employed as the first and second fixing means 24, 26. In addition, negative pre ssure suction using negative pressure air or the like, or magnetic suction using a permanent magnet or an electromagnet can be employed. In addition, it is desirable that the fixing mean s made of adhesive or the like apply substantially uniform fixing force over substantially the e ntire surface of the flat overlapping surfaces of the lower auxiliary plate 20 and the upper auxi liary plate 22. Adhesive strength can be obtained, and problems such as locally different supp ort characteristics of the polishing pad 16 on the surface of the polishing pad auxiliary plate 1 0 can be avoided.

For example ,

the fixing force can be turned ON/OFF by negative pressure suction or an electromagnet. au xiliary

It is desirable to set the fixing force of the upper auxiliary plate 22 to the lower auxiliary plate 20 by the second fixing means 26 to be smaller than the fixing force of the plate 20 . As a res ult, when the upper auxiliary plate 22 is peeled off from the lower auxiliary plate 20 and remo ved, the lower auxiliary plate 20 can be easily left fixed on the rotating surface plate 14.例文帳 に追加 The specific realization of such a difference in adhesion force is achieved by differentiati ng the adhesion means itself such as the material of the adhesive and pressure-sensitive adh esive, as well as the adhesion area and the condition of the adhesion surface (surface roughn ess, presence or absence of plasma treatment, etc.) can also be realized by making the .

Further, the surface (upper surface) of the upper auxiliary plate 22 serves as a

polishing pad supporting surface, and the polishing pad 16 is superimposed and mounted th ereon. As such a polishing pad 16, conventionally known various types of polishing pads can b e employed. The back surface of the polishing pad 16 is fixed to the surface of the upper auxil iary plate 22 using a conventionally known adhesive tape or suitable adhesive for attaching th e polishing pad.

It is desirable that the fixing means for fixing

the polishing pad 16 to the upper auxiliary plate 22 has a larger fixing force than the second fixing means 26 described above. As a result, when the upper auxiliary plate 22 is removed fr om the lower auxiliary plate 20 with the polishing pad 16 still fixed, the polishing pad 16 does

not move from the upper auxiliary plate 22 even if the upper auxiliary plate 22 is bent or the l ike. It is possible to effectively prevent the peeling off. The outer diameter of the polishing p ad 16 is generally a standard value, but in many cases it is set equal to or smaller than the ou ter diameter of the upper surface 18 of the rotating surface plate 14 to which it is attached . [0053]

Further, for example, at least one of between the upper surface 18 of the rotating surface pl ate 14 and the lower auxiliary plate 20, between the lower auxiliary plate 20 and the upper au xiliary plate 22, and between the upper auxiliary plate 22 and the polishing pad 16 A suitable cushioning layer may be provided. By providing such a cushion layer, it becomes possible to a chieve uniform polishing efficiency over the entire surface of the workpiece when polishing wit h the polishing pad 16 .

[0054]

As such a cushion layer, for example, a resin sheet, an elastomer sheet, a rubber sheet, or t he like to which a certain degree of compressibility is imparted by foaming can be suitably em ployed. A cushion layer can also be configured by the first fixing means 24 , the second fixing means 26 , and the means for fixing the polishing pad 16 to the upper auxiliary plate 22 . In o rder to prevent local distortion on the support surface of the polishing pad 16, the cushion lay er is formed so as to have a size and a constant thickness over substantially the entire suppor t area of the polishing pad 16. is desirable. Positioning means 28 are provided between the l ower auxiliary plate 20 and the upper auxiliary plate 22 that constitute the polishing pad auxil iary plate 10 to align the centers of the plates with each other

.

In the present embodiment, a circular stepped surface 30 is formed on the outer peripheral p ortion of the lower auxiliary plate 20 and extends around the central axis of the lower auxiliar y plate 20 over the entire circumference. By reducing the thickness of the lower auxiliary plat e 20 on the outer peripheral side of the stepped surface 30, the notch cross-sectional shape t hat opens to the outer peripheral surface of the lower auxiliary plate 20 continues to the entir e circumference in the circumferential direction. An annular engaging recess 32 that extends i nward is formed integrally with the lower auxiliary plate 20 so as to protrude therefrom.

[0056]

On the other hand, in the present embodiment, a circular stepped surface 34 is formed on th e outer peripheral portion of the upper auxiliary plate 22 so as to extend around the central a xis of the upper auxiliary plate 22 over the entire circumference. Since the thickness of the up per auxiliary plate 22 is increased on the outer peripheral side of the stepped surface 34, an a nnular engagement continuously extends along the outer peripheral edge of the upper auxiliar y plate 22 along the entire circumference in the circumferential direction. A mating projection 36 is integrally formed so as to protrude from the upper auxiliary plate 22 . Incidentally, the e

ngaging convex portion 36 and the engaging concave portion 32 may be formed on either of t he upper and lower auxiliary plates 22 and 20 .

The stepped surface 30 and the engaging recess 32 of the lower auxiliary plate 20 are aligne d with the stepped surface 34 and the engaging projection 36 of the upper auxiliary plate 22 . It constitutes an engagement outer peripheral surface and an engagement inner peripheral su rface. When the upper auxiliary plate 22 is superimposed on the lower auxiliary plate 20, the engaging convex portion 36 is fitted into the engaging concave portion 32, and the stepped su rface 34 is superimposed on the stepped surface 30 in the radial direction. is formed. As a res ult, the engaging concave portion 32 and the engaging convex portion 36 constitute the positi oning means 28, and the lower auxiliary plate 20 and the upper side support plate 20 are alig ned in the radial direction with their central axes aligned with each other. Auxiliary plates 22 a re superimposed. In addition, the positioning means 28 is positioned on the inner peripheral si de of the outer peripheral surfaces of the upper and lower auxiliary plates 22 and 20, thereby preventing the upper and lower auxiliary plates 22 and 20 and the polishing apparatus 12 fro m becoming large. . In the polishing apparatus 12 provided with the polishing pad auxiliary plate 10 having such a structure, the upper and lower auxiliary plates 22 are mounted on the upper surface 18 of the rotating platen 14 as shown in FIG

.

, 20 is fixedly attached, and the polishing pad 16 is fixedly supported on the upper surface of the upper auxiliary plate 22. Then, the rotating platen 14 is driven to rotate, and the substrat e or the like is processed. CMP (Chemical Mechanical Polishing) is applied to objects. The polis hing apparatus 12 can exhibit the following special technical effects by being provided with th e polishing pad auxiliary plate 10 having a specific structure.

[0059]

First, as shown in FIG. 2, while the polishing pad 16 is fixed to the upper surface of the uppe r auxiliary plate 22, the upper auxiliary plate 22 is fixed to the rotating surface plate 14 by th e first fixing means 24. By removing the side auxiliary plate 20, the polishing pad 16 can be r emoved from the rotating surface plate 14. - 特許庁 Even when the surface (polishing surface) of the polishing pad 16 is removed from the rotating platen 14 and cleaned or reprocessed, th e polishing pad 16 can be kept fixed to the upper surface of the upper auxiliary plate 22 . As a result, the upper auxiliary plate 22 provides reinforcement not only when the polishing pad 16 is attached to and detached from the rotating surface plate 14, when the polishing pad 16 is c leaned and reprocessed, but also when the polishing pad 16 is transported or stored. By this a ction, the polishing pad 16 can be prevented from being bent or damaged, and the polishing p ad 16 can be kept in good condition.

Further

, even when the polishing pad 16 is removed from the rotating surface plate 14 together wit h the upper auxiliary plate 22 , the lower auxiliary plate 20 remains on the upper surface 18 o

f the rotating surface plate 14 . When the polishing pad 16 is again mounted on the rotating p laten 14, the positioning means 28 provided between the upper auxiliary plate 22 and the low er auxiliary plate 20 moves the upper auxiliary plate 22 and thus the polishing pad 16 to the l ower auxiliary plate. The center axis of the plate 20 and thus the rotating platen 14 can be ali gned with high accuracy and easily.

[0061]

Here, since the engaging concave portion 32 and the engaging convex portion 36 constitutin g the positioning means 28 are overlapped with almost no gap in a mutually fitted state, the s upport characteristics of the polishing pad 16 are improved. can be prevented from adversely affecting Of the outer peripheral portions of the upper and lower auxiliary plates 22 and 20, p articularly in the present embodiment, an engaging portion, in other words, a positioning mea ns 28, is formed on the outer peripheral edge portion, and the diameter of the polishing pad 1 6 that serves as the main region for polishing is formed. Since it is out of the middle part in th e direction, even if there is a slight gap between the engaging concave portion 32 and the eng aging convex portion 36, the supporting characteristics of the polishing pad 16 are such that a serious problem occurs in the polishing characteristics. can be avoided. Moreover, the engagi ng concave portion 32 and the engaging convex portion 36 constituting the positioning means 28 are formed on the superimposed surfaces of the upper and lower auxiliary plates 22 and 2 0, in other words, on the outer circumferences of the rotating surface plate 14 and the polishi ng pad auxiliary plate 10

.

Since it is formed on the inner peripheral side of the end face, the upper and lower auxiliary pl ates 22 and 20 can be prevented from projecting onto the outer peripheral surface. Therefore, as shown in FIGS. 1 and 2, for example, even when the protective member 38 is installed clos e to the outer peripheral side of the rotating surface plate 14 in the polishing apparatus 12, th e protective member 38 cannot be protected. Polishing provided with upper and lower auxiliar y plates 22, 20 provided with positioning means 28 while avoiding interference

A device 12 is made possible. Furthermore, as described above, while preventing damage to the polishing pad 16, the polishing pad 16 can be quickly attached to and detached from the r otating platen 14 with accurate positioning accuracy

.

The operating time of the expensive polishing equipment is not unnecessarily limited for such work, and the operating efficiency of the polishing equipment can be improved, and thus the production efficiency of substrates and the like (polishing work efficiency) can be improved. In addition, since the polishing pad 16 can be easily attached to and detached from the rotati ng surface

plate 14, the reuse of the polishing pad 16 can be realized on a practical level without specia l skill or knowledge. That is, for example, the polishing pad 16 once removed from the rotatin g platen 14 can be reused when changing the type of the object to be polished such as a subs

trate, or the polishing pad 16 can be re-processed by another processing device such as surfa ce grooving as a countermeasure against deterioration. It is also possible to consider reusing t he polishing pad 16 once removed from the rotating surface plate 14 after reprocessing at a p ractical level. Although the first embodiment of the present invention has been described ab ove, the specific structure of the present invention should not be construed as limited by the fi rst embodiment

.

A plurality of other embodiments of the present invention having different positioning means between the upper and lower auxiliary plates 22 and 20 are illustrated below, but these embo diments are not intended to limit the configuration of the present invention. In the following e mbodiments, members and parts having the same structure as in the first embodiment are de noted by the same reference numerals as those in the first embodiment in the corresponding parts in each figure. , their detailed description is omitted. 3 and 4 show a polishing apparat us 42 provided with a polishing pad auxiliary plate 40 as a second embodiment of the present invention

.

In this polishing pad auxiliary plate 40, an engaging recess 44 is formed by an annular groov e continuously extending in the circumferential direction on the outer peripheral portion of the upper surface of the lower auxiliary plate 20. As shown in FIG . On the other hand, on the out er peripheral portion of the lower surface of the upper auxiliary plate 22, an engagement conv ex portion 46 is formed by an annular protrusion extending continuously in the circumferential direction. The engaging projection 46 may be formed integrally with the upper auxiliary plate 22, or may be formed separately as illustrated. That is, in this embodiment, an annular circu mferential groove 48 that opens in the lower surface of the upper auxiliary plate 22 and exten ds in the circumferential direction is formed. block is fitted and fixed at one end in the axial di rection to form an engagement convex portion 46 . The engaging concave portion 44 of the l ower auxiliary plate 20 and the engaging convex portion 46 of the upper auxiliary plate 22 are both formed at corresponding radial positions around the central axis

.

are overlapped, the engagement projections 46 are fitted into the engagement recesses 44, t hereby aligning the upper and lower auxiliary plates 22 and 20 with each other in the radial di rection. In the present embodiment, two side walls of the engaging recess 44 of the lower aux iliary plate 20 and the inner and outer peripheral surfaces of the engaging protrusion 46 of th e upper auxiliary plate 20 are superimposed on each other in the corresponding radial directio n. A pair of inner and outer engagement surfaces are provided. 5 and 6 show a polishing ap paratus 52 provided with a polishing pad auxiliary plate 50 as a third embodiment of the pres ent invention

. [0070]

In this polishing pad auxiliary plate 50, the lower auxiliary plate 20 has a stepped surface 54 as a circular engagement inner peripheral surface extending all around the central axis on the outer peripheral portion thereof. By increasing the thickness of the lower auxiliary plate 20 on the outer peripheral side of the stepped surface 54, an annular shape continuously extends al ong the outer peripheral edge of the lower auxiliary plate 20 along the entire circumference in the circumferential direction. The engaging convex portion 56 of
It is formed integrally with the side auxiliary plate 20 . On the other hand, on the outer perip heral portion of the upper auxiliary plate 22, there is formed a stepped surface 58 as a circula r engagement outer peripheral surface extending all around the central axis
.
Since the thickness of the upper auxiliary plate 22 is reduced on the outer peripheral side of t he step surface 58, the upper auxiliary plate 22 has a notched cross-sectional shape that ope ns to the outer peripheral surface and extends continuously along the entire circumference in the circumferential direction. An annular engaging recess 60 is formed integrally with the upp er auxiliary plate 22 .
Further, the step surface 54 of the lower auxiliary plate 20 is formed with
female threads, while the step surface 58 of the upper auxiliary plate 22 is formed with male threads. Then, the female thread of the stepped surface 54 of the lower auxiliary plate 20 is s crewed with the male thread of the stepped surface 58 of the upper auxiliary plate 22 so that the stepped surface 54 of the lower auxiliary plate 20 and the stepped surface 58 of the upper auxiliary plate 22 are screwed together. are superimposed on each other in the radial directio n, the upper auxiliary plate 22 is superimposed on the upper surface of the lower auxiliary pla te 20 . Further, in such a superimposed state, the screwing structure of the stepped surfaces 58, 54 of the upper and lower auxiliary plates 22, 20 constitutes a second fixing means 62 for detachably fixing the upper and lower auxiliary plates 22, 20. . The direction of the male and female threads in such a threaded structure is set in consideration of the rotational reaction fo rce exerted on the rotating surface plate 14 of the polishing device 12 during polishing so that the screws do not loosen
.
It is desirable that
FIGS.
7 and 8 show a polishing apparatus 66 having a polishing pad auxiliary plate 64 as a fourth embodiment of the present invention.
[0075]
In this polishing pad auxiliary plate 64 , a cylindrical engaging convex portion 68 projecting upward is formed at the central portion of the upper surface of the lower auxiliary plate 20 . T

he engaging projection 68 may be formed integrally with the lower auxiliary plate 20, or may be formed separately as shown in the drawing. That is, in this embodiment, a circular fitting r ecess 70 is formed on the central axis of the lower auxiliary plate 20, and a cylindrical block f ormed separately from the fitting recess 70 is provided. An engaging convex portion 68 is for med by being fitted and fixed at one end in the axial direction. On the other hand, in the centr al portion of the lower surface of the upper auxiliary plate 22, there is formed a bottomed circ ular engaging recess 72 that opens to the lower surface on the central axis. Incidentally, the e ngaging convex portion 68 and the engaging concave portion 72 may be formed on either of t he upper and lower auxiliary plates 22 and 20. As shown in FIG. When the upper and lower auxiliary plates 22 and 20 are superimposed, the engaging convex portion 68 is fitted into the engaging concave portion 72, thereby aligning the upper and lower auxiliary plates 22 and 20 with each other in the radial direction

.

It is designed to be In this embodiment, the engagement outer peripheral surface and the eng agement inner peripheral surface are formed by the outer peripheral surface of the engaging protrusion 68 of the lower auxiliary plate 20 and the inner peripheral surface of the engaging recess 72 of the upper auxiliary plate 22. It is configured.

FIG.

9 shows a polishing apparatus 76 provided with a polishing pad auxiliary plate 74 as a fifth e mbodiment of the present invention.

[0078]

In this polishing pad auxiliary plate 74 , a cylindrical engaging convex portion 78 projecting upward is formed on the outer peripheral portion of the upper surface of the lower auxiliary pl ate 20 . This engaging projection 78 may be formed integrally with the lower auxiliary plate 2 0, or may form a fitting recess in the lower auxiliary plate 20 like the engaging projection in t he fourth embodiment. Alternatively, a separate pin or the like may be fixed by press-fitting o r the like. Also, as shown in FIGS. 10 and 11, a plurality of such engaging projections 78 are f ormed independently of each other at the outer peripheral portion of the lower auxiliary plate 20 at predetermined intervals in the circumferential direction. Particularly preferably, the plura lity of engaging protrusions 78 are formed at regular intervals in the circumferential direction and positioned on the same circle on the central axis.

On the other hand, on the outer peripheral portion of the lower surface of the upper auxiliar y plate 22, bottomed circular engagement grooves are provided at positions corresponding to the formation positions of the plurality of engaging projections 78 on the lower auxiliary plate 20, respectively . A concave portion 80 is formed to open downward. Incidentally, the engagin g convex portion 78 and the engaging concave portion 80 may be formed on either of the upp er and lower auxiliary plates 22 and 20. As shown in FIG. When the upper and lower auxiliar y plates 22 and 20 are superimposed, the engaging convex portions 78 are fitted into the eng

aging concave portions 80, respectively, so that the upper and lower auxiliary plates 22 and 20 are positioned radially relative to each other

.

are designed to be matched. In the present embodiment, the outer circumferences of the lower auxiliary plate 20 and the upper auxiliary plate 22 are formed by the outer circumference of the engagement projection 78 of the lower auxiliary plate 20 and the inner circumference of the engagement recess 80 of the upper auxiliary plate 22 . An engaging outer peripheral surface and an engaging inner peripheral surface located in a portion are configured. In particular, as in this embodiment, by adopting positioning means consisting of a plurality of engaging projections 78 and engaging recesses 80 independent in the circumferential direction, the superimposed upper and lower auxiliary plates 22, 20 can be diametrically aligned

.

Mutual positioning is possible not only in the direction but also in the circumferential direction. Instead of the plurality of independent engaging recesses 80 formed in the upper auxiliary plate 22 ,

a circumferential groove continuously extending circularly in the circumferential direction around the central axis of the upper auxiliary plate 22 may be employed. Alternatively, as shown in the sixth embodiment of the present invention in FIG. 12, a circular stepped surface 82 is formed around the central axis of the outer peripheral portion of the upper auxiliary plate 22 and extends over the entire circumference. By making the thickness dimension of the outer peripheral side smaller than 82, it is also possible to form an annular engagement concave portion 83 that has a notched cross-sectional shape that opens to the outer peripheral surface of the upper auxiliary plate 22 and that extends continuously all around in the circumferential direction. It is possible.

[0083]

In this way, in the upper auxiliary plate 22, the engaging surfaces of the engaging projections 78 of the lower auxiliary plate 20 are formed continuously over the entire circumference, so that when the upper and lower auxiliary plates 20 and 22 are superimposed, the upper and lower auxiliary plates 20 and 22 can be overlapped. Since it is no longer necessary to align the auxiliary plates 20 and 22 with each other in the circumferential direction, the mounting work can be easily performed.

FIG.

13 shows a polishing pad auxiliary plate 84 as a seventh embodiment of the present invention.

In this polishing pad auxiliary plate 84, the upper portion of the outer peripheral surface of the lower auxiliary plate 20 and the lower portion of the outer peripheral surface of the upper

auxiliary plate 22 are each provided with a small diameter portion. By superimposing the upper and lower auxiliary plates 22 and 20, the small diameter portions of the upper and lower auxiliary plates 22 and 20 form an annular ring that extends across the entire circumference i

n the circumferential direction by widening a predetermined width across the upper and lower auxiliary plates 22 and 20. A shaped receiving recess 86 is formed. A groove-shaped engagi ng recess 88 is formed at the lower end of the small diameter portion of the lower auxiliary pl ate 20

.

The engagement recess 88 opens to the outer peripheral surface of the lower auxiliary plate 2 0 at the bottom surface of the accommodation recess 86 . Here, the bottom surface of the acc ommodation recess 86 refers to an annular surface extending over the upper and lower auxili ary plates 22 and 20 and extending in the vertical direction in FIG. On the other hand, a plate -shaped engaging projection 90 made of an elastic material is attached to the small-diameter portion of the upper auxiliary plate 22 that constitutes the accommodation recess 86 so that it s proximal end is fixed by a fixing pin 92 . The engaging protrusions 90 are accommodated in accommodation recesses 86 formed on the outer peripheral surfaces of the upper and lower a uxiliary plates 22 , 20 and extend from the upper auxiliary plate 22 onto the outer peripheral surface of the lower auxiliary plate 20 . there is An engaging claw portion 94 formed at the tip portion of the engaging projection portion 90 is engaged with an engaging recess portion 88 f ormed in the small diameter portion of the lower auxiliary plate 20, and the engaging projecti on portion 90 is locked. It is held in a locked state based on elasticity.

Furthermore, a plurality of such engaging projections 90 are provided on the outer periphera l surfaces of the upper and lower auxiliary plates 22 and 20 at predetermined intervals in the circumferential direction . And attached to the outer peripheral surface of the upper auxiliary plate 22

Each of the engaging projections 90 is elastically pressed against the outer peripheral surface of the lower auxiliary plate 20, thereby forming positioning means for positioning the upper a nd lower auxiliary plates 22, 20 relative to each other on the central axis. Further, by engagin g the engaging claw portion 94 of the engaging convex portion 90 with the engaging concave portion 88, a fixing means is also configured to hold the upper and lower auxiliary plates 22 a nd 20 in a superimposed state and apply a fixing force. there is Instead of the engaging prot rusions 90 having the engaging claws 94 that engage with the engaging recesses 88 as descri bed above, for example, an eighth embodiment of the present invention shown in FIG

.

In addition, a connecting plate 100 extending across the upper and lower auxiliary plates 22 a nd 20 and superimposed on the bottom surface of the housing recess 86 is adopted, and both ends of the connecting plate 100 are connected to one of the upper and lower auxiliary plates 22 and 20. It is also possible to fix to the outer peripheral surface of the by connecting pins 1 02 , 102 . At least one of the connecting pins 102, 102 is detachable from the lower auxiliary plate 20 or the upper auxiliary plate 22, so that the connection of the upper and lower auxiliar y plates 22, 20 by the connecting plate 100 can be released. , the attachment and detachmen

t of the upper auxiliary plate 22 to which the polishing pad 16 is fixed with respect to the lowe r auxiliary plate 20 is permitted. The first fixing means 24 and the second fixing means 26 m ade of double-faced tape or the like shown in the first to eighth embodiments are used when r emoving the upper and lower auxiliary plates 22 and 20 and the rotating surface plate 14

.

In addition, it is desirable to be held on the fixing surface on the side of a specific member. Th is facilitates handling of the upper and lower auxiliary plates 22, 20 and the first and second fi xing means 24, 26 in a detached state. In addition, the fixing surfaces on which the first and second fixing means 24 and 26 remain are determined by making the fixing force of both surf aces of the first fixing means and the second fixing means 24 and 26 themselves different fro m each other. It is possible to set by differentiating the surface roughness, material, etc. of th e fixed upper and lower auxiliary plates 22 and 20 and the rotating platen 14 from each other. In particular, it

is desirable that the first fixing means 24 is held on the fixing surface on the side of the lowe r auxiliary plate 20 when the lower auxiliary plate 20 is removed. becomes easier. On the othe r hand, as shown in FIG. 2 in the first embodiment, the second fixing means 26 is held on the fixing surface on the side of the upper auxiliary plate 22 when the upper auxiliary plate 22 is r emoved. Alternatively, it may remain on the upper surface of the lower auxiliary plate 20 as in the ninth embodiment of the present invention shown in FIG. By holding the second fixing me ans 26 on the fixing surface on the side of the upper auxiliary plate 22, the removed upper au xiliary plate 22 can be attached to the rotating surface plate of the device for reprocessing suc h as grooving of the polishing pad 16. At the time of mounting, it is also possible to use the se cond fixing means 26 held by the upper auxiliary plate 22 for mounting. On the other hand, b y holding the second fixing means 26 on the fixing surface of the lower auxiliary plate 20, whe n mounting another upper auxiliary plate 22 with another polishing pad 16 mounted thereon t o the lower auxiliary plate 20, It is also possible to attach using the second fixing means 26 h eld by the lower auxiliary plate 20 .

Further, the engaging recesses 32, 44, 60, 72, 80, (83), 88 and the engaging projections 36, 46, 56,

70, 78, 90 shown in the first to seventh embodiments may be provided on opposite sides of the lower auxiliary plate 20 side and the upper auxiliary plate 22 side. For example, as the te nth embodiment of the present invention is shown in FIG. The stepped surface 30 and the eng aging recess 32 may be formed on the upper auxiliary plate 22 , while the stepped surface 34 and the engaging convex portion 36 forming the inner peripheral surface of the engagement may be formed on the lower auxiliary plate 20 . It is possible.

[0092]

Furthermore, the engaging recesses 32, 44, 60, 72, 80, (83) and the engaging protrusions 3 6, 46, 56, 70, 78 shown in the first to sixth embodiments are overlapped with each other. It is also possible to form an inclination angle with respect to the outer peripheral surface of the en

gaging projection and the inner peripheral surface of the engaging recess for positioning the u pper and lower auxiliary plates 22 and 20 by using the upper and lower auxiliary plates 22 an d 20 as shown in FIG. For example, as an eleventh embodiment of the present invention is sh own in FIG. On the other hand, while the engaging convex portion 36 is tapered in the incline d direction in which it gradually tapers in the projecting direction,

A stepped surface 30 serving as an engaging outer peripheral surface of an engaging recess 3 2 formed in the outer peripheral portion of the upper auxiliary plate 22 can be tapered at an i nclination direction and an inclination angle corresponding to the stepped surface 34 . As a re sult, the operation of fitting the engaging convex portion 36 into the engaging concave portio n 32 and overlapping the upper and lower auxiliary plates 22, 20 can be further facilitated by using the tapers provided on both the stepped surfaces 34, 30 as guide surfaces. It becomes possible to do it easily. Incidentally, as shown in the twelfth embodiment of the invention sh own in FIG. 18 and the thirteenth embodiment of the invention shown in FIG

.

Even when adopting a plurality of projection-shaped engaging projections 78 formed independ ently in the direction and a plurality of hole-shaped engaging recesses 80 formed at respectiv e corresponding positions of the upper auxiliary plate 22, the engagement A tapered portion 1 04 having a tapered shape can be formed by giving an inclination angle to the outer periphera l surface of the projecting tip portion of the convex portion 78 . In FIG. 19, an engagement pi n 106 formed separately is press-fitted into a fitting hole 105 formed in the lower auxiliary pla te 20 to form the engagement convex portion 78. The lower end of the locking pin 106 also h as a tapered portion 104 similar to the upper end. As a result, the locking pin 106 has no dire ctivity and is easy to handle, and the operation of press-fitting it into the fitting hole 105 is als o facilitated.

[0094]

Further, in the fourteenth embodiment of the present invention shown in FIG. 20, a straddle between the upper and lower auxiliary plates 22, 20 is used as a kind of positioning means for aligning the central axis of the upper and lower auxiliary plates 22, 20 in a superimposed stat e. A locating sleeve 108 is thus shown fitted over. The positioning sleeve 108 has an inner dia meter that is the same as or slightly larger than the outer diameter of the upper and lower au xiliary plates 22 and 20, which are disk-shaped and have substantially the same outer diamet er. formed. Such a positioning sleeve 108 is used when superimposing the upper and lower au xiliary plates 22 and 20, and by superimposing the upper and lower auxiliary plates 22 and 20 within the positioning sleeve 108, the central axes of the upper and lower auxiliary plates 22 and 20 are aligned. They can be axially superimposed and secured to each other with a secon d securing means 26 . Therefore, the positioning sleeve 108 can be removed after the upper a nd lower auxiliary plates 22 and 20 are superimposed and fixed to each other, thereby positio ning the upper and lower auxiliary plates 22 and 20 so as to protrude on the outer peripheral surface. It is possible to attach them to each other without means and in precise alignment.

[0095]

Furthermore, in the fifteenth embodiment of the present invention shown in FIG. 21, a slit-shaped engagement groove 110 is formed extending across the overlapping direction when the upper and lower auxiliary plates 22 and 20 are overlapped. ing. The engaging grooves 110 are open to the outer peripheral surfaces of the upper and lower auxiliary plates 22 and 20 and have a predetermined depth radially inward. It is A plate-shaped engaging plate 112 is fitted into the engaging groove 110 from the opening of the outer peripheral surface, so that the upper and lower auxiliary plates 22 and 20 are positioned by the engaging plate 112 and is in a connected state. Although the engaging plate 112 is formed separately from the upper and lower auxiliary plates 22 and 20, it may be formed integrally with one of the upper and lower auxiliary plates 22 and 20 so as to protrude toward the other. . In that case, the engagement groove 110 is formed only in the other auxiliary plate.

Furthermore, in the sixteenth embodiment of the present invention shown in FIG. 22 ,

a fitting recess 114 is formed as an engaging recess opening in the lower surface of the upper auxiliary plate 22 . In particular, in this embodiment, the fitting recess 114 is formed as an annular groove extending continuously in the circumferential direction around the central axis of the upper auxiliary plate 22 . On the other hand, the lower auxiliary plate 20 has a fitting convex portion 116 as an engaging convex portion that protrudes upward on the upper surface that overlaps with the upper auxiliary plate 22 . In addition, in this embodiment, the fitting protrusion 116 is formed as an annular protrusion corresponding to the fitting recess 114 . When the upper and lower auxiliary plates 22 and 20 are superimposed, the fitting convex portion 116 is positioned so as to enter the fitting concave portion 114 .

[0097]

The fitting projection 116 has a hollow structure, and the inside of the fitting projection 116 is provided with an external space.

A fluid reservoir 118 is formed which is sealed between them. Further, at least the inner peripheral wall and the outer peripheral wall of the wall portion of the fitting convex portion 116 that defines the fluid reservoir 118 are bulged and deformable in the radial direction. Specifically, for example, by forming the fitting convex portion 116 with a rubber elastic material or the like, it is possible to realize an inner peripheral wall that can bulge radially inward and an outer peripheral wall that can bulge radially outward. be. Further, the lower auxiliary plate 22 is formed with a fluid passage 120 that communicates with the fluid reservoir 118 and extends radially outward and opens to the outer peripheral surface

.

A pressure screw 122 is screwed into the end opening. In addition, a sealed area composed of the fluid passage 120 and the fluid reservoir 118 sealed by the pressurizing screw 122 is filled with an incompressible fluid such as oil.

Thus

, by screwing the pressure screw 122, the internal pressure of the fluid reservoir 118 can be

increased through the fluid passage 120, and the inner and outer peripheral walls of the fluid reservoir 118 can be expanded outward. As a result, the fitting convex portion 116 is expande d and pressed against the inner surface of the fitting concave portion 114, so that the upper a nd lower auxiliary plates 22 and 20 can be positioned by mutual frictional force and the like, a nd can also exert a fixing force. there is

When removing the upper auxiliary plate 22 from the lower auxiliary plate 20 ,

the pressure screw 122 is rotated in the direction of loosening and moved to the outer perip heral side of the lower auxiliary plate 20, whereby the fluid reservoir 118 is removed. , the pr essing force of the fitting protrusion 116 against the fitting recess 114 can be released.

[0101]

In addition, although not listed individually, the present invention can be implemented with v arious changes, modifications, improvements, etc. based on the knowledge of those skilled in the art. It is also possible to attach an O-ring or a sealing material to the portion to prevent fo reign matter from entering the overlapping surfaces of the upper and lower auxiliary plates.

In addition to the auxiliary plates 20 and 22 having the two-layer structure described above, i t

is also possible to add additional auxiliary plates in a laminated state and fixed by fixing mea ns. By adopting the auxiliary plate of the third layer in this way, it becomes possible to realize an elastic support state or to dispose of the intermediate layer.

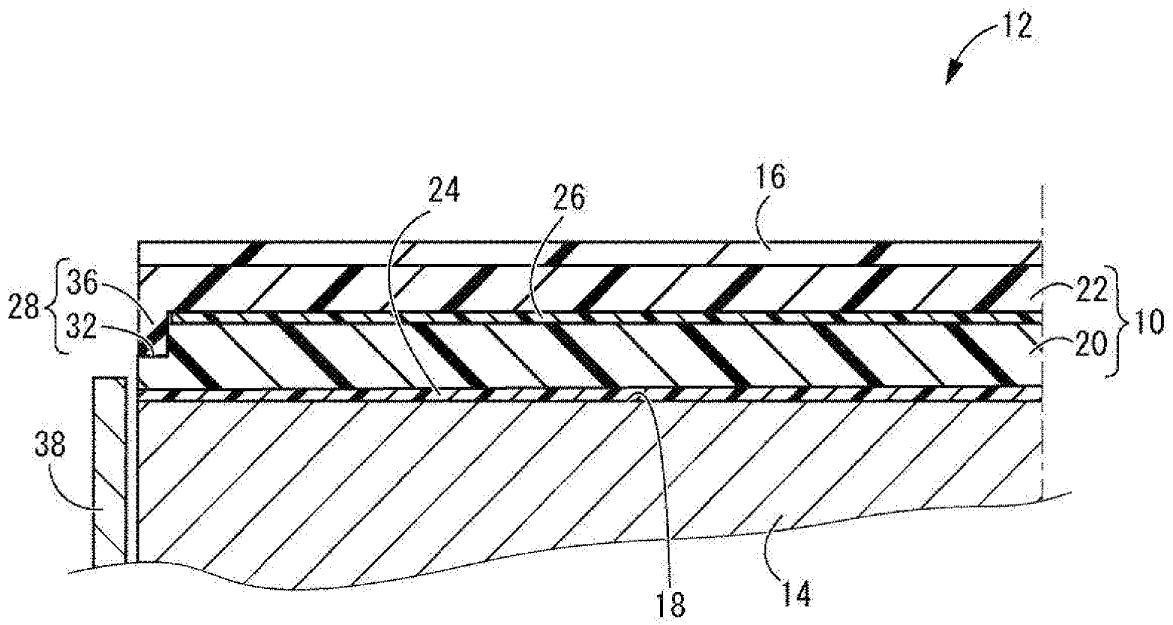
[Description of Reference Symbols]

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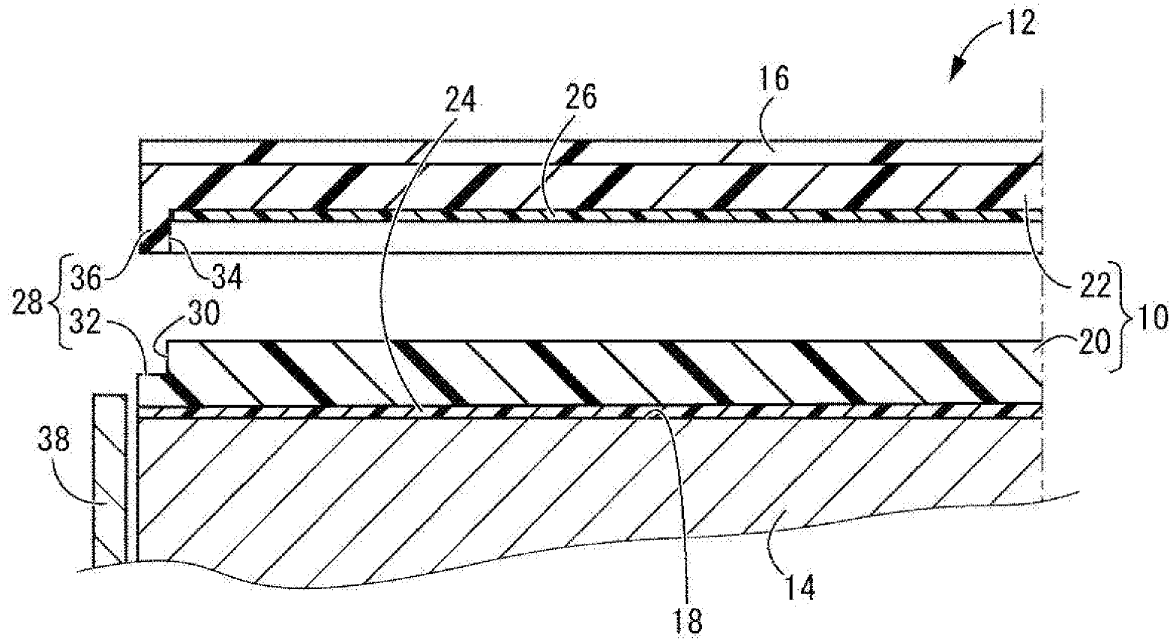
, 40, 50, 64, 74, 84: polishing pad auxiliary plate, 12, 42, 52, 66, 76: polishing device, 14: ro tating platen, 16: polishing pad, 18: upper surface, 20: lower auxiliary plate, 22: upper auxili ary plate, 24: first fixing means, 26, 62: second fixing means, 28: positioning means, 30, 58: step surface (engagement outer circumference surface), 32, 44, 60, 72, 80, 88: engagement concave portion, 34, 54: step surface (engagement inner peripheral surface), 36, 46, 56, 68, 78, 90: engagement convex portion, 38: Protective member

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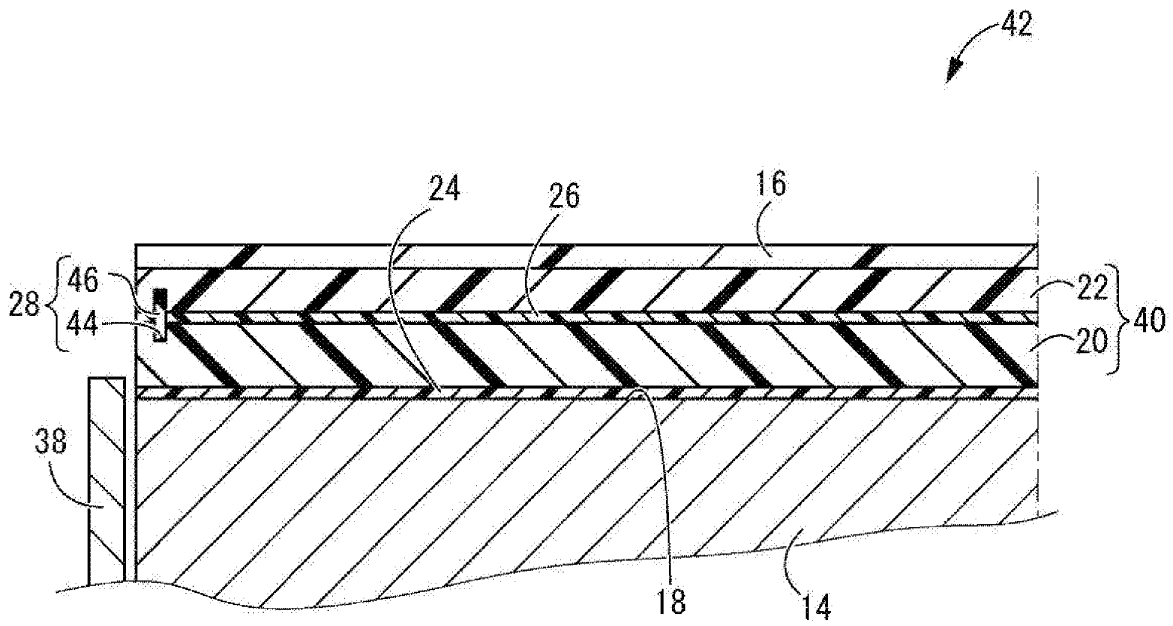
[Fig. 1]



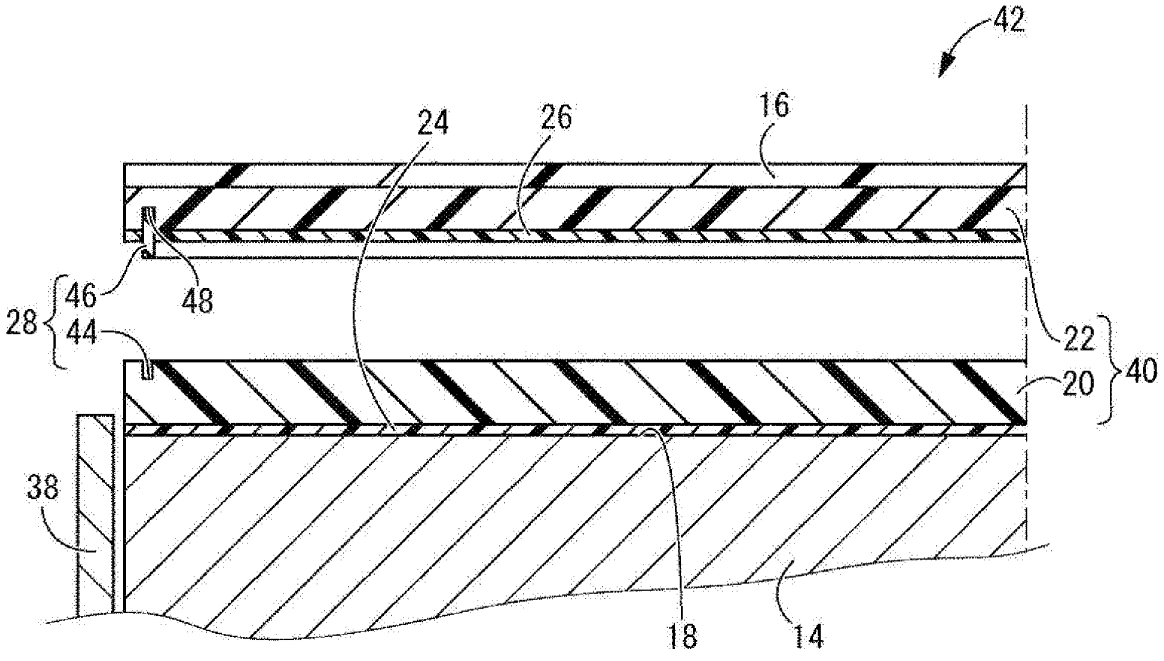
[Figure 2]



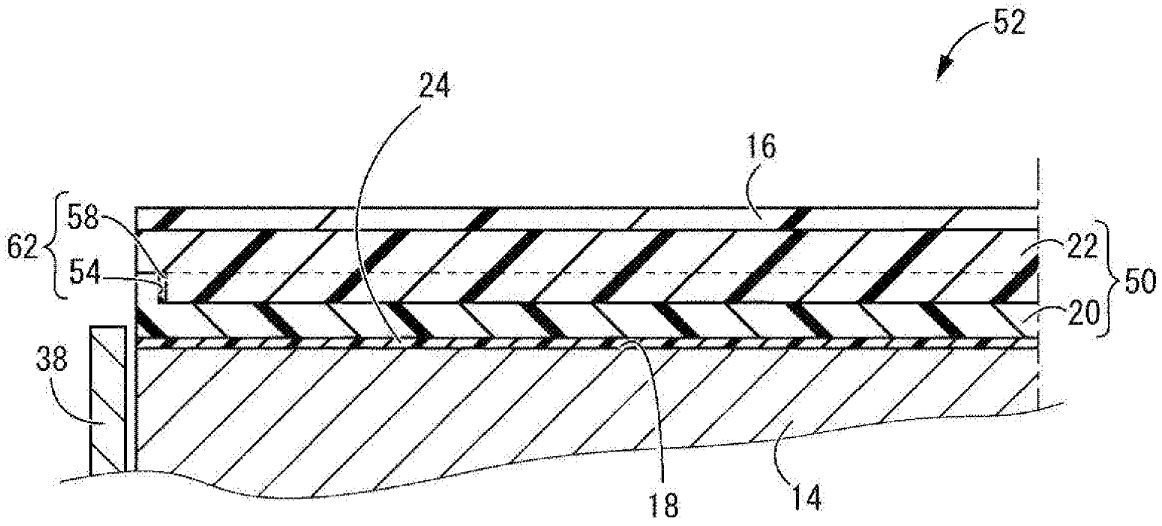
[Figure 3]



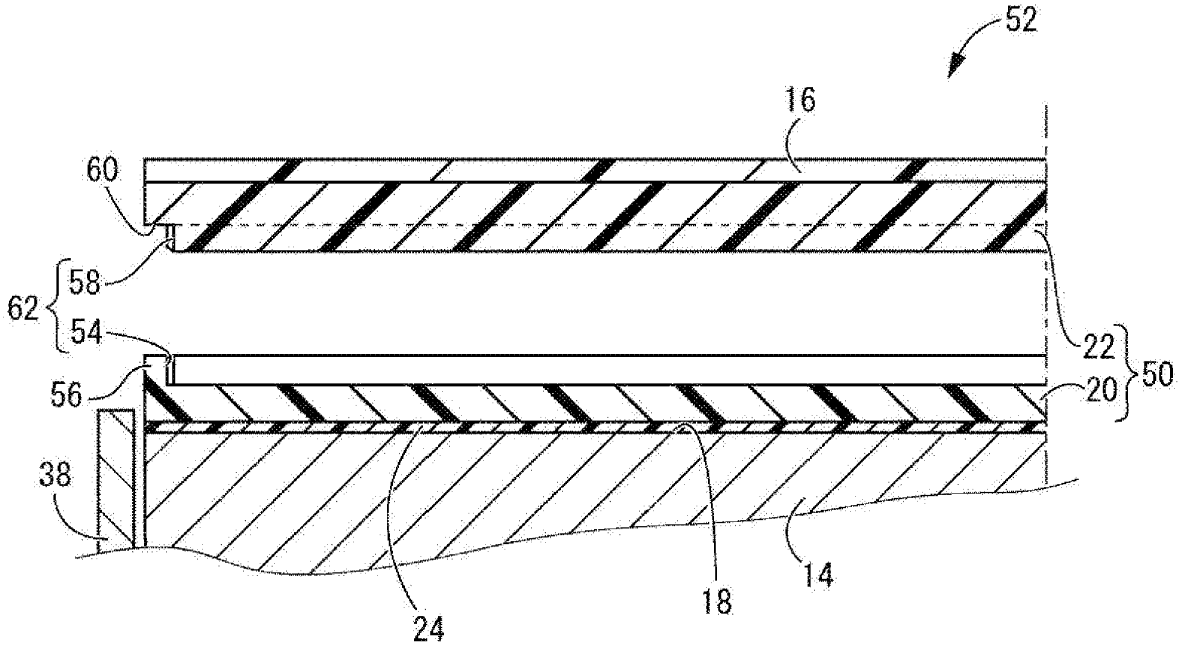
[Figure 4]



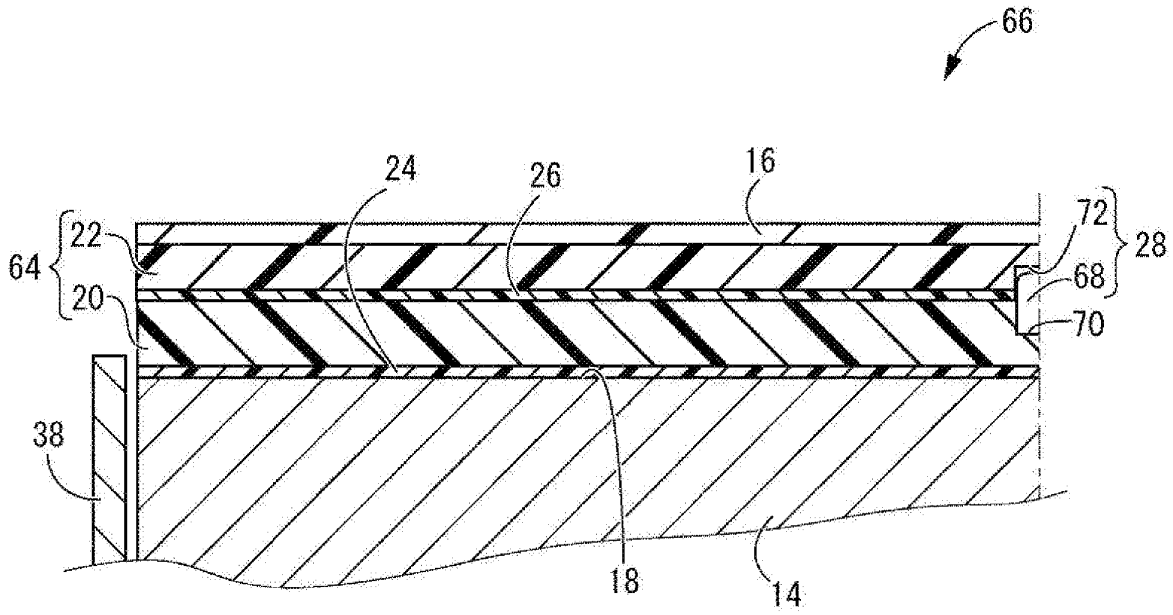
[Figure 5]


52
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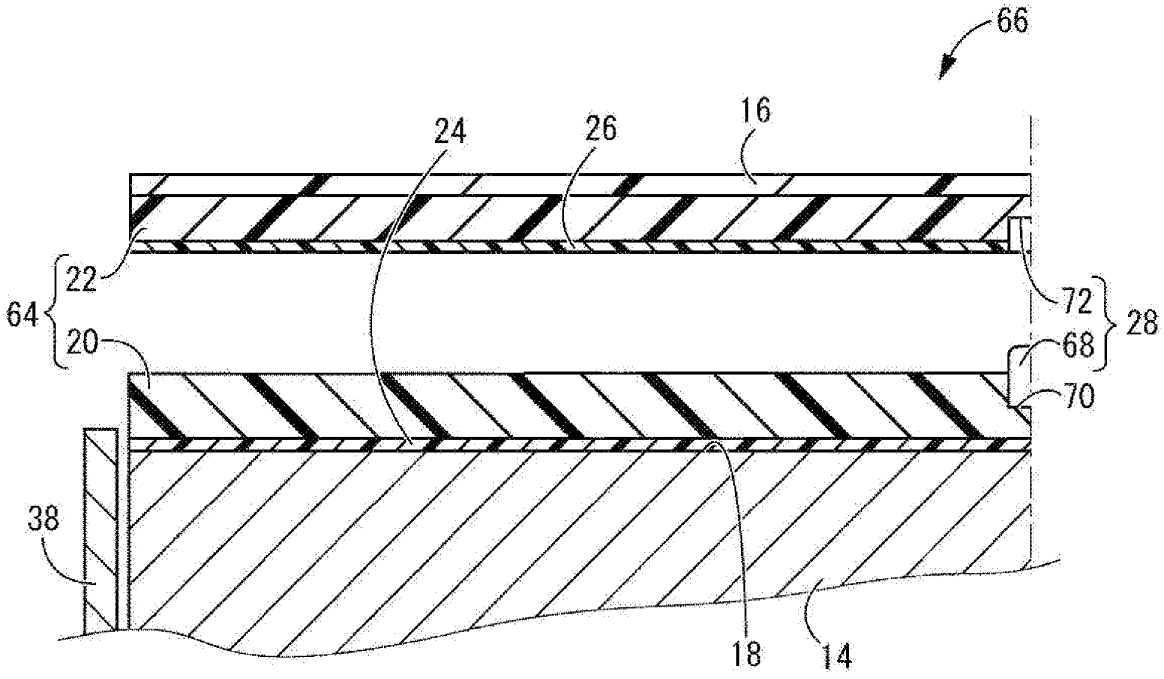
[Fig. 6]


52
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60
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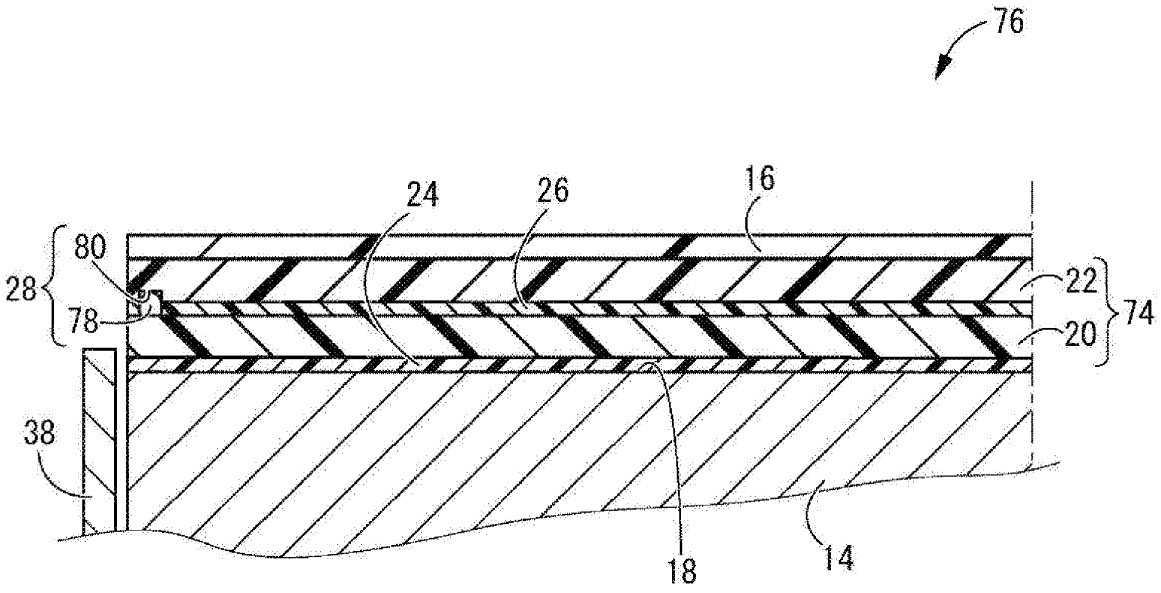
[Fig. 7]


66
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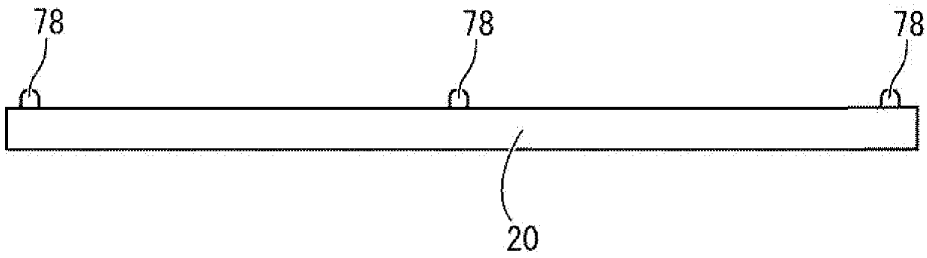
[Fig. 8]


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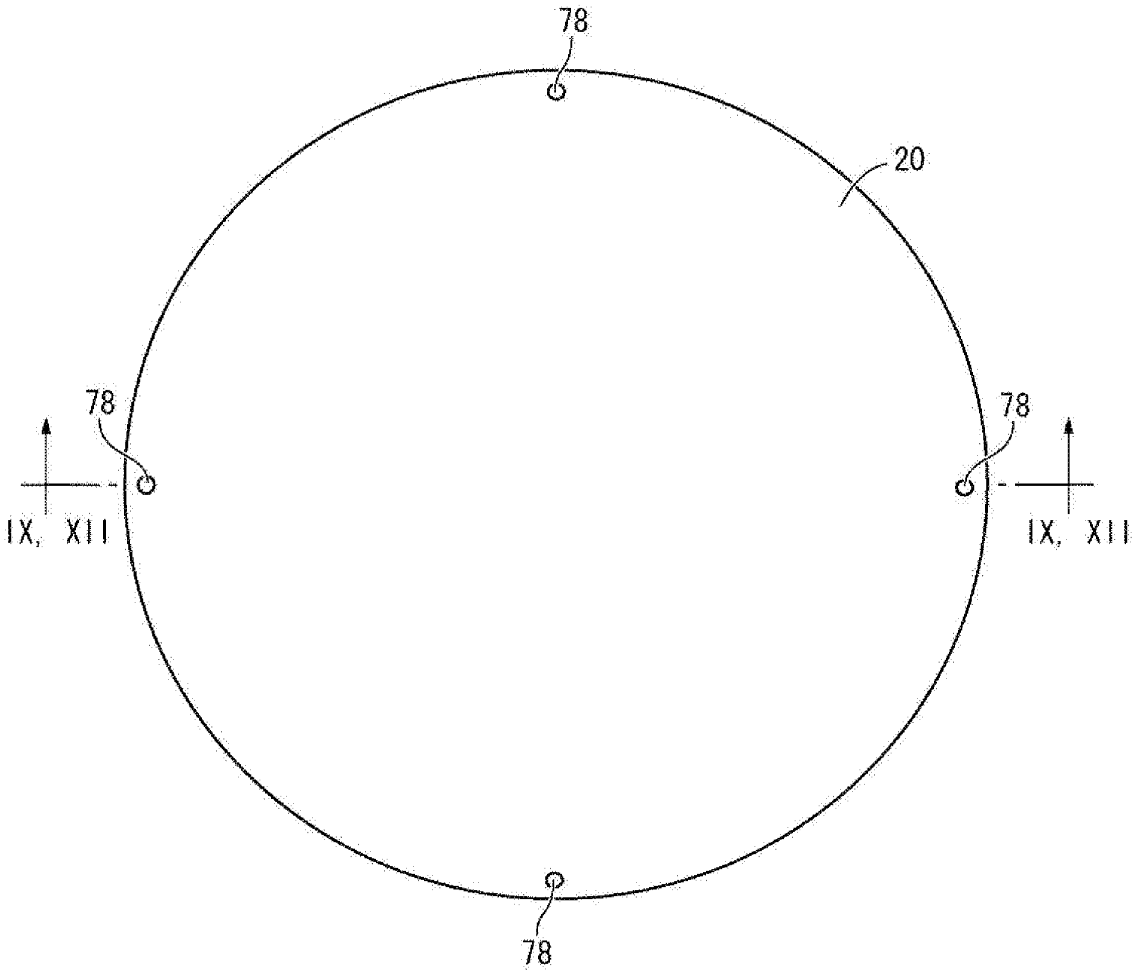
[Fig. 9]



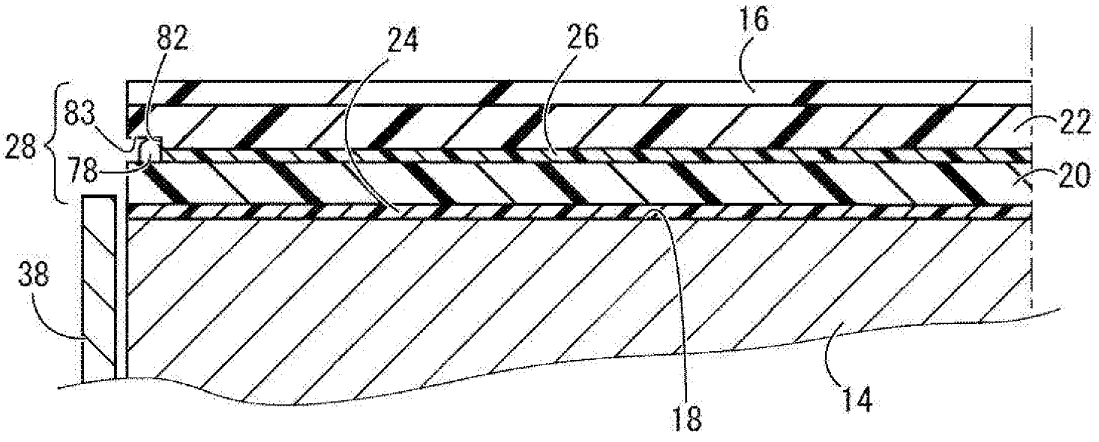
[Fig. 10]



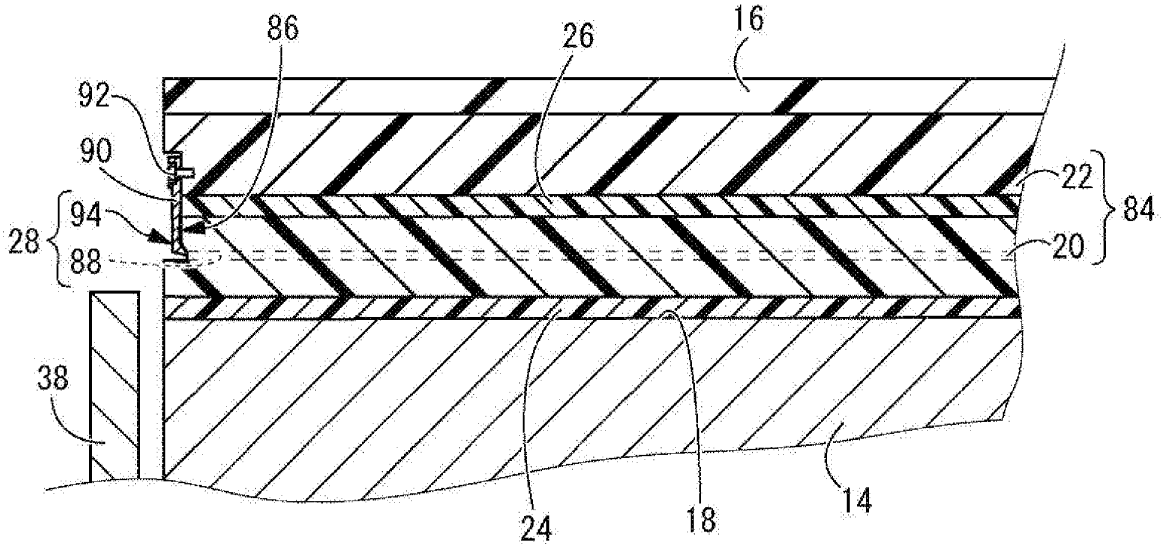
[Fig. 11]



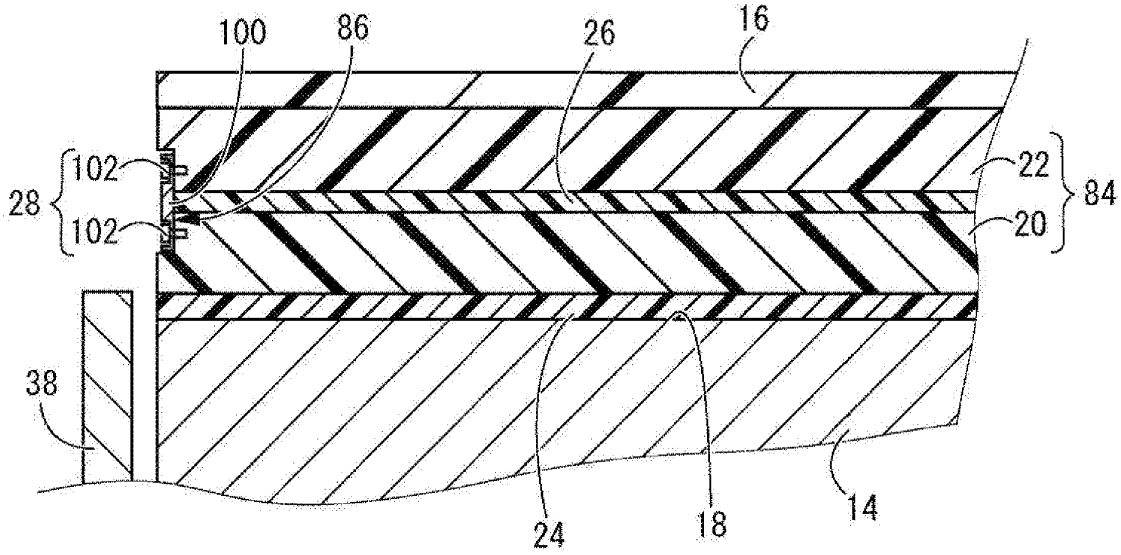
[Fig. 12]



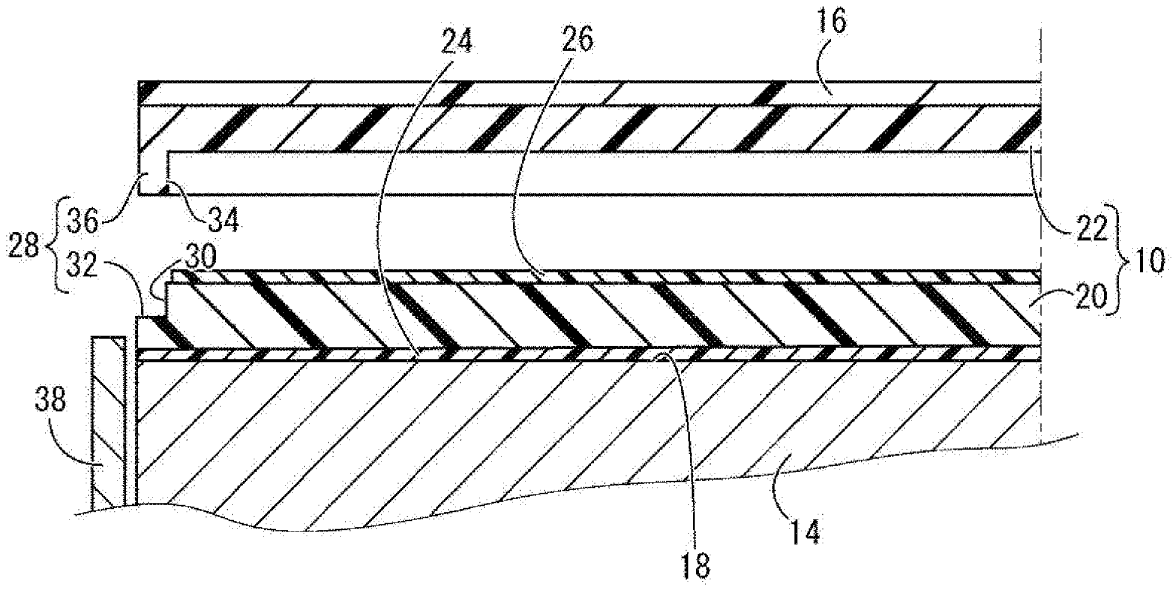
[Fig. 13]


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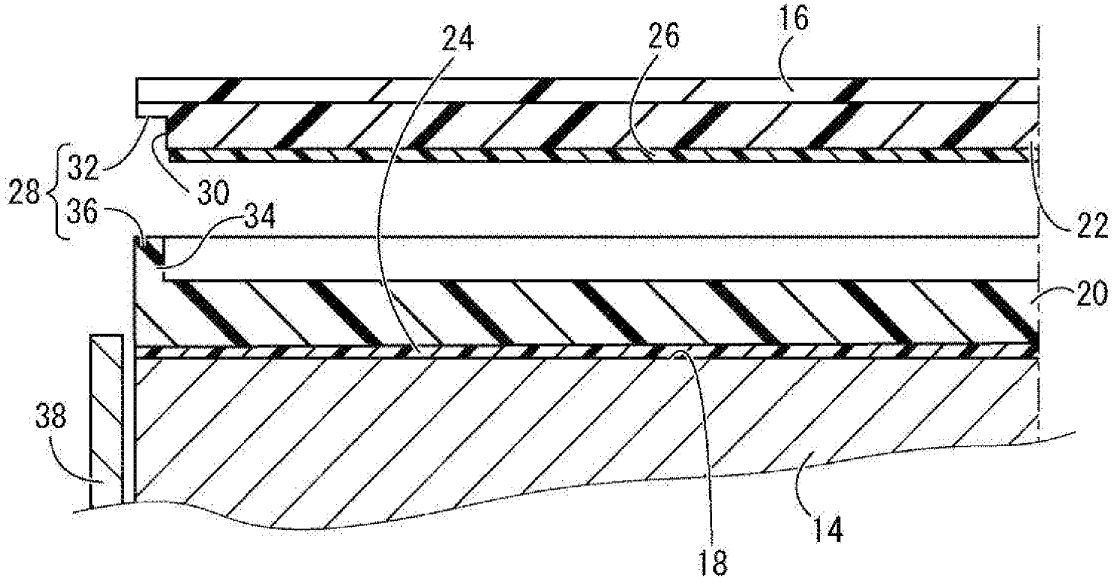
[Fig. 14]


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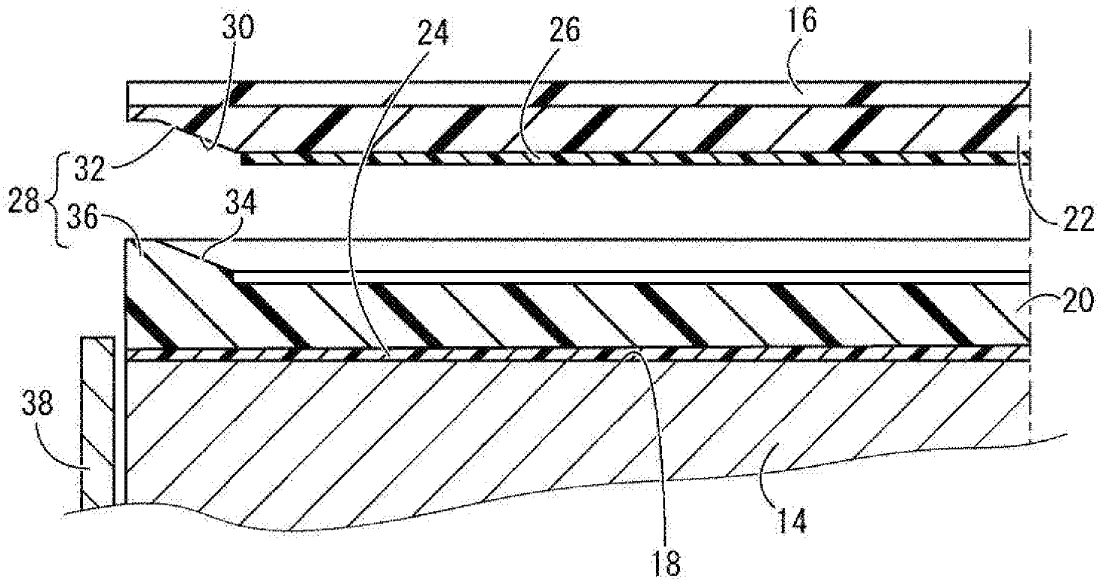
[Fig. 15]


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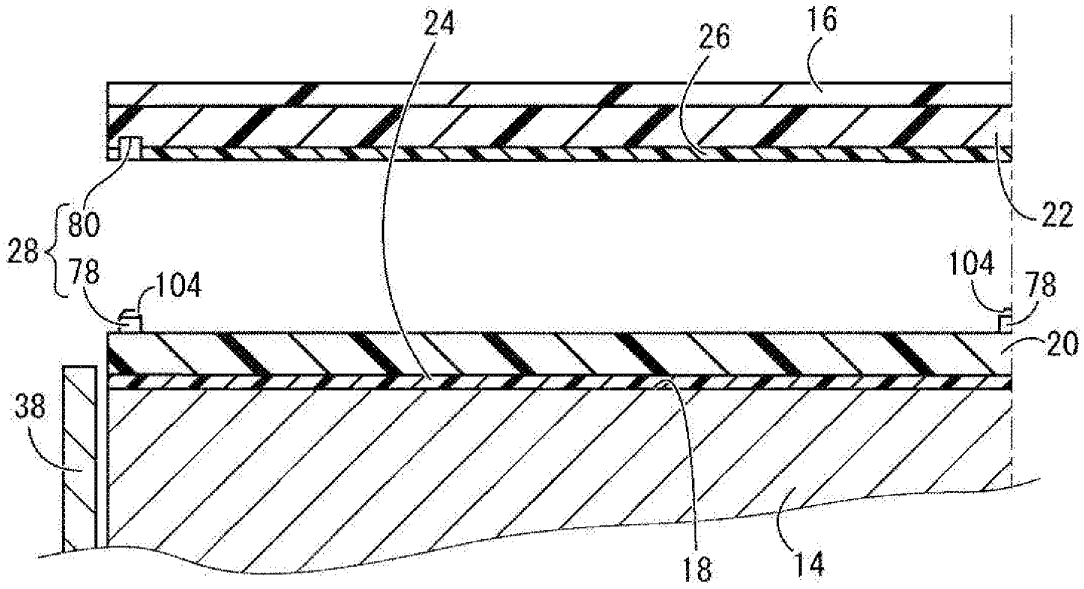
[Fig. 16]


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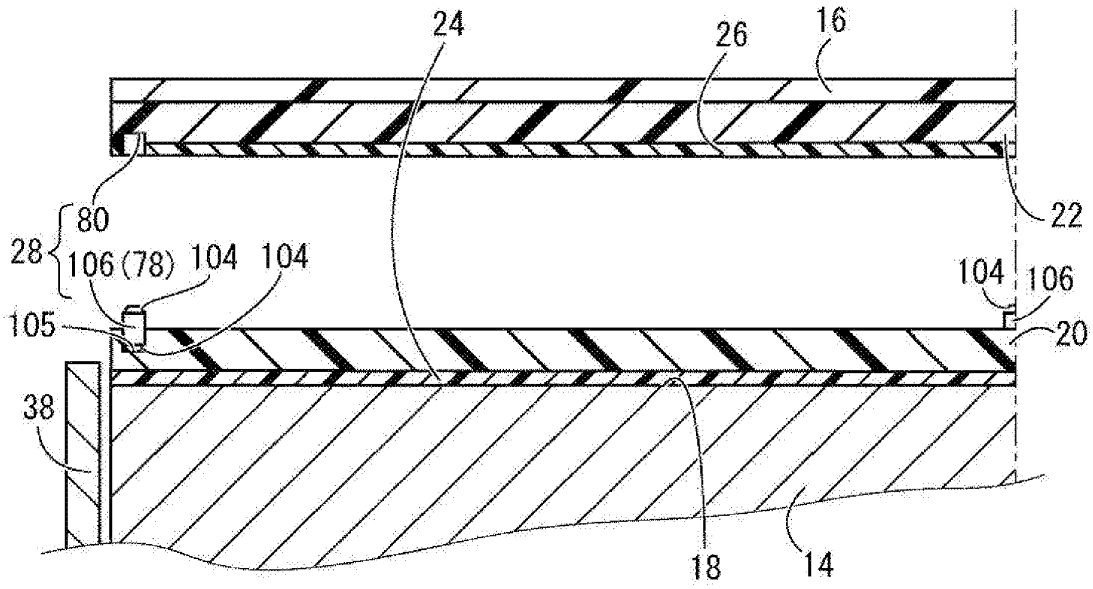
[Fig. 17]


30
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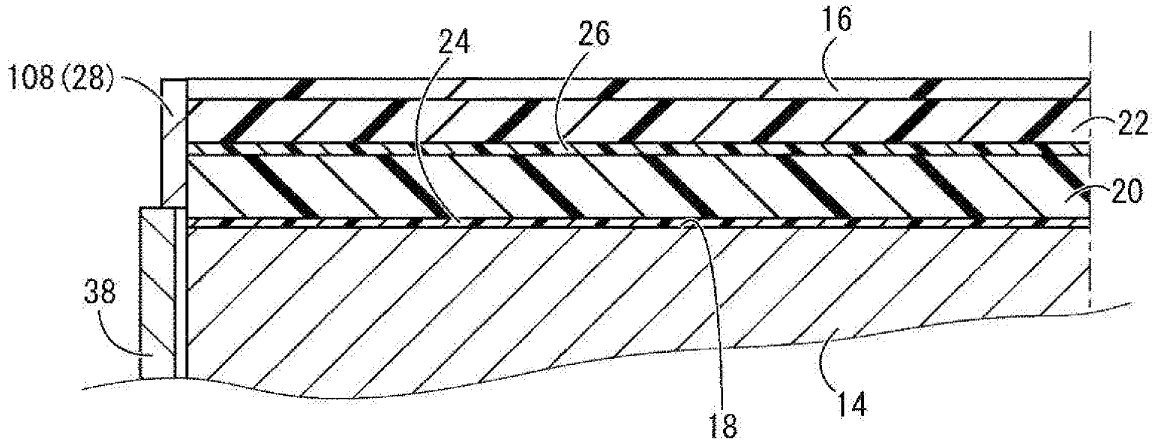
[Fig. 18]


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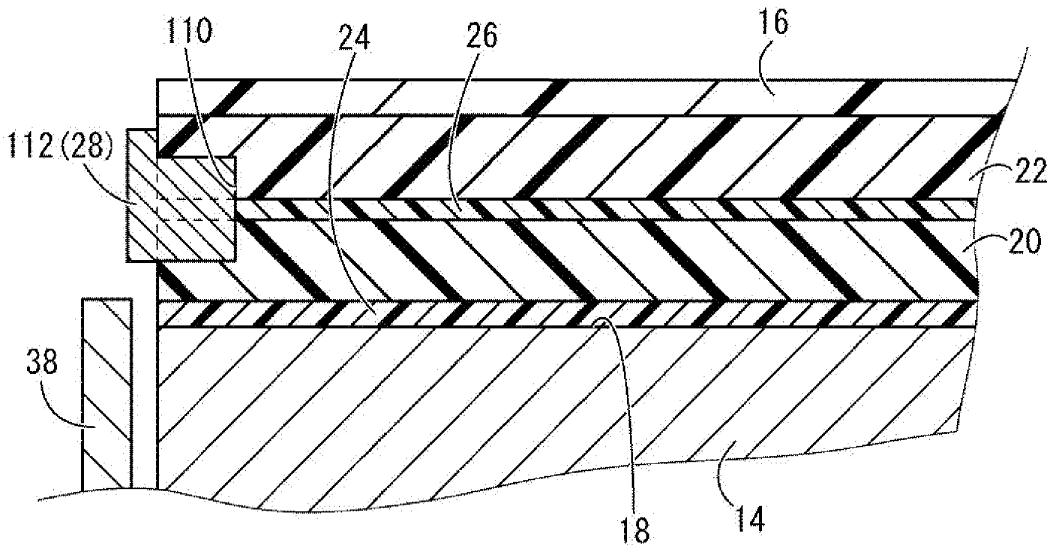
[Fig. 19]


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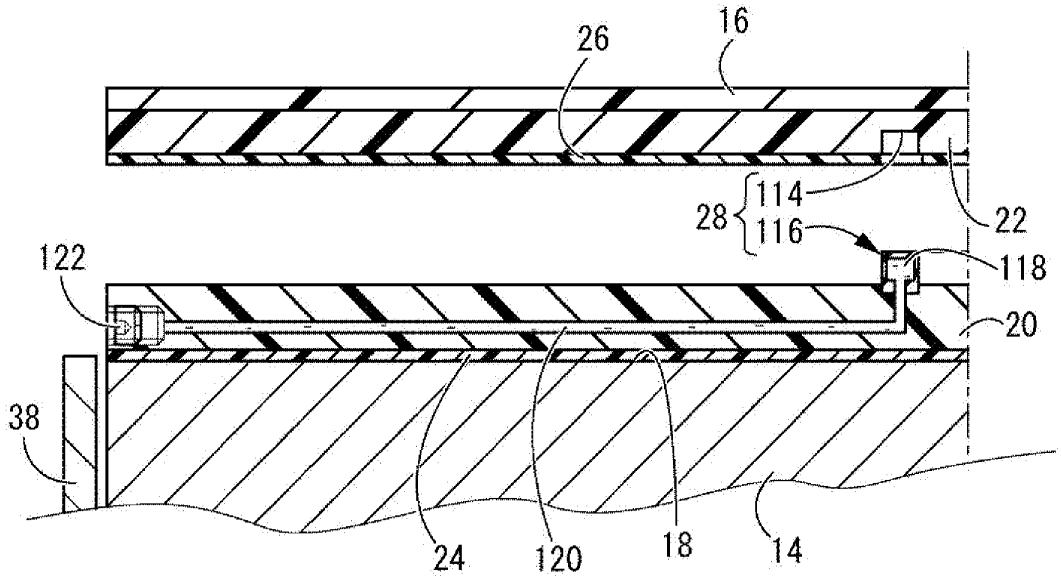
[Fig. 20]


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108 (28)
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[Fig. 21]



[Fig. 22]



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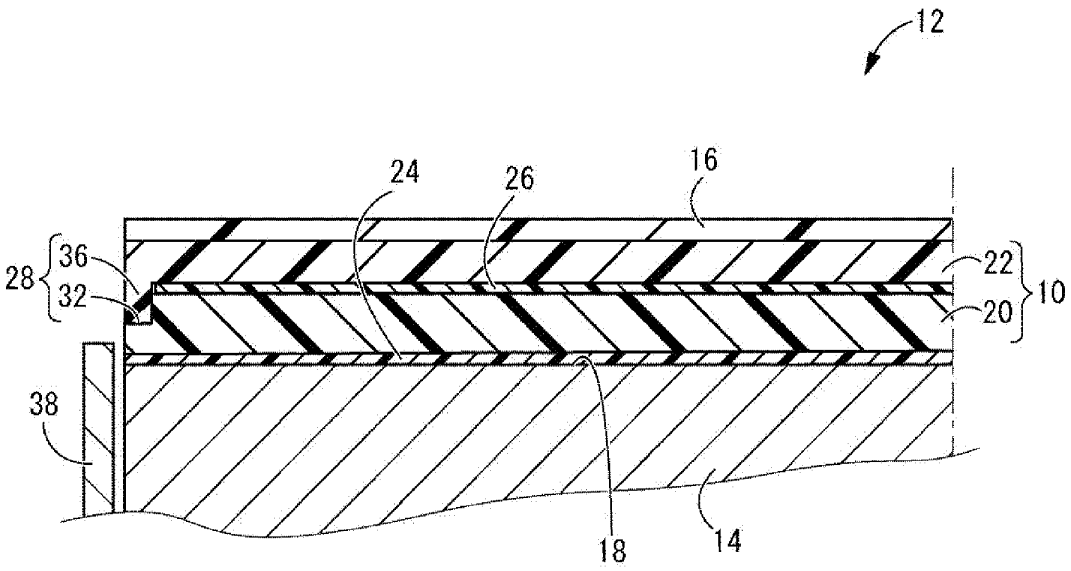


Figure 1

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最終頁に続く

(54)【発明の名称】研磨パッド用補助板および研磨パッド用補助板を備えた研磨装置

(57)【特許請求の範囲】
【請求項１】
研磨装置の回転定盤に装着されて、研磨パッドを該回転定盤に対して着脱可能に取り付ける研磨パッド用補助板において、
前記回転定盤の上面に重ね合わされて配される下側補助板と、
該下側補助板を該回転定盤に固着する第一の固着手段と、
前記研磨パッドが重ね合わされて固着されるパッド支持面を備えており、該下側補助板の上面に重ね合わされて配される上側補助板と、
該上側補助板を該下側補助板に固着する第二の固着手段と、
該下側補助板と該上側補助板とを相互に位置決めして中心軸を合わせる位置決め手段とを、有しており、前記研磨装置の前記回転定盤に対して前記下側補助板が前記第一の固着手段による固着状態に保持されて、該回転定盤に固着された該下側補助板から前記上側補助板を取り外すことにより、該上側補助板の前記パッド支持面に固着されたままの状態で前記研磨パッドを該回転定盤から取り外すことが可能とされていると共に、取り外した該上側補助板を該下側補助板に対して前記位置決め手段による位置合わせ状態で再び固着せしめて取り付けることが可能とされており、且つ、
前記第二の固着手段による前記下側補助板と前記上側補助板との固着力が、前記第一の固着手段による前記回転定盤と該下側補助板との固着力よりも小さくされていることを特徴とする研磨パッド用補助板。
【請求項２】

前記位置決め手段が、前記下側補助板および前記上側補助板の外周面よりも内周側に位置して設けられている請求項１に記載の研磨パッド用補助板。
【請求項３】
前記位置決め手段が、
前記下側補助板と前記上側補助板との一方に設けられて他方に向かって突出する係合凸部と、該下側補助板と前記上側補助板との他方に設けられて該係合凸部が係合せしめられる係合凹部とによって構成されている請求項２に記載の研磨パッド用補助板。
【請求項４】
前記係合凸部および前記係合凹部が、前記下側補助板および前記上側補助板の外周部分に位置する係合部をもって形成されている請求項３に記載の研磨パッド用補助板。
【請求項５】
前記係合凸部および前記係合凹部における前記係合部が、前記下側補助板および前記上側補助板の周方向に連続して延びて相互に嵌め合わされる環状の係合外周面および係合内周面によって構成されている請求項４に記載の研磨パッド用補助板。
【請求項６】
前記下側補助板および前記上側補助板の外周部分における周上の複数箇所において、前記下側補助板と前記上側補助板との相互の重ね合わせ面の一方において他方に向かって開口する前記係合凹部と、該下側補助板と前記上側補助板との相互の重ね合わせ面の他方において一方に向かって突出する前記係合凸部とが、互いに対応する位置に形成されており、該係合凹部に対する該係合凸部の嵌まり込みによって前記係合部が構成されている請求項４に記載の研磨パッド用補助板。
【請求項７】
前記下側補助板と前記上側補助板との一方の外周部分における周上の複数箇所から他方に向かって突出する前記係合凸部が弾性材によって形成されており、該下側補助板と前記上側補助板との他方における外周面に開口して設けられた前記係合凹部に対して該係合凸部の先端が係合されることにより前記係合部が構成されている請求項４に記載の研磨パッド用補助板。
【請求項８】
前記係合凸部および前記係合凹部が、前記下側補助板および前記上側補助板の中心軸上に設けられている請求項３に記載の研磨パッド用補助板。
【請求項９】
前記係合凸部の外周面と前記係合凹部の内周面とにおいて互いに螺合するねじ溝が形成されており、前記位置決め手段を構成する該係合凸部と該係合凹部との螺合により前記第二の固着手段が構成されている請求項８に記載の研磨パッド用補助板。
【請求項１０】
前記下側補助板と前記上側補助板との一方に設けられた前記係合凸部が、該下側補助板と該上側補助板との一方と同じ材質で形成されている請求項３，４，５，６，８，９の何れか１項に記載の研磨パッド用補助板。
【請求項１１】
請求項１～１０の何れか１項に記載の研磨パッド用補助板が回転定盤の上面に装着されると共に、該回転定盤の外周側に隙間を隔てて保護部材が配設されており、該回転定盤および該研磨パッド用補助板の外周端面よりも内周側に位置して、前記位置決め手段が設けられていることを特徴とする請求項１～１０の何れか１項に記載の研磨パッド用補助板を備えた研磨装置。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は、シリコンウエハや半導体基板、ガラス基板等のような高い平坦加工精度が要求される被加工物である基板を対象とする研磨に関連する技術に係り、特に、かかる基板の表面を研磨する際に用いられる研磨パッドの再使用を実現可能とする技術に関するもの

である。

【背景技術】

【０００２】

良く知られているように、半導体の製造に際しては、構成材となるシリコンウエハや半導体基板、ガラス基板等の基板の表面を平坦化する研磨処理が行われている。かかる研磨処理は、一般に、樹脂材等からなる円板形状の研磨パッドを研磨装置の回転定盤の上に両面テープで直接固定し、砥粒を含んだ研磨液を供給しつつ、研磨パッドと基板を相対的に回転運動させて研磨を行うことによって実施されている。

【０００３】

そして、このような研磨処理を実施するための研磨パッドとしては、特開２００２－１１６３０号公報（特許文献１）等に記載されているように、発泡又は無発泡のウレタン等からなる樹脂パッドが採用されている。また、かかる研磨パッドの研磨表面には、多くの場合、同心円状や格子状、放射状等の溝加工が施されたり、発泡樹脂の気泡が開口される等している。

【０００４】

ところで、研磨パッドを用いた研磨加工を行う場合には、研磨対象である基板の品種切り替え等に際して、研磨加工に使用する研磨パッドを回転定盤から引き剥がして別の研磨パッドに交換しなければならない場合がある。また、例えば、研磨加工に伴って劣化した研磨パッドを、その再使用等を目的として、別の加工装置で表面溝入れ等の再加工するような場合等においても、研磨パッドを回転定盤から引き剥がすことが必要となる。

【０００５】

ところが、薄肉円板形状の研磨パッドは、研磨装置の回転定盤に対して粘着テープで強固に固着されていることから、この研磨パッドを回転定盤から引き剥がす際に、研磨パッドに対して曲がりや折れ、シワ、破れ等の損傷が発生し易い。それ故このような損傷が原因で、かかる研磨パッドを、寿命がきていないにもかかわらず、再使用できずに廃棄せざるを得なくなることが多いという問題があった。

【０００６】

しかも、損傷しないように細心の注意を払いつつ研磨パッドを回転定盤から引き剥がす作業は、熟練と注意を要することから作業者に大きな負担をかけるという問題もあった。加えて、研磨パッドを回転定盤から引き剥がす作業に相当の時間が必要となることから、高価で貴重な設備である研磨装置を長時間に亘って停止させなければならず、設備の稼働時間が制限されてしまうという問題もあった。

【０００７】

そこで、本発明者は、先に特開２０１０－２１４５７９号公報（特許文献２）において、研磨パッドの裏面に補助板を取り付け、この補助板を介して、研磨パッドを研磨装置の回転定盤に対して両面テープ等で固着するようにした補助板付き研磨パッドを提案した。かかる補助板付き研磨パッドでは、研磨パッドが補助板で支持されたままの状態を保ちつつ回転定盤に対して着脱されることから、着脱に際しての研磨パッドの損傷が補助板で補強される。それ故、研磨パッドの損傷を防止しつつ、回転定盤に対して研磨パッドを良好な作業性をもって着脱することが可能となる。

【０００８】

ところが、本発明者が更なる研究と検討を重ねたところ、特許文献２で提案した補助板付き研磨パッドでは、必ずしも全ての研磨装置への対応が容易であると言い難いことがわかった。

【０００９】

すなわち、研磨パッドを回転定盤に重ね合わせて固着する際には、研磨パッドの中心を回転定盤の回転中心に位置合わせする必要があり、特に研磨表面に溝等が施された研磨パッドでは中心位置合わせに精度が要求される。そして、上述の如き補助板を採用することで回転定盤に対する研磨パッドの着脱回数が増加すると、より一層、研磨パッドを回転定盤に装着する際の中心位置合わせの作業が難しくて労力負担が大きいということが大きな

問題となるのである。

【００１０】

また、特許文献２で提案した補助板付き研磨パッドでは、補助板を回転定盤に対して中心位置合わせしつつ着脱可能に取り付けるために、補助板と回転定盤との間において、例えば回転定盤の外周面上に外周リングなどの固着手段が設けられる場合がある。一方、研磨装置のなかには、回転定盤の外周側に保護カバー等が装着されて、回転定盤の外周側のスペースが非常に狭くなっているものもある。それ故、仮に、そのような外周リングを採用しようとした場合に、たまたま回転定盤の外周側のスペースが狭い研磨装置を用いる際には、研磨装置の改造などが必要となるおそれもあったのである。

【先行技術文献】

【特許文献】

【００１１】

【特許文献１】特開２００２－１１６３０号公報

【特許文献２】特開２０１０－２１４５７９号公報

【発明の概要】

【発明が解決しようとする課題】

【００１２】

本発明は上述の如き事情を背景として為されたものであり、回転定盤に対する研磨パッドの固着力を充分に確保しつつ、回転定盤に対する研磨パッドの着脱を容易に行うことを可能と為し、特に回転定盤から研磨パッドを取り外すに際しての研磨パッドの損傷を防止することが出来て、例えば研磨パッドの再利用の実現にも有利とされ得る、新規な構造の研磨パッド用補助板を提供することにある。

【００１３】

それに加えて、本発明は、研磨パッドを回転定盤に装着する際の中心合わせの作業を容易に且つ精度良く行うことが出来て、労力負担も軽減され得ると共に、従来の各種仕様の研磨装置における回転定盤にも特別な改造を必要とすることなく容易に且つ有利に適用され得る、改良された構造の研磨パッド用補助板を提供することも、目的とする。

【００１４】

さらに、本発明は、かかる新規な構造とされた研磨パッド用補助板を備えた研磨装置を提供することも、目的とする。

【課題を解決するための手段】

【００１５】

かかる課題を解決するために、研磨パッド用補助板に関する本発明の第一の態様は、（Ａ）研磨装置の回転定盤に装着されて、研磨パッドを該回転定盤に対して着脱可能に取り付ける研磨パッド用補助板において、（Ｂ）前記回転定盤の上面に重ね合わされて配される下側補助板と、（Ｃ）該下側補助板を該回転定盤に固着する第一の固着手段と、（Ｄ）前記研磨パッドが重ね合わされて固着されるパッド支持面を備えており、該下側補助板の上面に重ね合わされて配される上側補助板と、（Ｅ）該上側補助板を該下側補助板に固着する第二の固着手段と、（Ｆ）該下側補助板と該上側補助板とを相互に位置決めして中心軸を合わせる位置決め手段とを、有しており、前記研磨装置の前記回転定盤に対して前記下側補助板が前記第一の固着手段による固着状態に保持されて、該回転定盤に固着された該下側補助板から前記上側補助板を取り外すことにより、該上側補助板の前記パッド支持面に固着されたままの状態で前記研磨パッドを該回転定盤から取り外すことが可能とされていると共に、取り外した該上側補助板を該下側補助板に対して前記位置決め手段による位置合わせ状態で再び固着せしめて取り付けることが可能とされており、且つ、前記第二の固着手段による前記下側補助板と前記上側補助板との固着力が、前記第一の固着手段による前記回転定盤と該下側補助板との固着力よりも小さくされている研磨パッド用補助板を特徴とする。

【００１６】

本発明に従う構造とされた研磨パッド用補助板では、研磨パッドを、上側補助板および

下側補助板を介して、回転定盤に固着して装着することとなる。これにより、下側補助板を回転定盤に固着したまま、下側補助板から上側補助板を取り外すことが出来、研磨パッドを上側補助板に固着されたままの状態で回転定盤から取り外すことが可能となる。

【００１７】

それ故、研磨パッドが上側補助板で補強および保護された状態で、研磨パッドの損傷を防止しつつ、研磨パッドを回転定盤から取り外すことが出来、薄肉の研磨パッドの取り扱いも容易となる。そして、例えば研磨対象物や研磨条件の変更等に際して研磨パッドの着脱を繰り返す際や、磨耗した研磨パッドを取り外して再生処理後に再装着する際などにおいて、回転定盤への研磨パッドの着脱や研磨パッドに対する再生処理等の作業を容易に行うことも可能となる。

【００１８】

しかも、回転定盤に固着されたままの下側補助板と、研磨パッドと共に取り外される上側補助板とが、位置決め手段により相互に中心軸合わせされることから、回転定盤への位置合わせが必要となる研磨パッドの着脱作業を一層容易に行うことができる。特に、かかる位置決め手段が、下側補助板と上側補助板との間に設けられていることから、回転定盤に対して特別な加工等を施す必要がない。また、かかる位置決め手段が、回転定盤よりも外周側に大きく突出することが回避され得、例えば回転定盤の外周側に保護カバー等が設けられている研磨装置などにも、特別な改造を施すことなく適用可能とされる。

【００１９】

上記本発明の第一の態様に係る研磨パッド用補助板においては、前記第二の固着手段による前記下側補助板と前記上側補助板との固着力が、前記第一の固着手段による前記回転定盤と該下側補助板との固着力よりも小さくされている態様が、採用されている。

【００２０】

このような第一の態様に従えば、第一及び第二の固着手段における固着力を相互に調整して設定したことにより、研磨パッドが固着されたままの上側補助板を、回転定盤に固着されたままの下側補助板から取り外す作業が一層容易となる。要するに、下側補助板を回転定盤に対して固着状態に保つための特別な操作等を必要とすることなく、下側補助板を回転定盤への固着状態に残しつつ研磨パッドを上側補助板に固着されたままの状態で回転定盤から容易に取り外すことが可能になる。

【００２１】

本発明の第二の態様は、前記第一の態様に係る研磨パッド用補助板において、前記位置決め手段が、前記下側補助板および前記上側補助板の外周面よりも内周側に位置して設けられているものである。

【００２２】

本態様の研磨パッド用補助板では　位置決め手段における上下補助板の外周側への突出が完全に回避される。それ故、例えば上下補助板の外径寸法を回転定盤の外径寸法と同じか僅かに小さく設定して装着する場合でも、研磨パッドの支持面を十分に大きく確保しつつ、回転定盤から外周側に位置決め手段が突出することを回避することが出来、回転定盤の外周側に保護カバー等が設置されていても、本発明に係る研磨パッド用補助板の適用に際して障害となることが回避される。

【００２３】

本発明の第三の態様は、前記第二の態様に係る研磨パッド用補助板において、前記位置決め手段が、前記下側補助板と前記上側補助板との一方に設けられて他方に向かって突出する係合凸部と、該下側補助板と前記上側補助板との他方に設けられて該係合凸部が係合せしめられる係合凹部とによって構成されているものである。

【００２４】

本態様の研磨パッド用補助板では、係合凸部と係合凹部との相互係合作用に基づいて、機械的に大きな位置決め力を容易に得ることが可能となる。また、係合凸部や係合凹部の形状や大きさ、数などを調節することにより、位置決め作用の方向や作用力を大きな自由度で容易に設定することも可能となる。

【００２５】
本発明の第四の態様は、前記第三の態様に係る研磨パッド用補助板において、前記係合凸部および前記係合凹部が、前記下側補助板および前記上側補助板の外周部分に位置する係合部をもって形成されているものである。
【００２６】
本態様の研磨パッド用補助板では、研磨パッド用補助板の中央から離れた外周部分に位置して、相互に凹凸嵌合せしめられる係合凸部の係合外周面と係合凹部の係合内周面とを形成することにより、上下補助板の相対的な位置決め精度、特に径方向の位置決め精度の向上が図られ得る。なお、後述の第六及び第七の態様にも示されているように、係合凸部の係合外周面および係合凹部の係合内周面は、研磨パッド用補助板の中心周りで研磨パッド用補助板の外周縁部に沿って周方向に延びる形態であっても良いし、研磨パッド用補助板の外周部分に形成された係合凸部と係合凹部のように周上で部分的に位置する形態であっても良い。
【００２７】
本発明の第五の態様は、前記第四の態様に係る研磨パッド用補助板において、前記係合凸部および前記係合凹部における前記係合部が、前記下側補助板および前記上側補助板の周方向に連続して延びて相互に嵌め合わされる環状の係合外周面および係合内周面によって構成されているものである。
【００２８】
本態様の研磨パッド用補助板において、より好適には、研磨パッド用補助板の中心軸回りに広がる環状の係合内外周面をもって係合凹部と係合凸部が形成されることとなり、それによって、上側補助板の下側補助板への装着時に周方向での相互の位置合わせが必要なくなり、容易且つ速やかに作業することが可能となる。
【００２９】
本発明の第六の態様は、前記第四の態様に係る研磨パッド用補助板であって、前記下側補助板および前記上側補助板の外周部分における周上の複数箇所において、前記下側補助板と前記上側補助板との相互の重ね合わせ面の一方において他方に向かって開口する前記係合凹部と、該下側補助板と前記上側補助板との相互の重ね合わせ面の他方において一方に向かって突出する前記係合凸部とが、互いに対応する位置に形成されており、該係合凹部に対する該係合凸部の嵌まり込みによって前記係合部が構成されているものである。
【００３０】
本態様の研磨パッド用補助板では、上下補助板の相互の位置合わせを軸直角方向だけでなく中心軸回りの周方向でも容易に実現することが可能となる。
【００３１】
本発明の第七の態様は、前記第四の態様に係る研磨パッド用補助板において、前記下側補助板と前記上側補助板との一方の外周部分における周上の複数箇所から他方に向かって突出する前記係合凸部が弾性材によって形成されており、該下側補助板と前記上側補助板との他方における外周面に開口して設けられた前記係合凹部に対して該係合凸部の先端が係合されることにより前記係合部が構成されているものである。
【００３２】
本態様の研磨パッド用補助板では、上下補助板の外周面上に係合部を露出させて形成することが可能であり、それによって係合部の係合状態を目視等で容易に確認することが可能となる。また、本態様では、係合凸部の弾性を利用して係合部における係合状態が安定して保たれ得る。
【００３３】
本発明の第八の態様は、前記第三の態様に係る研磨パッド用補助板において、前記係合凸部および前記係合凹部が、前記下側補助板および前記上側補助板の中心軸上に設けられているものである。
【００３４】
本態様の研磨パッド用補助板では、上下補助板の中心軸上に係合凸部および係合凹部を

設けたことにより、一つの係合部によって上下補助板の中心軸合わせを行うことが可能になる。また、中心軸上に設けられた係合凸部と係合凹部の相互の位置合わせに際しては、上下補助板の周方向での相互の位置合わせが必要なく、それら係合凸部と係合凹部を容易に係合状態とすることも可能になる。

【００３５】

本発明の第九の態様は、前記第八の態様に係る研磨パッド用補助板において、前記係合凸部の外周面と前記係合凹部の内周面とにおいて互いに螺合するねじ溝が形成されており、前記位置決め手段を構成する該係合凸部と該係合凹部との螺合により前記第二の固着手段が構成されているものである。

【００３６】

本態様の研磨パッド用補助板では、位置決め手段により、上側補助板と下側補助板との固着力を得ることができる。それ故、かかる位置決め手段のみによって第二の固着手段を構成したり、第二の固着手段による上下補助板間の固着力を位置決め手段で補助的に構成することも可能となる。

【００３７】

本発明の第十の態様は、前記第三，四，五，六，八，九の何れかの態様に係る研磨パッド用補助板において、前記下側補助板と前記上側補助板との一方に設けられた前記係合凸部が、該下側補助板と該上側補助板との一方と同じ材質で形成されているものである。

【００３８】

本態様の研磨パッド用補助板では、上下で重ね合わされた補助板における研磨パッドの支持特性が、係合凸部の形成部分で局所的に大きく異なることを防止することが可能となる。それ故、パッド研磨加工に際して押圧力が研磨パッド表面に作用した際、かかる研磨パッドを支持している上下補助板における係合凸部や係合凹部の形成部位において、押圧反力や研磨パッド弾性などの特性が局部的に異なることに起因する研磨精度などの不具合を軽減乃至は回避することが可能になる。

【００３９】

さらに、本発明は、前記第一～十の何れかの態様に記載の本発明に係る研磨パッド用補助板が回転定盤の上面に装着されると共に、該回転定盤の外周側に隙間を隔てて保護部材が配設されており、該回転定盤および該研磨パッド用補助板の外周端面よりも内周側に位置して、前記位置決め手段が設けられている研磨装置も、特徴とする。

【発明の効果】

【００４０】

本発明に従う構造とされた研磨パッド用補助板を採用し、または本発明に従う構造とされた研磨装置を用いることによって、研磨パッドの損傷を防止しつつ、研磨パッドを回転定盤から容易に取り外したり装着したりすることが可能となるのであり、研磨パッドの装着に際しての回転定盤への位置合わせも容易に且つ精度良く行うことが可能となる。

【図面の簡単な説明】

【００４１】

【図１】本発明の第一の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。

【図２】図１に示された研磨装置において研磨パッドを取り外した状態を示す縦断面の説明図。

【図３】本発明の第二の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。

【図４】図３に示された研磨装置において研磨パッドを取り外した状態を示す縦断面の説明図。

【図５】本発明の第三の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。

【図６】図５に示された研磨装置において研磨パッドを取り外した状態を示す縦断面の説明図。

【図７】本発明の第四の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。
【図８】図７に示された研磨装置において研磨パッドを取り外した状態を示す縦断面の説明図。
【図９】本発明の第五の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。
【図１０】図９に示された研磨パッド用補助板を構成する下側補助板の側面図。
【図１１】図１０に示された下側補助板の平面図。
【図１２】本発明の第六の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。
【図１３】本発明の第七の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。
【図１４】本発明の第八の実施形態としての研磨パッド用補助板を装着した研磨装置の要部を示す縦断面図。
【図１５】本発明の第九の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【図１６】本発明の第十の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【図１７】本発明の第十一の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【図１８】本発明の第十二の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【図１９】本発明の第十三の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【図２０】本発明の第十四の実施形態としての研磨パッド用補助板を位置決めした状態を示す縦断面の説明図。
【図２１】本発明の第十五の実施形態としての研磨パッド用補助板を位置決めした状態を示す縦断面の説明図。
【図２２】本発明の第十六の実施形態としての研磨パッド用補助板を取り外した状態を示す縦断面の説明図。
【発明を実施するための形態】
【００４２】
以下、本発明の実施形態について、図面を参照しつつ説明する。先ず、図１～２には、本発明の第一の実施形態としての研磨パッド用補助板１０が示されている。この研磨パッド用補助板１０は、研磨装置１２の回転定盤１４に装着されて用いられ、回転定盤１４に対して研磨パッド１６を着脱可能に取り付けるようになっている。
【００４３】
研磨装置は、例えば特開２０１０－１４１１５５号公報等に記載されているように例えばＣＭＰ装置として用いられるものであって、基本構造は周知であるが要部を説明すると、先ず基礎ベース上に固定設置された装置本体によって鉛直方向に延びる回転軸が回転可能に支持されており、この回転軸の上端部に円盤形状の回転定盤１４が固設されている。かかる回転定盤１４は、水平方向に広がる平坦な上面１８を有しており、この上面１８が研磨パッド１６の支持面とされている。また、回転軸には、電気モータの回転出力軸が連結されており、電気モータの駆動力が伝達されることで回転軸ひいては回転定盤１４が中心軸回りに回転駆動されるようになっている。なお、研磨パッド１６を支持する上面１８の上方には、研磨用スラリを供給するノズルが配置されると共に、研磨対象（被研磨物）であるウェハ等を保持して回転させつつ研磨パッド１６に押し付けることで研磨加工を施す研磨ヘッドが配設されている。
【００４４】
このような研磨装置において、その回転定盤１４に装着された研磨パッド用補助板１０

は、下側補助板２０および上側補助板２２を含んでいる。そして、回転定盤１４の上面１８に対して、下側補助板２０が第一の固着手段２４で固着されており、更に、下側補助板２０の上面に対して、上側補助板２２が第二の固着手段２６で固着されている。即ち、下側補助板２０と上側補助板２２は、第二の固着手段２６を介して相互に重ね合わされて固着されることにより、全体として二層構造とされた研磨パッド用補助板１０を構成しており、第一の固着手段２４により回転定盤１４の上面１８に取り付けられている。

【００４５】

下側補助板２０および上側補助板２２は、何れも、薄肉の略円形平板形状とされており、平坦な表面（上面）と裏面（下面）を有している。これらの上下補助板２２，２０は、装着される研磨パッド１６よりも硬質材料であるものや、研磨パッド１６よりも部材剛性が大きいものが望ましい。使用方法にもよるが、後述するように下側補助板２０は回転定盤１４への取り付け後に着脱を繰り返さない使用も可能である一方、上側補助板２２は回転定盤１４への取り付け後に着脱を繰り返すことが予定されることから、少なくとも上側補助板２２は、研磨パッド１６よりも部材剛性が大きいものを採用することが望ましい。

【００４６】

尤も、上側補助板２２は、研磨パッド１６を支持せしめて、研磨装置１２による研磨加工の他、研磨パッド表面へのドレッシング、清掃、再溝入などの各種の処理に際して要求される強度や剛性、形状安定性及び精度を満足するものであれば良く、その材質や厚さ寸法は限定されるものでない。特に、下側補助板２０だけでなく上側補助板２２も、それ単体で、研磨パッド１６の支持強度や剛性等を負うものでなく、例えば研磨加工に際しては研磨装置１２の回転定盤１４の上に重ね合わされて使用されることで、回転定盤１４で下面を支持されるものであることから、単体での強度や剛性がそれ程迄に要求されるものでない。それ故、ステンレス鋼等の金属の他、合成樹脂や繊維強化樹脂等も、下側補助板２０や上側補助板２２の形成材料として採用され得る。特に、合成樹脂材は金属材に比して軽量で加工や取扱いが容易であり、例えばポリカーボネート等は、厚さ寸法精度の安定性や温度変化に対する低歪み特性にも優れているといった利点がある。

【００４７】

また、研磨パッド１６の全体に亘って安定した支持力を得るためには、上側補助板２２の外径寸法を研磨パッド１６の外径寸法の値以上に設定することが望ましく、且つ下側補助板２０の外径寸法を上側補助板２２の外径寸法の値以上に設定することが望ましく、更に下側補助板２０の外径寸法を回転定盤１２の外径寸法の値以下に設定することが望ましい。特に、図１，２に示されているように、下側補助板２０および上側補助板２２の外径寸法を略同じにすると共に、装着される回転定盤１４の外径寸法とも略同じとすることにより、研磨パッド１６の支持面積を十分に大きく確保することが可能になる。これにより、回転定盤１４と略同じ大きさの研磨パッド１６を、その全体に亘って略同じ支持力をもって回転定盤１４に装着することが可能となる。

【００４８】

更にまた、第一の固着手段２４および第二の固着手段２６としては、研磨に際して及ぼされる外力に対抗して、回転定盤１４の上面１８へ下側補助板２０および上側補助板２２を固着状態に保持し得るものであればよく、特に限定されるものでない。具体的には、接着剤や粘着剤、または基材シートの両面に接着剤や粘着剤が付着等された両面テープなどが、第一及び第二の固着手段２４，２６として採用され得るが、その他、負圧エア等を利用した負圧吸引や、永久磁石又は電磁石を利用した磁力吸引なども採用可能である。また、これらの接着剤等からなる固着手段は、下側補助板２０や上側補助板２２において平坦な重ね合わせ面の略全面に亘って略均一に固着力を及ぼすことが望ましく、それによって、大きな固着力を得ることが出来ると共に、研磨パッド用補助板１０の表面において研磨パッド１６の支持特性が局所的に異なる不具合等を回避できる。

【００４９】

例えば負圧吸引や電磁石では固着力をＯＮ／ＯＦＦできるが、接着剤等のように一定の固着力が及ぼされる場合には、第一の固着手段２４による回転定盤１４に対する下側補助

板２０の固着力に比して、第二の固着手段２６により下側補助板２０に対する上側補助板２２の固着力が小さくなるように設定されることが望ましい。これにより、上側補助板２２を下側補助板２０から引き剥がして取り外す際、下側補助板２０を回転定盤１４上に固着せしめたまま残置させておくことが容易に実現可能となる。このような固着力の相違の具体的な実現は、接着剤や粘着剤の材質など固着手段そのものを相互に異ならせる他、固着面積や固着面の状態（面粗さやプラズマ等の処理有無など）を相互に異ならせること等によっても実現可能である。

【００５０】

さらに、上側補助板２２の表面（上面）は研磨パッド支持面となっており、研磨パッド１６が重ね合わされて取り付けられている。かかる研磨パッド１６は、従来から公知の各種の研磨パッドを採用することが出来る。そして、この研磨パッド１６の裏面が、上側補助板２２の表面に対して、研磨パッド貼付用として従来公知の粘着テープや適当な接着剤等を利用して固着されている。

【００５１】

なお、研磨パッド１６の上側補助板２２への固着手段は前述の第二の固着手段２６よりも、大きな固着力を設定することが望ましい。これにより、研磨パッド１６が固着されたままの状態で上側補助板２２を下側補助板２０から取り外す際に、上側補助板２２が湾曲等しても研磨パッド１６が上側補助板２２から予期せずに剥がれることが効果的に防止され得る。

【００５２】

また、研磨パッド１６の外径寸法は、一般に規格値とされるが、多くの場合、装着される回転定盤１４の上面１８の外径寸法と同じか小さく設定される。

【００５３】

さらに、例えば回転定盤１４の上面１８と下側補助板２０との間、下側補助板２０と上側補助板２２との間、上側補助板２２と研磨パッド１６との間の少なくとも一つにおいて、適当なクッション層を設けても良い。このようなクッション層を設けることにより、研磨パッド１６による研磨加工に際して、被加工物に対する研磨効率の全面に亘る均一化を図ることが可能となる。

【００５４】

かかるクッション層としては、例えば発泡によってある程度の圧縮性が付与された樹脂シートや、エラストマーシート、ゴムシート等が好適に採用され得る。また、第一の固着手段２４や第二の固着手段２６、研磨パッド１６の上側補助板２２への固着手段によって、クッション層を構成することも可能である。なお、クッション層は、研磨パッド１６の支持面における局部的な歪を防止するために、研磨パッド１６の支持領域の略全体に亘る大きさをもって一定厚さで存在するように、形成されることが望ましい。

【００５５】

また、研磨パッド用補助板１０を構成する下側補助板２０と上側補助板２２との間には、相互に位置決めして中心軸を合わせる位置決め手段２８が設けられている。本実施形態では、下側補助板２０の外周部分に、下側補助板２０の中心軸回りで全周に亘って延びる円形の段差面３０が形成されている。そして、この段差面３０よりも外周側では下側補助板２０の厚さ寸法が小さくされることで、下側補助板２０の外周面に開放する切欠断面形状をもって周方向の全周に連続して延びる環状の係合凹部３２が、下側補助板２０に突出して一体形成されている。

【００５６】

一方、本実施形態では、上側補助板２２の外周部分には、上側補助板２２の中心軸回りで全周に亘って延びる円形の段差面３４が形成されている。そして、この段差面３４よりも外周側では上側補助板２２の厚さ寸法が大きくされることで、上側補助板２２の外周端縁に沿って周方向の全周に連続して延びる環状の係合凸部３６が、上側補助板２２に突出して一体形成されている。なお、係合凸部３６および係合凹部３２は、上下補助板２２，２０のどちらに形成されていても良い。

【００５７】
上述の下側補助板２０の段差面３０および係合凹部３２は、上側補助板２２の段差面３４および係合凸部３６に対して相互に位置合わせされており、本実施形態において係合外周面および係合内周面を構成している。そして、下側補助板２０に上側補助板２２が重ね合わされる際、係合凹部３２に係合凸部３６が嵌まり込み、段差面３０に段差面３４が径方向で重ね合わされ、係合部が形成される。これにより、係合凹部３２と係合凸部３６とによって位置決め手段２８が構成されており、中心軸が相互に一致させられて径方向で位置合わせされた状態で、下側補助板２０と上側補助板２２が重ね合わされるようになっている。なお、位置決め手段２８は、上下補助板２２，２０の外周面よりも内周側に位置して設けられ、それにより、上下補助板２２，２０、ひいては研磨装置１２が大型化しないようにしている。

【００５８】
このような構造とされた研磨パッド用補助板１０を備えた研磨装置１２にあっては、図１に示されているように、回転定盤１４の上面１８に上下の補助板２２，２０からなる研磨パッド用補助板１０を固着せしめて装着すると共に、上側補助板２２の上面に研磨パッド１６を固着支持せしめた状態で、回転定盤１４を回転駆動させて基板等の被加工物に対してＣＭＰ（化学機械研磨）を施すようにされる。そして、かかる研磨装置１２は、特定構造の研磨パッド用補助板１０を備えていることにより、以下の如き特別な技術的効果を発揮し得る。

【００５９】
先ず、図２に示されているように、研磨パッド１６を上側補助板２２の上面に固着させたままで、上側補助板２２を、第一の固着手段２４により回転定盤１４に固着された下側補助板２０から取り外すことにより、研磨パッド１６を回転定盤１４から取り外すことが出来る。そして、回転定盤１４から取り外して研磨パッド１６の表面（研磨面）をクリーニングや再加工等する場合でも、研磨パッド１６を上側補助板２２の上面に固着させたままで行うことが出来る。これにより、回転定盤１４に対する研磨パッド１６の着脱の際や、研磨パッド１６のクリーニングや再加工の際などは勿論、研磨パッド１６の移送時や保存時等においても、上側補助板２２による補強作用により研磨パッド１６の曲がりや損傷を防止できて、研磨パッド１６を良好な状態に保つことが出来る。

【００６０】
また、研磨パッド１６を上側補助板２２と共に回転定盤１４から取り外した際にも、回転定盤１４の上面１８には下側補助板２０が残置される。そして、研磨パッド１６を再び回転定盤１４に装着する際、上側補助板２２と下側補助板２０との間に設けられた位置決め手段２８により、上側補助板２２ひいては研磨パッド１６が下側補助板２０ひいては回転定盤１４に対して高精度に且つ容易に中心軸合わせされ得る。

【００６１】
ここにおいて、かかる位置決め手段２８を構成する係合凹部３２と係合凸部３６は、相互に嵌合された状態で殆ど隙間なく重ね合わされるようになっていることから、研磨パッド１６の支持特性への悪影響が防止され得る。また、上下補助板２２，２０の外周部分のうち特に本実施形態では外周端縁部に係合部、言い換えると位置決め手段２８が形成されており、研磨パッド１６において研磨用の主たる領域となる径方向中間部分を外れていることから、係合凹部３２と係合凸部３６の嵌合部分に多少の隙間があっても、研磨特性に大きな問題が発生する程の研磨パッド１６の支持特性への悪影響が回避され得る。

【００６２】
しかも、位置決め手段２８を構成する係合凹部３２と係合凸部３６は、上下補助板２２，２０の重ね合わせ面、換言すると、回転定盤１４および研磨パッド用補助板１０の外周端面よりも内周側に形成されており、上下補助板２２，２０の外周面上への突出が回避され得る。それ故、例えば図１，２に示されているように、研磨装置１２において回転定盤１４の外周側に近接して保護部材３８が設置されている場合でも、そのような保護部材３８への干渉を回避しつつ、位置決め手段２８を備えた上下補助板２２，２０を備えた研磨

装置１２が実現可能とされる。

【００６３】

さらに、上述のように研磨パッド１６の損傷を防止しつつ、正確な位置合わせ精度で速やかに研磨パッド１６を回転定盤１４に対して着脱することが出来る結果、研磨パッド１６の着脱等の作業のために高価な研磨設備の稼働時間が不必要に制限されることがなくなり、研磨設備の稼働効率の向上ひいては基板等の生産効率（研磨作業効率）の向上が達成され得る。

【００６４】

また、研磨パッド１６の回転定盤１４に対する着脱が容易に実現されることから、特別な熟練や知識がなくとも研磨パッド１６の再利用が実用レベルで実現可能となる。即ち、例えば、基板等の被研磨物の品種切り替え等に際して一旦回転定盤１４から外した研磨パッド１６を再利用したり、劣化対策として別の加工装置で表面溝入れ等の再加工するのに一旦回転定盤１４から取り外した研磨パッド１６を再加工後に再利用したりすることなども、実用化レベルで検討することが可能となるのである。

【００６５】

以上、本発明の第一の実施形態について説明してきたが、本発明の具体的構造はかかる第一の実施形態によって限定的に解釈されるものでない。上下補助板２２，２０間において別構造の位置決め手段を備えた、本発明の別の実施形態の複数を以下に例示するが、これらの実施形態も本発明の構成を限定的に示すものでない。なお、以下の実施形態において、第一の実施形態と同様な構造とされた部材および部位については、それぞれ、第一の実施形態と同一の符号を各図中の対応する部位に記載することにより、それらの詳細な説明を省略する。

【００６６】

図３～４には、本発明の第二の実施形態としての研磨パッド用補助板４０を備えた研磨装置４２が示されている。

【００６７】

この研磨パッド用補助板４０においては、下側補助板２０の上面の外周部分を周方向に連続して延びる円環形状の溝によって係合凹部４４が形成されている。一方、上側補助板２２の下面の外周部分には、周方向に連続して延びる円環形状の突起によって係合凸部４６が形成されている。この係合凸部４６は、上側補助板２２に一体形成されていても良いが、図示されているように、別体形成されていても良い。即ち、本実施形態では、上側補助板２２の下面に開口して周方向に延びる円環形状の周溝４８が形成されており、この周溝４８に対して、別体形成された円環形状のブロックが軸方向一端側で嵌め込まれて固着されることにより係合凸部４６が形成されている。

【００６８】

下側補助板２０の係合凹部４４と、上側補助板２２の係合凸部４６は、何れも中心軸回りで対応する径方向位置に形成されており、上下補助板２２，２０が重ね合わされた際、係合凹部４４に対して係合凸部４６が嵌め入れられることにより、上下補助板２２，２０が相互に径方向で位置合わせされるようになっている。なお、本実施形態では、下側補助板２０の係合凹部４４における両側壁面と、上側補助板の係合凸部４６における内外周面との、各対応する径方向の重ね合わせ面によって、二組の係合内周面および係合外周面が構成されている。

【００６９】

図５～６には、本発明の第三の実施形態としての研磨パッド用補助板５０を備えた研磨装置５２が示されている。

【００７０】

この研磨パッド用補助板５０においては、下側補助板２０の外周部分には、中心軸回りで全周に亘って延びる円形の係合内周面としての段差面５４が形成されている。そして、この段差面５４よりも外周側では下側補助板２０の厚さ寸法が大きくされることで、下側補助板２０の外周端縁に沿って周方向の全周に連続して延びる環状の係合凸部５６が、下

側補助板２０に一体形成されている。

【００７１】

一方、上側補助板２２の外周部分には、中心軸回りで全周に亘って延びる円形の係合外周面としての段差面５８が形成されている。そして、この段差面５８よりも外周側では上側補助板２２の厚さ寸法が小さくされることで、上側補助板２２の外周面に開放する切欠断面形状をもって周方向の全周に連続して延びる環状の係合凹部６０が、上側補助板２２に一体形成されている。

【００７２】

さらに、下側補助板２０の段差面５４には雌ねじが形成されている一方、上側補助板２２の段差面５８には雄ねじが形成されている。そして、下側補助板２０の段差面５４の雌ねじに対して上側補助板２２の段差面５８の雄ねじを螺合させて、下側補助板２０の段差面５４と上側補助板２２の段差面５８とを径方向に重ね合わせることにより、下側補助板２０の上面に上側補助板２２が重ね合わされるようになっている。また、かかる重ね合わせ状態下では、上下補助板２２，２０の段差面５８，５４の螺着構造により、上下補助板２２，２０を取り外し可能に固着する第二の固着手段６２が構成されている。

【００７３】

なお、このような螺着構造における雌雄ねじは、研磨装置１２の回転定盤１４に対して及ぼされる研磨時の回転反力を考慮して、ねじが緩まないようにねじ方向が設定されることが望ましい。

【００７４】

図７～８には、本発明の第四の実施形態としての研磨パッド用補助板６４を備えた研磨装置６６が示されている。

【００７５】

この研磨パッド用補助板６４においては、下側補助板２０の上面の中央部分で上方に向かって突出する円柱形状の係合凸部６８が形成されている。この係合凸部６８は、下側補助板２０に一体形成されていても良いが、図示されているように、別体形成されていても良い。即ち、本実施形態では、下側補助板２０の中心軸上に円形の嵌着凹所７０が形成されており、この嵌着凹所７０に対して、別体形成された円柱形状のブロックが軸方向一端側で嵌め込まれて固着されることにより係合凸部６８が形成されている。一方、上側補助板２２の下面の中央部分には、中心軸上で下面に開口する有底円形の係合凹部７２が形成されている。なお、係合凸部６８および係合凹部７２は上下補助板２２，２０のどちらに形成されていても良い。

【００７６】

そして、上下補助板２２，２０が重ね合わされた際、係合凹部７２に対して係合凸部６８が嵌め入れられることにより、上下補助板２２，２０が相互に径方向で位置合わせされるようになっている。なお、本実施形態では、下側補助板２０の係合凸部６８の外周面と上側補助板２２の係合凹部７２の内周面とによって、係合外周面と係合内周面とが構成されている。

【００７７】

図９には、本発明の第五の実施形態としての研磨パッド用補助板７４を備えた研磨装置７６が示されている。

【００７８】

この研磨パッド用補助板７４においては、下側補助板２０の上面の外周部分で上方に向かって突出する円柱形状の係合凸部７８が形成されている。この係合凸部７８は、下側補助板２０に一体形成されていても良いし、前記第四の実施形態における係合凸部のように下側補助板２０に嵌着凹所を形成して別体のピンなどを圧入等で固着しても良い。また、図１０～１１に示されているように、かかる係合凸部７８は、下側補助板２０の外周部分で周方向で所定距離を隔てて互いに独立して複数形成されている。特に好適には、周方向で等間隔に且つ中心軸上の同一円上に位置して、それら複数の係合凸部７８が形成される。

【００７９】
一方、上側補助板２２の下面の外周部分には、下側補助板２０における複数の係合凸部７８の形成位置に対して各対応する位置に、それぞれ、有底円形の係合凹部８０が下方に向かって開口して形成されている。なお、係合凸部７８および係合凹部８０は上下補助板２２，２０のどちらに形成されていても良い。
【００８０】
そして、上下補助板２２，２０が重ね合わされた際、係合凹部８０に対してそれぞれ係合凸部７８が嵌め入れられることにより、上下補助板２２，２０が相互に径方向で位置合わせされるようになっている。なお、本実施形態では、下側補助板２０の係合凸部７８の外周面と上側補助板２２の係合凹部８０の内周面とによって、下側補助板２０および上側補助板２２の外周部分に位置する係合外周面と係合内周面とが構成されている。
【００８１】
特に本実施形態のように、周方向で独立した複数の係合凸部７８と係合凹部８０とからなる位置決め手段を採用することにより、重ね合わされた上下補助板２２，２０を径方向だけでなく周方向においても相互に位置決めすることが可能となる。
【００８２】
なお、上側補助板２２に形成される独立した複数の係合凹部８０に代えて、上側補助板２２の中心軸回りで周方向に連続して円形に延びる周溝を採用したり、或いは図１２における本発明の第六の実施形態に示されているように、上側補助板２２の外周部分を中心軸回りで全周に亘って延びる円形の段差面８２を形成し、この段差面８２よりも外周側の厚さ寸法を小さくすることで、上側補助板２２の外周面に開放する切欠断面形状をもって周方向の全周に連続して延びる環状の係合凹部８３を形成することも可能である。
【００８３】
このように上側補助板２２において、下側補助板２０の係合凸部７８の係合面を全周に亘って連続して形成することにより、上下補助板２０，２２の重ね合わせに際して、上下補助板２０，２２を相互に周方向で位置合わせする必要がなくなって装着作業を容易に行うことが可能となる。
【００８４】
図１３には、本発明の第七の実施形態としての研磨パッド用補助板８４が示されている。
【００８５】
この研磨パッド用補助板８４においては、下側補助板２０の外周面の上側部分と、上側補助板２２の外周面の下側部分とに、それぞれ小径部が設けられている。そして、これら上下補助板２２，２０が重ね合わされることにより、それぞれの小径部によって、上下補助板２２，２０間に跨がって所定幅で広がって周方向の全周に亘って延びる円環形状の収容凹所８６が形成されている。
【００８６】
また、下側補助板２０の小径部下端には、溝状の係合凹部８８が形成されている。この係合凹部８８は、収容凹所８６の底面において、下側補助板２０の外周面に開口せしめられている。ここで、収容凹所８６の底面とは、収容凹所８６を構成する面のうち、上下補助板２２，２０に跨り、図１３の上下方向に広がる環状の面を指す。一方、収容凹所８６を構成する上側補助板２２の小径部には、弾性材からなる板状の係合凸部９０が、その基端部において固定ピン９２で固定されて取り付けられるている。この係合凸部９０は、上下補助板２２，２０の外周面に形成された収容凹所８６に収容配置されており、上側補助板２２から下側補助板２０の外周面上に延び出している。そして、係合凸部９０の先端部分に形成された係合爪部９４が、下側補助板２０の小径部に形成された係合凹部８８に対して係止され、係合凸部９０の弾性に基づいて係止状態に保持されるようになっている。
【００８７】
更にまた、このような係合凸部９０が、上下補助板２２，２０の外周面上で周方向に所定距離を隔てて複数設けられている。そして、上側補助板２２の外周面に取り付けられた

各係合凸部９０が、下側補助板２０の外周面に対して弾性的に押し付けられることで、上下補助板２２，２０が中心軸上で相互に位置決めする位置決め手段が構成されている。また、係合凸部９０の係合爪部９４が係合凹部８８に係止されることにより、上下補助板２２，２０を重ね合わせ状態に保持せしめて固着力を及ぼす固着手段も構成されている。

【００８８】

なお、上述の如き係合凹部８８に係合する係合爪部９４を備えた係合凸部９０に代えて、例えば図１４に示された本発明の第八の実施形態のように、上下補助板２２，２０間に跨がって延びて収容凹所８６の底面に重ね合わされる連結板１００を採用し、かかる連結板１００の両端部分を上下補助板２２，２０の各一方の外周面に対して連結ピン１０２，１０２で固着することも可能である。なお、連結ピン１０２，１０２の少なくとも一方は下側補助板２０又は上側補助板２２に対して着脱可能とされることにより、上下補助板２２，２０の連結板１００による連結が解除可能とされて、研磨パッド１６が固着された上側補助板２２の下側補助板２０に対する着脱が許容されることとなる。

【００８９】

また、第一～八の実施形態に示された両面テープ等からなる第一の固着手段２４や第二の固着手段２６は、上下補助板２２，２０や回転定盤１４を取り外す際に、特定の部材側の固着面に保持されることが望ましい。これにより、取り外した状態での上下補助板２２，２０や第一及び第二の固着手段２４，２６の取り扱いが容易となるからである。なお、第一及び第二の固着手段２４，２６が何れの固着面に残るかは、第一の固着手段や第二の固着手段２４，２６自体における両面の固着力を相互に異ならせる他、固着される上下補助板２２，２０や回転定盤１４の面粗度や材質等を相互に異ならせることなどによって設定することが可能である。

【００９０】

特に、第一の固着手段２４は、下側補助板２０を取り外す際に下側補助板２０側の固着面に保持されることが望ましく、それによって回転定盤１４の上面１８のメンテナンスが容易となる。一方、第二の固着手段２６は、第一の実施形態における図２に示されているように、上側補助板２２を取り外す際に上側補助板２２側の固着面に保持されるようになっていても良いし、例えば図１５に示す本発明の第九の実施形態のように、下側補助板２０の上面に残るようにしても良い。なお、第二の固着手段２６を上側補助板２２側の固着面に保持させることにより、研磨パッド１６の溝入れなどの再加工用装置の回転定盤に対して、取り外した上側補助板２２を装着する際に、上側補助板２２に保持された第二の固着手段２６を利用して取り付けることも可能となる。一方、第二の固着手段２６を下側補助板２０側の固着面に保持させることにより、別の研磨パッド１６を装着した別の上側補助板２２を下側補助板２０に装着する際に、下側補助板２０に保持された第二の固着手段２６を利用して取り付けることも可能となる。

【００９１】

また、第一～七の実施形態に示された係合凹部３２，４４，６０，７２，８０，（８３），８８と係合凸部３６，４６，５６，７０，７８，９０は、下側補助板２０側と上側補助板２２側とにおいて相互に反対側に設けられていても良い。例えば本発明の第十の実施形態が図１６に示されているように、第一の実施形態として図１～２に示された研磨パッド用補助板１０に対して、その係合外周面を構成する段差面３０と係合凹部３２とを上側補助板２２に形成する一方、係合内周面を構成する段差面３４と係合凸部３６とを下側補助板２０に形成することも可能である。

【００９２】

更にまた、第一～六の実施形態に示された係合凹部３２，４４，６０，７２，８０，（８３）と係合凸部３６，４６，５６，７０，７８において、相互に重ね合わされて上下補助板２２，２０を位置決めする係合凸部の外周面と係合凹部の内周面とに対して傾斜角を付すことも可能である。例えば本発明の第十一の実施形態が図１７に示されているように、下側補助板２０の外周部分に突出形成した係合凸部３６の係合内周面としての段差面３４に対して、係合凸部３６が突出方向で次第に先細となる傾斜方向のテーパを付す一方、

上側補助板２２の外周部分に形成した係合凹部３２の係合外周面としての段差面３０に対して、段差面３４に対応する傾斜方向および傾斜角度のテーパを付すことができる。これにより、係合凸部３６を係合凹部３２に嵌め入れて上下補助板２２，２０を重ね合わせる作業を、両段差面３４，３０に付されたテーパを案内面として利用することで、一層容易に行うことが可能となる。

【００９３】

因みに、図１８に記載の本発明の第十二の実施形態や、図１９に記載の本発明の第十三の実施形態に示されているように、下側補助板２０の周方向で独立して複数形成される突起形状の係合凸部７８と、上側補助板２２の各対応する位置に形成される複数の穴形状の係合凹部８０とを採用する場合でも、係合凸部７８の突出先端部分の外周面に対して傾斜角を付して、先細形状のテーパ部１０４を形成することができる。なお、図１９では、下側補助板２０に形成された嵌着穴１０５に対して、別体形成された係止ピン１０６が圧入等で固着されて係合凸部７８が構成されており、かかる係止ピン１０６の下端にも、上端と同様なテーパ部１０４が付されている。これにより、係止ピン１０６に方向性が無くなって取り扱いが容易となると共に、嵌着穴１０５への圧入作業も容易となる。

【００９４】

また、図２０に示された本発明の第十四の実施形態では、上下補助板２２，２０の重ね合わせ状態で中心軸を合わせる位置決め手段の一種として、それら上下補助板２２，２０間に跨がって外挿される位置決めスリーブ１０８が示されている。この位置決めスリーブ１０８は、互いに略同じ外径寸法の円板形状とされた上下補助板２２，２０の外径寸法と同じか僅かに大きな内径寸法を有しており、金属材や合成樹脂材によって形成されている。このような位置決めスリーブ１０８を、上下補助板２２，２０の重ね合わせに際して用いて、位置決めスリーブ１０８内で上下補助板２２，２０を重ね合わせるとにより、上下補助板２２，２０を中心軸合わせしつつ軸方向に重ね合わせて、第二の固着手段２６で相互に固着することができる。それ故、上下補助板２２，２０を重ね合わせて相互に固着せしめた後で、位置決めスリーブ１０８を取り外すことが出来るのであり、それによって、上下補助板２２，２０を、外周面上に突出する位置決め手段を有しない状態で且つ正確な位置合わせ状態で相互に固着することが可能となる。

【００９５】

更にまた、図２１に示された本発明の第十五の実施形態では、上下補助板２２，２０の重ね合わせ状態で重ね合わせ方向に跨がって延びるスリット状の係合溝１１０が形成されている。この係合溝１１０は、上下補助板２２，２０の外周面に開口して径方向内方に所定深さを有しており、上下補助板２２，２０の周方向で互いに独立して複数設けられている。そして、かかる係合溝１１０に対して、外周面の開口部からプレート形状の係合板１１２が嵌め入れられることにより、かかる係合板１１２で上下補助板２２，２０が相互に位置決めされると共に、相互に連結状態とされている。なお、かかる係合板１１２は、上下補助板２２，２０と別体形成されているが、例えば上下補助板２２，２０の何れか一方において他方に向かって突出する形状をもって一体形成されていても良い。その場合には、係合溝１１０は、当該他方の補助板にだけ形成されることとなる。

【００９６】

さらに、図２２に示された本発明の第十六の実施形態では、上側補助板２２の下面に開口する係合凹部としての嵌合凹部１１４が形成されている。特に本実施形態では、かかる嵌合凹部１１４が、上側補助板２２の中心軸回りで周方向に連続して延びる環状溝として形成されている。一方、下側補助板２０には、上側補助板２２に重ね合わされる上面において上方に突出する係合凸部としての嵌合凸部１１６が形成されている。なお、本実施形態では、かかる嵌合凸部１１６が、嵌合凹部１１４に対応する環状凸部として形成されている。そして、上下補助板２２，２０の重ね合わせ状態で、嵌合凸部１１６が嵌合凹部１１４に入り込んで位置せしめられるようになっている。

【００９７】

また、嵌合凸部１１６は中空構造とされており、嵌合凸部１１６の内部において外部空

間に対して密閉された流体溜１１８が形成されている。更に、この流体溜１１８を画成する嵌合凸部１１６の壁部は、少なくとも内周壁と外周壁が径方向に向かって膨出変形可能にされている。具体的には、例えば嵌合凸部１１６をゴム弾性体などで形成することによって、径方向内方に膨出可能な内周壁と径方向外方に膨出可能な外周壁とが実現可能である。

【００９８】

更にまた、下側補助板２２には、流体溜１１８に連通して、径方向外方に延び出し外周面に開口する流体通路１２０が形成されていると共に、この流体通路１２０の外周端開口部に加圧ねじ１２２がねじ込まれている。また、加圧ねじ１２２で封止された流体通路１２０と流体溜１１８からなる密閉領域には、オイルなどの非圧縮性流体が充填されている。

【００９９】

これにより、加圧ねじ１２２をねじ込むことにより、流体通路１２０を通じて流体溜１１８の内圧を上昇させて、流体溜１１８の内周壁および外周壁を外方に膨出させることが出来る。その結果、嵌合凸部１１６が拡張されて、嵌合凹部１１４の内面に押し付けられ、相互の摩擦力等によって上下補助板２２，２０を相互に位置決めすると共に固着力も及ぼし得るようになっている。

【０１００】

なお、上側補助板２２を下側補助板２０から取り外すに際しては、加圧ねじ１２２を緩ませる方向に回転操作して下側補助板２０の外周側に移動させることにより、流体溜１１８の圧力を低下させて嵌合凸部１１６の嵌合凹部１１４への押し付け力を解除することができる。

【０１０１】

その他、一々列挙はしないが、本発明は当業者の知識に基づいて種々なる変更，修正，改良などを加えて実施することが可能であり、例えば、係合凸部と係合凹部の係合部分にＯリングやシール材を装着して上下補助板の重ね合わせ面等への異物の侵入を防止することも可能である。

【０１０２】

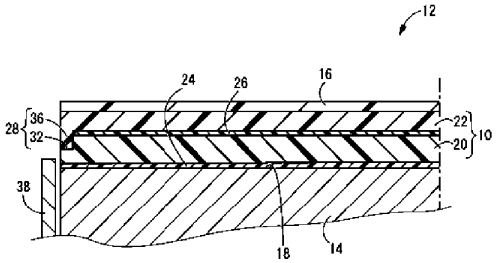
また、上述の二層構造の補助板２０，２２に加えて、更に補助板を積層状態で且つ固着手段で固着せしめて追加することも可能である。このように第三層の補助板を採用することで、弾性支持状態を実現したり、或いは中間層を使い捨てする等の態様も可能となる。

【符号の説明】

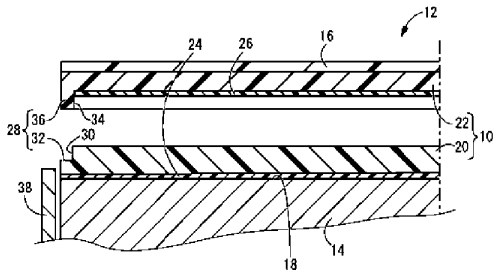
【０１０３】

１０，４０，５０，６４，７４，８４：研磨パッド用補助板、１２，４２，５２，６６，７６：研磨装置、１４：回転定盤、１６：研磨パッド、１８：上面、２０：下側補助板、２２：上側補助板、２４：第一の固着手段、２６，６２：第二の固着手段、２８：位置決め手段、３０，５８：段差面（係合外周面）、３２，４４，６０，７２，８０，８８：係合凹部、３４，５４：段差面（係合内周面）、３６，４６，５６，６８，７８，９０：係合凸部、３８：保護部材

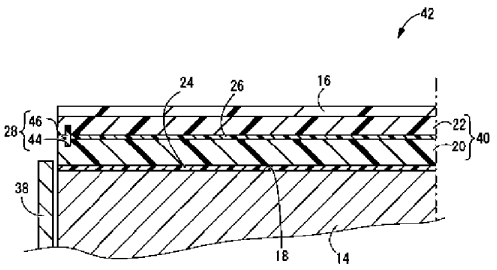
【図１】



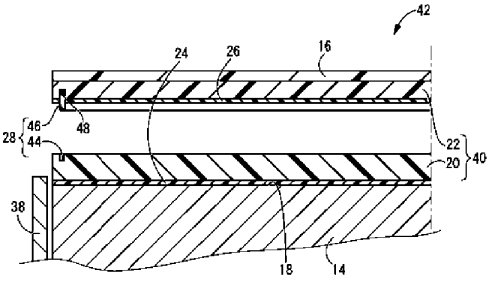
【図２】



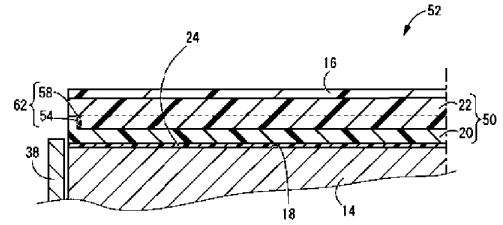
【図３】



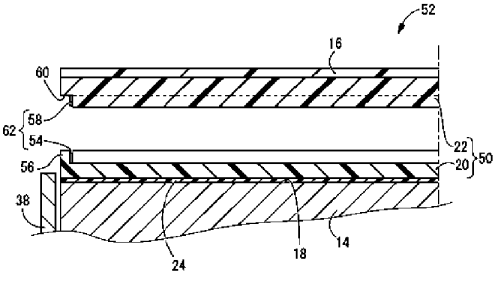
【図４】



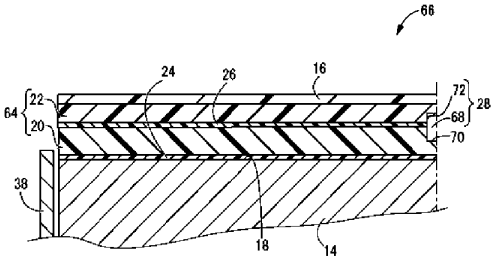
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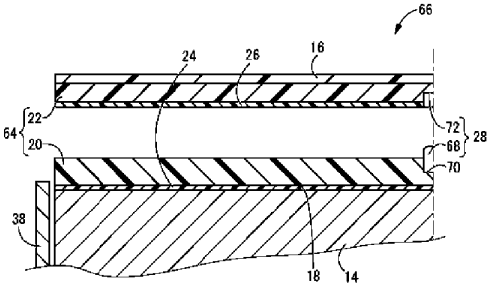
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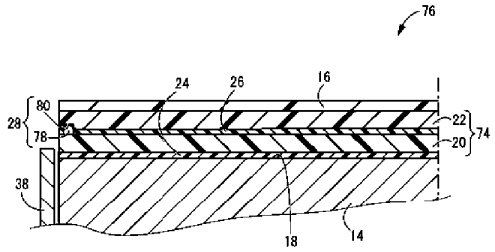
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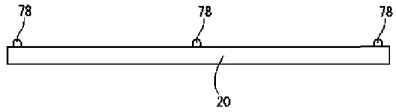
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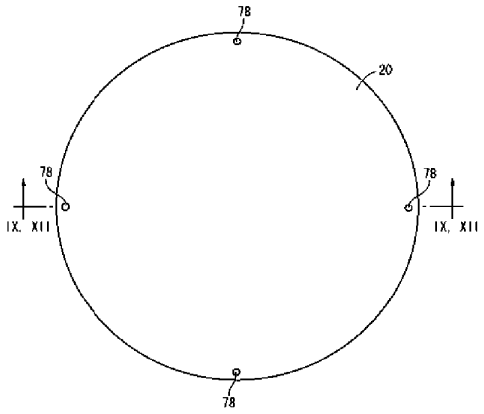
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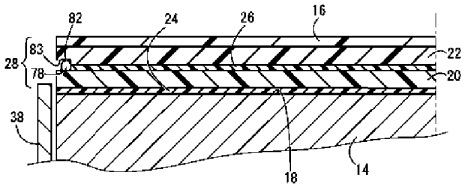
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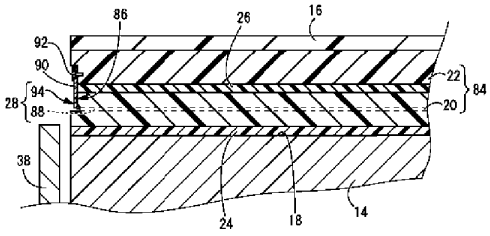
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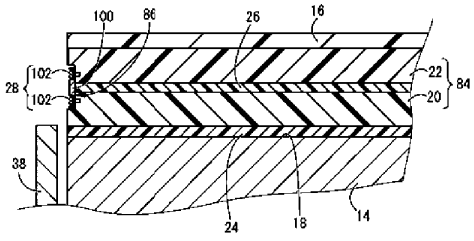
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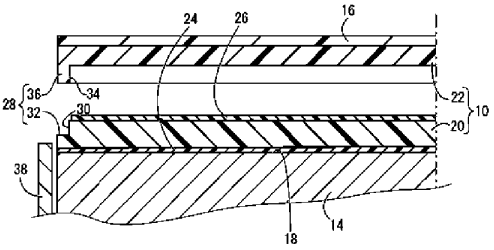
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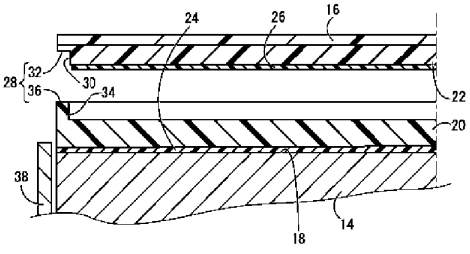
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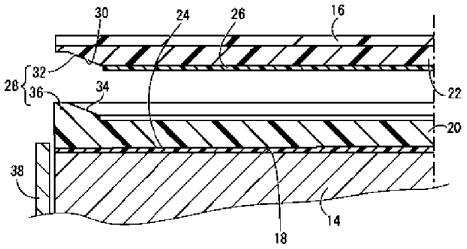
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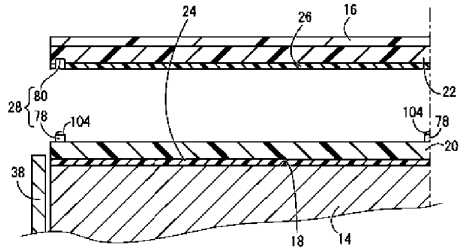
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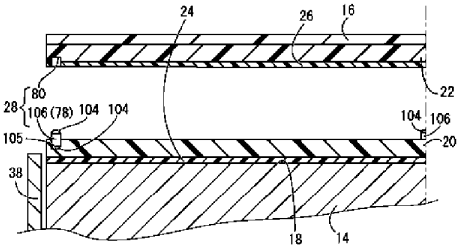
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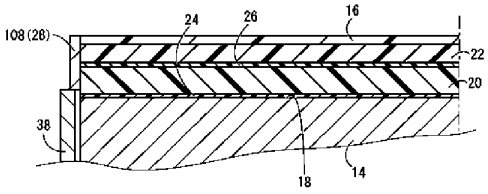
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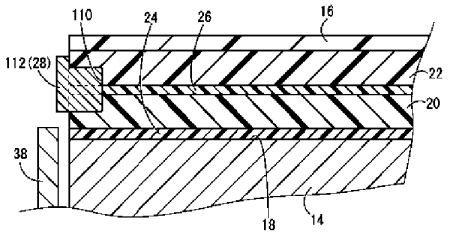
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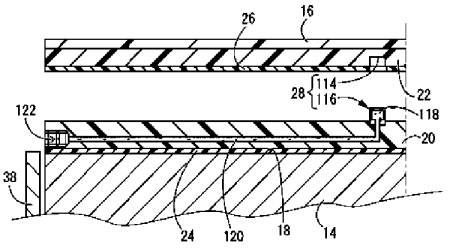
【図２０】



【図２１】



【図２２】



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(58)調査した分野(Int.Cl.，ＤＢ名)
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Judge: Toyohide Watanabe
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The scope of the claims open —

(57) [Claim]

[Claim 1]

A process for making a multiphase mixture, comprising

the step of flowing a first fluid stream through a process microchannel, wherein the first fluid stream is a liquid stream comprising , said process microchannel having an open section com prising a plurality of openings , said open section flowing through said process microchannel; a second fluid stream having a length along the flow path of a fluid stream and a thickness di mension perpendicular to the flow path of said first fluid stream flowing in said process microc hannel

; into the process microchannel and in contact with the first fluid stream to form the multiph ase mixture, wherein the second fluid stream is a gas stream comprising wherein the first flui d stream forms a continuous phase within the multiphase mixture and the second fluid stream forms a dispersed discontinuous phase within the continuous

phase ,

said second fluid stream flows through said open section from a second fluid stream channel adjacent said process microchannel, said heat exchange

channel being said process microchannel, said second fluid stream channel, or adjacent to b oth the process microchannel and the second fluid stream channel, between the process micr ochannel and the heat exchange channel, between the second fluid stream channel and the h eat exchange channel, or a process microchannel and said second fluid flow channel

A process in which heat is exchanged between both a cell and a heat exchange channel, and a heat exchange liquid is in the heat exchange channel.

2. The process of claim 1,

wherein said first fluid stream and said second fluid stream contact each other in a mixing zo ne within said process microchannel.

3.

The process of claim 1 or 2, wherein said process microchannel has a mixing zone with a nar rowed cross-section.

4.

The process microchannel has spaced apart walls and open sections in each of the spaced ap art walls, wherein the second fluid stream passes through each of the open sections to the pr ocess microchannel. 4. The process according to any one of claims 1 to 3, flowing into the

5. Said

process microchannel is a first process microchannel and is in a multiphase mixture forming unit, said multiphase mixture forming unit comprising a second process microchannel and sai d first process microchannel. a second fluid stream channel located between a process microc hannel and said second process microchannel, each process microchannel having a wall with a n open section, said first fluid stream comprising said flowing through a first process microcha nnel and said second process microchannel, said second fluid stream passing from said secon d fluid stream channel through said open section into said first process microchannel; 5. Any of claims 1-4, wherein the microchannel flows in and into contact with the first fluid stream an d through the open section into the second process microchannel and in contact with the first fluid stream. The process of paragraph 1.

6.

A process for making a multiphase mixture comprising:

flowing a first fluid stream through a process microchannel, said first fluid stream being a liq uid stream comprising ; a step having an open section , said open section being a length alon g a flow path of said first fluid stream flowing within said process microchannel and a flow pat h of said first fluid stream flowing within said process microchannel; and flowing a second flui d stream through a second fluid stream channel ,

said second fluid stream being a liquid stream comprising

at least one liquid. wherein said process microchannel has an apertured section comprising a plurality of apertures allowing said second fluid stream to enter said process microchannel, sai d apertured section receiving said second fluid stream having a length along the flow path of s aid second fluid stream flowing within said channel and a thickness dimension perpendicular t o the flow path of said second fluid stream flowing within said second fluid stream

channel ; flowing a fluid stream through a third fluid stream channel, said third fluid stream being a gas stream comprising third fluid stream to a second fluid stream; having another ope n section comprising a plurality of openings to allow flow into two fluid flow channels, said sep arate open section flowing through said third fluid flow channel; having a length along a fluid f low path and a thickness dimension perpendicular to the flow path of said third fluid stream fl owing within said third fluid flow channel ;

The third fluid stream flows from the third fluid stream channel through the another open se ction having the thickness into the second fluid stream channel to contact the second fluid str eam and form another forming a multi-phase mixture, flowing said another multi-phase mixtu re through said open section having said thickness into said process microchannel and contact ing said first fluid stream to form said multi-phase

mixture , a

heat exchange channel is adjacent to said process microchannel and/or either said second fl uid stream channel or said third fluid stream channel, wherein heat is transferred between sai d process channel and said heat exchange channel; exchanged and the heat exchange liquid i s in the heat exchange channel;

process including.

7.

The process of any one of claims 1 to 6, wherein the process microchannels are formed from parallel spaced sheets and/or plates.

8.

The process of claim 7, wherein the second fluid flow channel is formed from parallel spaced sheets and/or plates.

9.

The process of claim 8, wherein said heat exchange channels are formed from parallel space d sheets and/or plates.

10.

The process is performed in a microchannel mixer, the microchannel mixer including a plurali ty of the process microchannels and a second fluid flow channel, each process microchannel h aving an open section. a wall and an adjacent second fluid stream channel, wherein the secon d fluid stream flows from the second fluid stream channel through the open section into the pr ocess microchannel to form the first fluid stream; wherein said process microchannel and seco nd fluid flow channel are formed from parallel spaced apart sheets and/or plates, said process microchannel and second fluid flow channel being adjacent to each other and side by side 10. A process according to any one of claims 1 to 9 arranged in alternating planes stacked on top of each other or alternating planes stacked one above the other.

11.

The microchannel mixer further comprises a plurality of heat exchange channels formed fro m parallel spaced apart sheets and/or plates, said heat exchange channels being connected to said process microchannels, said second fluid stream, and said heat exchange channels. 11. T he process of claim 10 adjacent to a channel, or both the process microchannel and the secon d fluid stream channel.

12.

The process of any one of claims 1 to 6, wherein said process microchannel and said second fluid flow channel comprise concentrically arranged circular tubes.

13.

The process is carried out in a microchannel mixer, the microchannel mixer comprising a plur ality of the process microchannels, wherein a separate multiphase mixture is formed within ea ch of the process microchannels. 13. The process of any one of claims 1 to 12, wherein the m ultiphase mixtures formed in at least two of the process microchannels are different from eac h other.

14.

A process according to any one of claims 1 to 13, wherein said apertured section comprises a sheet and/or plate and a plurality of apertures in said sheet and/or plate.

15.

having a coating over at least a portion of said sheet and/or plate and filling a portion of said openings; or said sheet and/or plate is heat treated; 15. The process of claim 14.

16. Clause 1,

wherein said apertured section is made of a porous material, said porous material being met allic, non-metallic, oxidized, or coated with alumina, nickel or combinations thereof. 16. The p rocess according to any one of paragraphs 1 to 15.

17. Said

first fluid stream comprises water or an organic liquid, said second fluid stream comprises at least one gas, or said second fluid stream comprises air, hydrogen, nitrogen 17. A process acc ording to any one of the preceding claims, comprising a gas selected from , carbon dioxide or mixtures of two or more thereof.

18.

The process microchannel of any one of claims 1 to 17, wherein the process microchannel ha s an internal dimension of 10 millimeters or less perpendicular to the flow of the first fluid stre am through the process microchannel. Described process.

19.

Said second fluid flow flows through said open section from a second fluid flow channel, said second fluid flow channel passing said second fluid flow channel through said second fluid flow channel. 19. A process according to any one of the preceding claims, having internal dimensio ns of 100 centimeters or less perpendicular to said flow of fluid stream.

20.

A process according to any one of claims 1 to 19, wherein said heat exchange channels have internal dimensions of 50 millimeters or less perpendicular to said flow of heat exchange fluid through said heat exchange channels.

21. The process

microchannels, second fluid flow channels and heat exchange channels are made of steel, m onel, inconel, aluminum, titanium, nickel, copper, brass, alloys of any of these metals, polyme rs, ceramics. 21. The process of any one of claims 1 to 20, made of a material comprising: , g lass, a composite comprising polymer and glass fibers, quartz, silicon, or a combination of two or more thereof.

22.

A process according to any one of claims 1 to 21, wherein said heat exchange fluid undergoe s a phase change within said heat exchange channels.

23.

A process according to any one of claims 1 to 21, wherein endothermic or exothermic proces ses are carried out in said heat exchange channels.

[Claim 24]

the heat exchange fluid is air, water vapor, liquid water, carbon monoxide, carbon dioxide, ga seous nitrogen, liquid nitrogen, at least one gaseous hydrocarbon, at least one liquid hydrocar

bon, or a combination of two or more thereof; 24. The process of any one of claims 1-23, com prising the first fluid stream, the second fluid stream, or a mixture of the first and second fluid streams.

25.

The process of any one of claims 1 to 24, wherein said multiphase mixture comprises foam.

26. The

multiphase mixture comprises emulsifiers, surfactants, UV protection agents, waxes, consist ency agents, thickeners, superfatting agents, stabilizers, cationic, anionic, zwitterionic, ampho teric or Nonionic polymers, silicone compounds, fats, waxes, lecithins, phospholipids, biophar maceuticals, antioxidants, deodorants, antiperspirants, antidandruff agents, swelling agents, a nthelmintics, self-tanning agents, tyrosine inhibitors, 26. A process according to any precedin g claim, comprising one or more of solubilizers, preservatives, perfume oils or pigments, or mi xtures of two or more thereof.

27.

The process of any one of claims 1 to 26, wherein solids are dispersed in said multiphase mi xture. 28. A process according to any one of claims 1 to 27, wherein said first fluid stream c omprises a reaction medium for conducting a hydrogenation reaction and said second fluid str eam comprises hydrogen

. 29. The first fluid stream comprises a liquid stream, and the second fluid stream comprises one or more of air, oxygen, nitrogen, carbon dioxide, hydrogen, ammonia, chlorine gas, ozon e, and one or more of one or more. gaseous hydrocarbons, or a combination of two or more t hereof, or said first fluid stream comprises a liquid waste stream of

said second fluid stream comprises air; or said first fluid stream comprises a liquid hazardous waste stream; said second fluid stream comprises air; or said first fluid stream comprises liqui d salad dressing or mustard, said second fluid stream comprises nitrogen, or said first fluid str eam comprises liquid beverage or beer, said second fluid stream comprises carbon dioxide, or said first fluid stream comprises the fluid stream comprises liquid bleached pulp, said second f luid stream comprises chlorine, or said first fluid stream comprises coal dispersed in water, sai d second fluid stream comprises air, or said The first fluid stream comprises motor oil with ent rained water, the second fluid stream comprises nitrogen, or the first fluid stream comprises li quid-containing cells for a culture reaction, the second comprises oxygen or air, or said first fl uid stream comprises a liquid reaction medium and said second fluid stream comprises air or oxygen, or said first fluid stream comprises a mixture of oil and water said second fluid strea m comprising air or natural gas, or said first fluid stream comprising liquid bleached pulp, said second fluid stream comprising oxygen, or said first fluid the streams comprise edible oil, win e or juice, the second fluid stream comprises nitrogen, or the first fluid stream comprises wat

er used in fish farming, the second fluid stream comprises oxygen, or said first fluid stream co mprises water and said second fluid stream comprises ozone; or said first fluid stream compri ses a liquid waste or process stream and said second fluid stream comprises carbon dioxide or ammonia, or wherein the first fluid stream comprises a liquid waste stream comprising volatil e organic compounds and the second fluid stream comprises air. process.

30.

A process according to any one of claims 1 to 29, wherein the process produces at least 1 lit er of multiphase mixture per minute.

[Claim 31]

31. The process of any one of claims 1-30, wherein the process is performed in a microchan nel mixer, the microchannel mixer comprising at least two process microchannels.

32.

Said process is carried out in a microchannel mixer, said microchannel mixer comprising a pl urality of process microchannels and a plurality of second fluid flow channels, said process mic rochannels comprising at least one first fluid stream channel. connected to one fluid flow mani fold, wherein the first fluid flow flows through the at least one first fluid flow manifold to the p rocess microchannel; the second fluid flow channel is connected to the process microchannel; Adjacent to the microchannel, at least one second fluid flow manifold connects to said second fluid flow channel, said second fluid flow passing through said at least one second fluid flow m anifold to said first fluid flow manifold. 32. The process of any one of claims 1-31, wherein the process flows into two fluid flow channels.

33.

The microchannel mixer further comprises at least one heat exchange manifold connected to the heat exchange channels, wherein heat exchange fluid flows through the at least one heat exchange manifold into the heat exchange channels. 33. The process of claim 32.

34.

The process microchannel of claims 1 to 33, wherein the process microchannel includes surf ace features formed in and/or on one or more inner walls for altering flow within the process microchannel. A process according to any one of paragraphs.

[Claim 35]

The surface features are depressions in one or more of the inner microchannel walls oriented at an oblique angle to the direction of fluid flow through the process microchannel and/or the i nner microchannel walls. or said surface features are in the shape of at least two surface feat ure regions, and said mixing of said first and second fluids is in the form of a first carried out i n a flow through a surface feature region followed by a second surface feature region, said flo w pattern in said second surface feature region being formed by said first surface feature regi on; different from said flow pattern in the region or said opening

A section includes an interior portion forming one or more portions of the inner wall of the pro cess microchannel and a surface feature sheet overlying the interior portion of the open sectio

n, wherein the surface feature sheet includes: or the multiphase mixture comprises solid particles dispersed in the first and/or second fluid streams and is in the form of the fluidized bed; includes surface features formed in and/or on one or more of the inner walls thereof to alter flow within said process microchannel; or said surface features are stacked on top of each other; and or comprising two or more layers intertwined in a three-dimensional pattern, or wherein said surface features are circular, elliptical, square, rectangular, checkerboard, V-shaped, corrugated or combinations thereof; Alternatively, the surface features include sub-elements, and the main wall of the surface features is notched, corrugated, jagged, perforated, burr-shaped, checkered, fan-shaped, or a combination thereof. 35. The process of Claim 34, further comprising small surface features.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to multiphase mixing processes using microchannel process technology. BACKGROUND OF THE INVENTION The dispersion of air bubbles in liquids, with or without chemical reaction, is useful for gas-liquid contact to promote absorption or stripping or for foam product production . can be Examples of these are air injection to meet the BOD (Biological Oxygen Demand) requirements of waste streams, air injection to mix liquids in baths, stimulation of bacterial growth for hazardous waste treatment. Nitrogen blowing to extend salad dressings or mustards, CO2 blowing for carbonated drinks and beer, Chlorine blowing for bleaching pulp in the manufacture of paper, Coal flotation and other solids Blowing air for separation, blowing nitrogen to remove entrained water from motor oil, blowing oxygen or air to enhance cell growth in culture reactions, reacting air, oxygen or other gases for improved performance hydrogen blowing for various types of chemical hydrogenation reactions, air or natural gas blowing for oil removal from well spring water, for bleaching pulp in the manufacture of paper Oxygen blowing, Nitrogen blowing to remove oxygen from edible oils, wine and juices, Oxygen blowing to stimulate fish growth in fish farming, Ozone blowing to sterilize ultrapure water systems in pharmaceutical plants, waste or process streams CO_2 or NH_3 to adjust the pH in

Blowing, efficient heating, and direct steam injection to quell steam hammering, air blowing for removal of VOCs (volatile organic compounds) from waste streams, and similar operations.

One problem with many of these operations is the inefficiency of gas distribution. SUMMARY OF THE INVENTION The present invention provides a solution to this problem. In one embodiment, the present invention provides dispersion of relatively small gas bubbles having a relatively large surface area into a liquid. As a result, a relatively large gas/liquid contact area is obtained. The bubbles are small and have a large surface area, so the gas can be efficiently dissolved in the liquid. This results in a reduced gas consumption. It also reduces the time required to dissolve the gas into the liquid, resulting in faster processing and higher productivity. The present invention is a process for making a multiphase mixture comprising flowing a first fluid stream through a process microchannel, the first fluid stream comprising at least one liquid and a /or a step comprising at least one gas and the process microchannel having an open section, flowing a second fluid stream into the process microchannel through the open section;

contacting the streams to form a multi-phase mixture, the second fluid stream comprising at least one gas and/or at least one microbody-forming material, and the first fluid stream comprising a multi-phase mixture; Forming a continuous phase in the phase mixture, the second fluid stream comprising forming a discontinuous phase dispersed within the continuous phase.

[0005]

In one embodiment, the second fluid dissolves in the first fluid. This may occur within the process microchannels or after the multiphase mixture exits the process microchannels. One advantage of the process of the present invention is that, in at least one embodiment, the second fluid in the multiphase mixture has a higher density than the larger bubbles formed by conventional techniques that do not employ microchannel processing technology. The advantage is that it can contain relatively small air bubbles that dissolve more efficiently into the fluid.

[0006]

In one embodiment, the multiphase mixture further comprises solid particles dispersed in the first fluid stream.

[0007]

In one embodiment, heat is exchanged between the process microchannel and the heat source and/or heat sink. In one embodiment, the heat source and/or heat sink comprises at least one heat exchange channel.

[0008]

In one embodiment, the open section extends along at least part of the axial length of the process microchannel. In one embodiment, the open section is at least about 10% of the axial length of the process microchannel, in one embodiment at least about 20% of the axial length of the process microchannel, and in one embodiment at least about 20% of the axial length of

the process microchannel. At least about 35% of the directional length, in one embodiment at least about 50% of the axial length of the process microchannel, in one embodiment at least about 65% of the axial length of the process microchannel, in one embodiment the process It extends along at least about 80% of the axial length of the microchannel, and in one embodi ment at least about 95% of the axial length of the process microchannel.

In one

embodiment, the second fluid stream flows from the second fluid stream channel through th e open section.

[0010]

In one embodiment, between a process microchannel and a heat source and/or heat sink, be tween a second fluid stream channel and a heat source and/or heat sink, or between a proces s microchannel and a second fluid stream channel. and heat sources and/or heat sinks. Heat s ources and/or heat sinks may be used for heating, cooling, or both cooling and heating. The h eat source may include heat exchange channels and/or heating elements. The heat sink may i nclude heat exchange channels and/or cooling elements. In one embodiment, the heat source and/or heat sink can be adjacent to the process microchannel, the second fluid stream channe l, or both the process microchannel and the second fluid stream channel. In one embodiment, the heat source and/or heat sink may be remote from the process microchannel and/or the se cond fluid stream channel, but not into the process microchannel and/or the second fluid strea m channel or into the process microchannel. It should be sufficiently close to the process micr ochannel and/or the second fluid stream channel to transfer heat from the channel and/or the second fluid stream channel.

[0011]

In one embodiment, the process is performed in a polyphase mixer. Within the multi-phase mixer, one or more headers or manifolds are used to provide fluid flow into the process microc hannels, the second fluid stream channels and the heat exchange channels, the process micro channels and the heat exchange channels. One or more footers or manifolds are used to provi de fluid flow out of the exchange channels

.

In one embodiment, the first fluid stream and the second fluid stream contact each other in a mixing zone within the process microchannel. In one embodiment, heat is exchanged betwe en heat sources and/or heat sinks and at least a portion of the process microchannels in the mixing zone. In one embodiment, heat is exchanged between the heat source and/or heat sin k and at least a portion of the process microchannel upstream of the mixing zone. In one emb odiment, heat is exchanged between the heat source and/or heat sink and at least a portion o f the process microchannel downstream of the mixing zone. In one embodiment, the process microchannel has a restricted cross-section within the mixing zone

. In one embodiment, the process microchannel has spaced apart walls and open sections in each of the spaced apart walls, and the second liquid passes through each of the open section

s into the process microchannel. flow into. In one embodiment, the aperture section in each o f the spaced apart walls includes a plurality of apertures, the apertures in the aperture section of one wall being located directly across from the apertures in the aperture section of the opp osite wall. be done. In one embodiment, the opening section in each of the spaced apart walls includes a plurality of openings, and at least some of the openings in the opening section of o ne wall are the openings in the opening section of the other wall. They are staggered so that t hey are not directly opposite each other. [0015]

In one embodiment, the process microchannel is in the multiphase mixture forming unit. The multiphase mixture forming unit includes a first process microchannel, a second process micro channel, and a second fluid channel located between the first and second process microchann els, each The process microchannel has a wall with an open section, a first fluid stream flows t hrough the first process microchannel and a second process microchannel, and a second fluid stream flows through the second process microchannel. From the fluid stream channel, flow t hrough an open section in the first process microchannel to contact the first fluid stream, and flow through an open section in the second process microchannel to allow the first fluid to flo w. come into contact with the current.

[0016]

In one embodiment, a third fluid stream flows in a third fluid stream channel, the third fluid stream channel having another wall with another open section, the process comprising: flowin g a second fluid stream through another open section and contacting the third fluid stream to form another multiphase mixture; and flowing the other multiphase mixture through the open section into the process microchannel; Further comprising contacting with the first fluid strea m. In one embodiment, the process microchannels are formed from parallel spaced sheets a nd/or plates

.

In one embodiment, the second fluid flow channel is formed from parallel spaced apart sheets and/or plates, the second fluid flow channel adjoining the process microchannel. In one embo diment, the heat exchange channels are formed from parallel spaced apart sheets and/or plat es, and the heat exchange channels are process microchannels, second fluid stream channels, or process microchannels and second fluid stream channels. and adjacent to both.

[0018]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mi xer comprising a plurality of process microchannels and a second fluid flow channel, each proc ess microchannel having a wall with an open section. and an adjacent second fluid stream cha nnel, the second fluid stream flowing from the second fluid stream channel through the open

section into the process microchannel to contact the first fluid stream; The process microchan nels and the second fluid stream channels are formed from parallel spaced apart sheets and/o r plates, the process microchannels and the second fluid stream channels being adjacent to ea ch other and alternating side by side. Arranged in the form of planes or alternating planes sta cked on top of each other.

In one

embodiment, the process microchannel includes two or more open sections through each of which a separate second fluid stream flows. In one embodiment, separate second fluid stream s flowing through each of the open sections have different compositions. In one embodiment, separate second fluid streams flowing through each of the open sections have different proper ties.

In one embodiment

, the process is carried out in a microchannel mixer, the microchannel mixer comprising at le ast two process microchannels, in one embodiment at least about ten process microchannels, in one embodiment at least It contains about 100 process microchannels, and in one embodi ment at least about 1000 process microchannels.

[0021]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mi xer comprising a plurality of process microchannels connected to at least one first fluid flow m anifold, the first Fluid streams flow through at least one first fluid stream manifold to the proc ess microchannels. In one embodiment, the process microchannel is adjacent to a second flui d flow channel, the microchannel mixer further comprising at least one second fluid flow manif old connected to the second fluid flow channel, the second Fluid flows through at least one sec ond fluid flow manifold to the second fluid flow channels. In one embodiment, the process mic rochannels and/or liquid channels are adjacent to heat exchange channels, and the microchan nel mixer further comprises at least one heat exchange manifold connected to the heat excha nge channels, wherein the at least one heat exchange manifold is A heat exchange fluid flows through the heat exchange channels.

[0022]

In one embodiment, the second fluid stream flows from the second fluid stream channel thro ugh an open section into the process microchannel, the process microchannel and liquid chan nel comprising concentric annular tubes.

[0023]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mi xer comprising a plurality of process microchannels, with separate multiphase mixtures forme d in each of the process microchannels. , the multiphase mixtures formed in at least two of th e process microchannels are different from each other. These multiphase mixtures may have different compositions and/or different properties. This microchannel mixer can be referred to as a combinatorial synthesis and screening device. One advantage of this embodiment of the

present invention is that it provides for the formation and evaluation of multiple multiphase m ixture products simultaneously using the same equipment. This can be an advantage when it i s desired to screen multiple formulations as new product candidates.

[0024]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mi xer comprising a plurality of multiphase mixture forming units, either side by side or stacked on top of each other, each multiphase mixture The forming unit includes a process microchann el and an adjacent second fluid flow channel, the process microchannel and the adjacent seco nd fluid flow channel having a common wall and an open section within the common wall. , th e open section is adapted to channel a second fluid stream from the second fluid stream chan nel through the open section into the process microchannel, each process microchannel and t he second fluid stream channel being parallel spaced apart. Formed from a sheet, plate, or co mbination of such sheets and plates, the process comprises the steps of: flowing a first fluid s tream through a process microchannel; from a second fluid stream channel through an open s ection of the process microchannel; and mixing the first and second fluid streams in the proce ss microchannel to form a multiphase mixture.

In one embodiment, the process of the present invention can be operated with a relatively lo w flow pressure drop of the first fluid stream through the process microchannel . In one embo diment, the process of the present invention can be operated with a relatively low pressure dr op in the flow of the second fluid stream through the open section into the process microchan nel.

[0026]

In one embodiment, mixing within a process microchannel can be improved through the use of surface features formed on one or more inner walls of the process microchannel. In one em bodiment, the second fluid contacts the first fluid within the process microchannel and then su rface features are formed on one, two or more inner walls of the process microchannel. may fl ow through regions within the processed process microchannel. The surface features are depr essions in one or more of the inner microchannel walls and/or protrusions from the inner micr ochannel walls oriented at an oblique angle to the direction of fluid flow through the process microchannel. It is preferable that it has a shape. The angled component may be oriented wit h the direction of flow or against the direction of flow. The surface features may be placed at an angle (eg, from about 1° to about 89°, in one embodiment from about 30° to about 75°) with respect to the direction of flow. Fluid flow in contact with the surface features forces a po rtion of the fluid flow to flow into the depressions or surface features, while a portion of the fl uid flow continues to flow over the surface features. The flow within the surface feature confor ms to the surface feature and forms an angle to the bulk flow. As the fluid exits the surface fe ature, it can exert momentum in the x and y directions in an x, y, z coordinate system in whic h the bulk fluid flows in the z direction. This effect can stir or rotate the fluid stream. This patt

ern is particularly useful for mixing two-phase flows because the imparted velocity gradient pr oduces fluid shear and breaks up the second fluid into small, well-dispersed bubbles or particu lates. can be done.

[0027]

In one embodiment, mixing of the first and second fluids is achieved using a first surface fea ture area followed by at least one second feature area that creates another flow pattern. As pr acticable, surface feature regions within a process microchannel may be arranged in series. A second flow pattern may be used to separate or separate the first and second fluids. This step may be used to assist in gas or liquid recovery. This embodiment of the present invention pro vides that after the gas is introduced into the liquid, the resulting mixture is passed through a first surface feature region containing a heterogeneous catalyst, a homogeneous catalyst, or n o catalyst. can be particularly useful in the case of gas-liquid reactions that flow through the T he mixture is then subjected to a second surface feature region, where the flow pattern option ally generates centrifugal force, forcing the liquid in an annular flow pattern toward the inner wall of the process microchannel while the gas remains within the fluid core. may flow throug h This latter profile may help separate or draw away unreacted gases from the reactant mixtu re. One pattern of surface features that can create a strong central vortex in the fluid is a pair of angled slots at the top and bottom of the process microchannel. A central vortex flow patte rn can be created. In one embodiment, the foamy mixture may drive liquids toward the walls of the process microchannels and forces gases toward the center of the process microchannel s.

[0028]

In one embodiment, the open section may include interior portions that form part of one or more of the interior walls of the process microchannel. There may be a surface feature sheet over this interior portion of the open section. Surface features may be formed in and/or on th e surface feature sheet. A second fluid may flow through the apertured section and the surfac e component sheet. A flux of fluid entering through the open section can be directed away fro m the surface of the surface feature sheet while within the surface features of the surface feat ure sheet. A surface feature sheet may include angled features having a relatively small width or span compared to the overall flow length. The surface component sheet may provide mech anical support to the apertured section. In addition, the surface composition

The flow vortices or angled flow created by the element further impart shear to the second flu id flowing through the open section, thus reducing the size of particles or bubbles of the secon d fluid in the bulk flow path. can be preferred above. In one embodiment, the multiphase mi xture may comprise a liquid-solids flow or a gas-liquid-solids flow

.

The second fluid stream may comprise a dispersion of solids in either gas or liquid. The first fl uid stream may comprise a gas, a liquid, or solids dispersed in a gas or liquid. Flow of a multi phase mixture through a surface feature section in a process microchannel can act to keep th

e mixture well-mixed or dispersed with momentum different from the direction of imparted flo w. so it can be an advantage. This utilization can be useful for dispersion of solid catalysts in li quid reactants.

[0030]

In one embodiment, the multiphase mixture may comprise solid particles dispersed in the fir st and/or second fluid streams, is in the form of a fluidized bed, and the process microchannel s are process microchannels. It includes surface features formed in and/or on one or more of i ts inner walls to alter the flow therein. This may involve mixing a gas stream into the solid par ticle-containing fluid stream. Solids may be blown into the carrier fluid or entrained by the car rier fluid. Surface constituents may facilitate mixing of multiphase mixtures. In one embodi ment, solids may form in the multiphase mixture as a result of chemical reactions and/or prec ipitation

. [0032]

In one embodiment, the multiphase mixture is in foam form. In one embodiment, the multip hase mixture may optionally contain one or more surfactants. Some foams do not require the presence of surfactants, although they may be included to facilitate foam formation.

[0033]

In the accompanying drawings, similar parts and components have similar reference numera ls. BEST

MODE FOR CARRYING OUT THE INVENTION

The term "microchannel" means a channel within at least one of a height or width of up to a bout 10 millimeters (mm), in one embodiment up to about 5 mm, in one embodiment up to a bout 2 mm, and in one embodiment up to about 1 mm. Refers to a channel with dimensions. Fluid flow through a microchannel can proceed along the length of the microchannel perpendic ular to the height and width of the microchannel. An example of a process microchannel, opti onally a microchannel that can be used as a second fluid stream channel, a third fluid stream channel and/or a heat exchange channel in the process of the present invention is shown in FI G. A microchannel 10, an example of which is shown in FIG. 1, has a height (h), a width (w) a nd an axial length (l). Fluid flows through microchannel 10 along the length of the microchann el in the directions indicated by arrows 12 and 14 . The height (h) or width (w) of the microch annel is about 0.05 to about 10 mm, in one embodiment about 0.05 to about 5 mm, in one e mbodiment about 0.05 to about 2 mm, in one embodiment from about 0.05 to about 1.5 mm, in one embodiment from about 0.05 to about 1 mm, in one embodiment from about 0.05 to a bout 0.75 mm, in one embodiment from about 0.05 to about 0.5 mm should be in the range o f The other dimension of height or width is any dimension, such as up to about 3 meters, in o ne embodiment from about 0.01 to about 3 meters, in one embodiment from about 0.1 to abo

ut 3 meters. good. The axial length (l) of the microchannel can be any dimension, such as up to about 10 meters, in one embodiment from about 0.1 to about 10 meters, in one embodiment from about 0.2 to about 6 meters, in one embodiment Embodiments may be from about 0.2 to about 3 meters. Although the microchannel 10 illustrated in FIG. 1 has a rectangular cross-section, it should be understood that the microchannel may have a cross-section of any shape, such as square, circular, semi-circular, trapezoidal, etc. be. The cross-sectional shape and/or size of a microchannel

can change. For example, the height or width may taper from a relatively large dimension to a relatively small dimension or vice versa over the length of the microchannel.

[0035]

The term "adjacent", when referring to the relative position of one channel to another, means directly adjacent such that a single wall separates these two channels. . This wall may vary in thickness. However, "adjacent" channels are not separated by intervening channels that interfere with heat transfer between the channels.

The

term "surface feature" refers to depressions in and/or protrusions from the microchannel wall that alter flow within the microchannel. Surface features may be circular, oval, square, rectangular, checkered, V-shaped, wavy and similar shapes. A surface component may include sub-components. In this case, the main wall of the surface features further comprises smaller surface features, these surface features being notched, corrugated, jagged, perforated, burred, checked, fan-shaped and similar. There may be. A surface feature has a depth, a width, and a length if it is a non-circular surface feature. Examples are shown in FIGS. Surface features can be formed on or in one or more of the interior sidewalls of the process microchannels used in the processes of the present invention. Surface features can be formed on or in one or more of the interior sidewalls of the second fluid flow channels and/or heat exchange channels used in the process of the present invention. Surface constituents can be referred to as passive surface constituents or passive mixing constituents.

[0037]

The terms "upstream" and "downstream" refer to positions within channels used in the processes of the invention, including microchannels, relative to the direction of fluid flow through the channel. For example, a position within a channel that has not yet been reached by a portion of the fluid flowing through the channel toward that position is downstream of that portion of the fluid. A position within the channel already passed by a portion of the fluid flowing through the channel away from that position is upstream of that portion of the fluid. The terms "upstream" and "downstream" do not necessarily refer to vertical positions, as the process channels used in the process of the invention may be oriented horizontally, vertically, or at an angle.

[0038]

The term "microbody" refers to up to about 200 microns, in one embodiment about 0.01 to

about 200 microns, in one embodiment about 0.01 to about 100 microns, in one embodiment about 0.01 to about 50 microns. , in one embodiment from about 0.01 to about 25 microns, i n one embodiment from about 0.01 to about 10 microns, in one embodiment from about 0.01 to about 5 microns, in one embodiment from about 0.01 to about 2 microns, in one embodim ent from about 0.01 to about 1 micron, in one embodiment from about 0.01 to about 0.5 micr ons, in one embodiment from about 0.01 to about 0.2 microns, in one embodiment about 0.0 1 to about 0.1 microns, in one embodiment about 0.01 to about 0.08 microns, in one embodi ment about 0.01 to about 0.05 microns, in one embodiment about 0.01 to about Refers to a t hree-dimensional body having average dimensions (eg, diameter, height, width, length) in the range of about 0.03 microns. These microbodies include bodies with circular and/or elliptical s haped cross-sections. Microbodies may be spherical, spheroidal, ovoid and similar shapes. The microbodies may have a needle-like shape. Microbodies may be hollow or solid. A microbody may be a microsphere. A microbody may have a major dimension (eg, diameter, length) and a minor dimension (eg, diameter, height, width), wherein the ratio of the major dimension to t he minor dimension is from about 10:1 to about 1:1. 1, in one embodiment from about 5:1 to about 1:1, and in one embodiment from about 2:1 to about 1:1.

The term " fluid

" means a gas, a liquid, a gas or liquid containing dispersed solids, a gas containing droplets, a liquid containing bubbles, a gas containing droplets and dispersed solids, or a liquid containi ng bubbles and dispersed solids,

and analogues.

[0040]

The term "heat source" refers to an object or device that emits heat and can be used to heat another object or device. The heat source may be in the form of a heat exchange channel hav ing a heat exchange fluid therein and transferring heat to another object or device, the other object or device being, for example, adjacent to the heat exchange channel, or Or a channel c lose enough to receive the heat transferred from the heat exchange channel. A heat exchange fluid may be contained within and/or flow through the heat exchange channels. The heat sour ce may be in the form of a heating element, such as an electric heating element or a resistanc e heater. The term "heat sink" refers to an object or device that absorbs heat and can be used to cool another object or device. A heat sink may be in the form of a heat exchange channel h aving a heat exchange fluid therein that receives heat transferred from another object or devi ce. Another object or device is, for example, a channel adjacent to or sufficiently close to the heat exchange channel to conduct heat to the heat exchange channel. A heat exchange fluid may be contained within and/or flow through the heat exchange channels. The heat sink may be in the form of a cooling element, eg, a non-fluid cooling element.

[0041]

The term "heat source and/or heat sink" refers to an object or device that can emit heat or a bsorb heat. A heat source and/or heat sink has a heat exchange fluid therein that transfers he

at to another object or device adjacent to or near the heat exchange channel when the other object or device is heated. even in the form of a heat exchange channel that conducts or recei ves heat transferred from another object or device adjacent to or near the heat exchange cha nnel when the other object or device is cooled good. A heat exchange channel that functions a s a heat source and/or a heat sink may function as a heating channel at some times and a co oling channel at other times. A portion(s) of the heat exchange channels may function as heat ing channels, while another portion(s) of the heat exchange channels may function as cooling channels.

The term "heat exchange channel" refers to a channel having a

heat exchange fluid therein and capable of releasing heat and/or absorbing heat.

[0043]

The term "heat exchange fluid" refers to a fluid capable of producing and/or absorbing heat.

[0044]

Referring to FIG. 2, the process can be performed using a microchannel mixer 100, which in cludes a microchannel mixer core 102, a process fluid header 104, a product footer 106 and a heat exchange manifold 108. include. Microchannel mixer core 102 includes a plurality of proc ess microchannels, adjacent second fluid flow channels and heat exchange channels. The seco nd fluid flow channels and/or heat exchange channels may be microchannels. The process mic rochannels, second fluid stream channels and heat exchange channels may be arranged in lay ers, one above the other or side by side. The process header 104 allows a first fluid stream to flow into the process microchannels and a second fluid flow to flow into the second fluid flow c hannels to provide a uniform or substantially uniform flow distribution in these channels. provi de an aisle for The product footer 106 provides a passageway for the multiphase mixture prod uct to flow rapidly from the process microchannels and have a relatively high flow rate. A first fluid stream enters microchannel mixer 100 through header 104 , as indicated by arrow 110 . A second fluid stream enters microchannel mixer 100 through header 104 , as indicated by ar row 112 . The first fluid stream and the second fluid stream enter the microchannel mixer cor e 102 and mix to form a multiphase mixture. The multiphase mixture flows from the microcha nnel mixing core 102 to the product fluoride.

through footer 106 and out of product footer 106 as indicated by arrow 114 . In one embodim ent, the multiphase mixture may be recycled back through the microchannel mixer core 102 a ny number of times, eg, 1, 2, 3, 4, etc. times. Heat exchange fluid flows into heat exchange manifold 108 as indicated by arrow 116, from heat exchange manifold 108, through heat exch ange channels in microchannel mixer core 102, and back to heat exchange manifold 108, whe re arrow It exits the heat exchange manifold 108 as indicated at 118 . Microchannel mixer 10 0 may be used with reservoirs, pumps, valves, flow control devices and similar devices. These are not shown in the drawings but are obvious to those skilled in the art.

[0045]

The microchannel mixer core may contain multiple multiphase mixture forming units. Figure

s 3-9 and 12 show examples of useful embodiments of multiphase mixture forming units. Ref erring to FIG. 3, the process of the present invention can be carried out using a multiphase mi xture forming unit 200 that includes a process microchannel 210 having opposing sidewalls 21 2 and 214 and an open section 240 in sidewall 212. can. The open section 240 may be referre d to as a porous section or porous substrate. Aperture section 240 may include a sheet or plat e 242 having an array of apertures 244 extending throughout the aperture section. Adjacent s idewall 212 is a second fluid stream 270 that opens into process microchannel 210 through op ening 244 in open section 240 . Process microchannel 210 has non-open or non-porous region s 211 and 217 and mixing zone 213 . A non-apertured region 211 extends from the entrance to the process microchannel to the entrance to the mixing zone 313 . A non-apertured region 211 is upstream of the mixing zone 213 . Mixing section 213 is adjacent to aperture section 2 40 . A non-apertured region 217 extends from the end of the mixing zone 213 to the exit of t he process microchannel 210 . A non-apertured region 217 is downstream of the mixing zone 213 . Adjacent to sidewall 214 are heat exchange channels 290 . In operation, a first fluid stre am enters process microchannel 210 , through non-apertured region 211 and into mixing zon e 213 , as indicated by arrow 216 . A second fluid stream enters second fluid stream channel 270 , as indicated by arrow 272 , and then through open section 240 and into mixing zone 21 3 , as indicated by arrow 274 . Within the mixing zone 213, the second fluid stream contacts and mixes with the first fluid stream to form a multiphase mixture. The second fluid stream m ay form a discontinuous phase within the first fluid stream. The first fluid stream may form a continuous phase. The multiphase mixture passes from mixing zone 213 through non-apertur ed region 217 and into the process as indicated by arrow 218. out of the microchannel 210 . Heating or cooling can be an option. When heating or cooling is desired, a heat exchange fluid flows through heat exchange channels 290, as indicated by arrows 292, to heat or cool the flu id in process microchannels 210 and second fluid flow channels 270. . The degree of heating o r cooling may vary over the length of process microchannel 210 and second fluid stream chan nel 270 . Heating or cooling may be negligible or non-existent in some sections of the process microchannels and liquid channels, and may be moderate or relatively large in other sections. Alternatively, heating or cooling may be accomplished using other than heat exchange channe ls. For example, heating may be accomplished using electrical heating elements or resistance heaters. Electrical heating elements or resistive heaters may be used to form one or more wal ls of process microchannel 210 and/or second fluid flow channel 270 . Electric heating elemen ts or resistive heaters may be in one or more walls of process microchannel 210 and/or secon d fluid flow channel 270 . Cooling may be accomplished using non-fluid cooling elements. Mult iple heating or cooling zones may be used along the length of the process microchannel 210 . Similarly, varying temperatures of heat exchange fluid may be used in one or more heat exch ange channels along the length of process microchannel 210 and/or second fluid stream chan nel 270 . Some sections of the liquid channel may be negligible or non-existent, while others may be moderate or relatively large. Alternatively, heating or cooling may be accomplished us

ing other than heat exchange channels. For example, heating may be accomplished using elec trical heating elements or resistance heaters. Electrical heating elements or resistive heaters may be used to form one or more walls of process microchannel 210 and/or second fluid flow channel 270 . Electric heating elements or resistive heaters may be in one or more walls of pr ocess microchannel 210 and/or second fluid flow channel 270 . Cooling may be accomplished using non-fluid cooling elements. Multiple heating or cooling zones may be used along the len gth of the process microchannel 210 . Similarly, varying temperatures of heat exchange fluid may be used in one or more heat exchange channels along the length of process microchanne l 210 and/or second fluid stream channel 270 . Some sections of the liquid channel may be ne gligible or non-existent, while others may be moderate or relatively large. Alternatively, heatin g or cooling may be accomplished using other than heat exchange channels. For example, hea ting may be accomplished using electrical heating elements or resistance heaters. Electrical h eating elements or resistive heaters may be used to form one or more walls of process microc hannel 210 and/or second fluid flow channel 270 . Electric heating elements or resistive heate rs may be in one or more walls of process microchannel 210 and/or second fluid flow channel 270 . Cooling may be accomplished using non-fluid cooling elements. Multiple heating or cooli ng zones may be used along the length of the process microchannel 210 . Similarly, varying t emperatures of heat exchange fluid may be used in one or more heat exchange channels alon g the length of process microchannel 210 and/or second fluid stream channel 270 .

Multiphase mixture forming unit 200A, an example of which is shown in FIG .
It is identical to the multi-phase mixture forming unit 200 illustrated in FIG. The tapered secti on 220 reduces the width or height of the process microchannel 210 in the mixing zone 213, t hus providing a narrower cross-section for the process microchannel 210 in the mixing zone 2 13. FIG. This width or height may range from about 0.001 to about 5 mm, and in one embodi ment from about 0.01 to about 2 mm. The presence of the tapered section 220 results in an i ncrease in the velocity of the fluid flowing through the mixing section 213 . As the velocity of t he liquid flowing through mixing zone 213 increases, the shear force acting on the second flui d entering mixing zone 213 through openings 244 increases. This facilitates flow of the secon d fluid stream through opening 244 . The velocity through the mixing zone 213 of the fluid flo wing through the narrowed cross-section of the process microchannel 210 is from about 0.00 5 to about 100 meters per second (m/s), in one embodiment from about 0.01 to about It sho uld be in the range of 50 m/s.

[0047]

Multiphase mixture forming unit 200B illustrated in FIG. 5 is similar to the multiphase mixtur e illustrated in FIG. 3, except that multiphase mixture forming unit 200B also includes second fluid flow channel 270a and open section 240a. Similar to forming unit 200 . A second fluid flo w channel 270 a is located between the process microchannel 210 and the heat exchange cha nnel 290 . An open section 240a is formed in sidewall 214 . A second fluid flow channel 270a

opens into the process microchannel 210 through the open section 240a. Aperture section 24 0a may include a sheet or plate 242a having an array of apertures 244a extending therethrou gh. Process microchannel 210 has non-open or non-porous regions 211 and 217 and mixing z one 213 . Non-apertured region 211 extends from the entrance to the process microchannel t o the entrance to mixing zone 213 and is upstream of mixing zone 213 . Mixing section 213 is located between aperture sections 240 and 240a. A non-apertured region 217 extends from t he end of mixing zone 213 to the exit of process microchannel 210 . A non-apertured region 2 17 is downstream of the mixing zone 213 . In operation, a first liquid stream enters process m icrochannel 210 , as indicated by arrow 216 , through non-opened region 211 and into mixing zone 213 . A second fluid stream flows into second fluid stream channels 270 and 270a, as in dicated by arrows 272 and 272a, respectively. A second fluid stream enters mixing section 21 3 through open sections 240 and 240a, as indicated by arrows 274 and 274a, respectively. Wi thin the mixing zone 213, the second fluid stream contacts and mixes with the first fluid strea m to form a multiphase mixture. The second fluid stream may form a discontinuous phase wit hin the first liquid. The first fluid stream may form a continuous phase. The multiphase mixtur e exits process microchannel 210 through non-opened region 217 as indicated by arrow 218 . Heating or cooling may be an option. addition When heat or cooling is desired, heat exchange fluid flows through heat exchange channels 290, as indicated by directional arrows 292, to he at or cool the fluid in process microchannels 210 and second fluid flow channels 270. do. The degree of heating or cooling may vary over the length of the process microchannel and the se cond fluid stream channel. Heating or cooling may be negligible or non-existent in some sectio ns within the process microchannels and liquid channels, and may be moderate or relatively la rge in other sections.

The multiphase mixture forming unit 200C illustrated in FIG. 6 had openings 244 and 244a il lustrated in FIG . 244 and 244a are identical to the multi-phase mixture forming unit 200B illu strated in FIG. 5, except that 244 and 244a are offset from such direct orientation. In FIG. 5, streams of the second fluid stream flowing through openings 244 and 244a collide directly wit h each other, thereby promoting diffusion of the second fluid stream into the first fluid stream. . 6, the streams of the second fluid stream flowing through openings 244 and 244a are offset from each other, thereby promoting diffusion by providing a swirling effect within mixing zone 213. In FIG.

[0049]

Multiphase mixture forming unit 200D, an example of which is shown in FIG. An open sectio n 240 is formed in sidewall 212 and an open section 240a is formed in sidewall 212a. Apertur e sections 240 and 240a may be referred to as porous compartments or porous substrates. Th rough open sections 240 and 240a, a second fluid flow channel 270 opens to process microch annels 210 and 210a, respectively. Aperture section 240 may include a sheet or plate 242 hav ing an array of apertures 244 extending therethrough. Similarly, apertured section 240a may i

nclude a sheet or plate 242a having an array of apertures 244a extending therethrough. Proc ess microchannels 210 and 210a have non-open or non-porous regions 211 and 217, and 211 a and 217a, and mixing zones 213 and 213a, respectively. Non-apertured regions 211 and 21 1a extend from the inlets to process microchannels 210 and 210a to the inlets to mixing zone s 213 and 213a, respectively. Non-apertured regions 211 and 211a are upstream of mixing zo nes 213 and 213a, respectively. Mixing zones 213 and 213a adjoin open sections 240 and 240 a, respectively. Non-apertured regions 217 and 217a extend from the ends of mixing zones 2 13 and 213a to the exits of process microchannels 210 and 210a, respectively. Non-apertured regions 217 and 217a are downstream of mixing zones 213 and 213a, respectively. Adjacent t o process microchannel 210 are heat exchange channels 290 . In operation, a first fluid strea m flows through process microchannels 210 and 210a, respectively, as indicated by arrows 21 6 and 216a, through unopened regions 211 and 211a and into mixing zones 213 and 213a. As indicated by arrow 272, the second A second fluid stream enters two fluid stream channels 27 0 and then through open sections 240 and 240a into mixing zones 213 and 213a, respectivel y, as indicated by arrows 274 and 274a. Within mixing zones 213 and 213a, the second fluid s tream contacts and mixes with the first fluid stream to form a multiphase mixture. The second fluid stream may form a discontinuous phase within the first fluid stream. The first fluid strea m may form a continuous phase. The multiphase mixture flows through non-opened compart ments 217 and 217a and out of process microchannels 210 and 210a, respectively, as indicat ed by arrows 218 and 218a. Heating or cooling can be an option. When heating or cooling is d esired, heat exchange fluid flows through heat exchange channel 290 , as indicated by arrows 292 , to heat or cool the fluid in channels 210 , 210 a and 270 . The degree of heating or cooli ng may vary over the length of the channel. Heating or cooling may be negligible or nonexiste nt in some sections of process microchannels 210 and 210a and second fluid stream channel 270, and may be moderate or relatively large in other sections. Heats or cools the fluid in the cells 210, 210a and 270. The degree of heating or cooling may vary over the length of the cha nnel. Heating or cooling may be negligible or nonexistent in some sections of process microch annels 210 and 210a and second fluid stream channel 270, and may be moderate or relatively large in other sections. Heats or cools the fluid in the cells 210, 210a and 270. The degree of heating or cooling may vary over the length of the channel. Heating or cooling may be negligi ble or nonexistent in some sections of process microchannels 210 and 210a and second fluid s tream channel 270, and may be moderate or relatively large in other sections.

In one embodiment, multiple multiphase mixing

formulations and/or sets of processing conditions can be used to generate separate multipha se mixtures within a single microchannel mixer. For example, a single microchannel mixer use s two or more process microchannels, associated second fluid stream channels, and heat exch ange channels to achieve 2, 3, 4 , 5, 6, 7, 8, 9, 10, tens, hundreds, thousands, tens of thousa nds, hundreds of thousands, etc. distinct multiphase mixtures can be made. Mixers of this typ e may be referred to as combinatorial synthesis devices. This is illustrated in Figure 8, where

an example of a multi-phase mixture forming unit 300 is shown. The multiphase mixture form ing unit 300 uses four process microchannels so that up to four separate multiphase mixtures can be generated. The multiphase mixture forming unit 300 can be operated any desired num ber of times, such as 2, 3, 4, 5, 6, 7, 8, 9, 10, 10, 100, Thousands, tens of thousands, etc. of repetitions can provide the possibility of multiple distinct multiphase mixtures as indicated abo ve. The multiphase mixture forming unit 300 includes process microchannels 310, 320, 330 a nd 340, the

It includes two fluid flow channels 350 and 360 and heat exchange channels 370 and 380 . An open section 311 is formed in the sidewall 312 . An open section 321 is formed in the sidewall 322 . An open section 331 is formed in sidewall 332 . An open section 341 is formed in sidewa ll 342 . Apertures 313, 323, 333 and 343 are located in and extend through aperture sections 311, 321, 331 and 341, respectively. Process microchannels 310, 320, 330 and 340 include cl osed compartments 314, 324, 334 and 344 located upstream of mixing zones 315, 325, 335 and 345, respectively. Mixing zones 315, 325, 335 and 345 are located adjacent to aperture z ones 311, 321, 331 and 341, respectively. Process microchannels 310, 320, 330 and 340 also include closed compartments 316, 326, 336 and 346 located downstream of mixing zones 31 5, 325, 335 and 345, respectively. In operation, a first fluid stream flows into process microch annels 310, 320, 330 and 340, as indicated by arrows 317, 327, 337 and 347, respectively. T he first fluid streams entering process microchannels 310, 320, 330 and 340 may have the sa me composition as each other or may have different compositions. The first fluid stream enter s mixing zones 315, 325, 335 and 345 through non-open compartments 314, 324, 334 and 3 44, respectively. A second fluid stream enters second fluid stream channels 350 and 360 as in dicated by arrows 351 and 361 . The second fluid flow entering second fluid flow channel 350 may be the same as or different from the second fluid flow entering second fluid flow channel 360 . The difference between the second fluid stream entering the second fluid stream channe l 350 and the second liquid entering the liquid channel 360 may be due to composition, proces sing conditions, physical properties (e.g., viscosity, density, surface tension, etc.).) and/or m ay be based on operating parameters. A second fluid stream entering second fluid stream cha nnel 350, as indicated by arrow 351, flows through open sections 311 and 321 and into mixin g sections 315 and 325, as indicated by arrows 352 and 353. flow into each. Within mixing zo nes 315 and 325, the second fluid stream contacts and mixes with the first fluid stream to for m a multiphase mixture. Similarly, a second fluid stream flows into second fluid stream chann el 360, as indicated by arrow 361, and then through open sections 331 and 341, as indicated by arrows 362 and 363, into the mixing zone. 335 and 345 respectively. Within mixing zones 315, 325, 335 and 345, the second fluid stream contacts and mixes with the first fluid stream to form a multiphase mixture. The multiphase mixtures formed in mixing zones 315, 325, 335 and 345 may be the same or different. When different, multiphase mixtures may vary in com position and/or physical properties or operational parameters (e.g., dispersed and/or continuo us phase composition, particle size, particle size distribution, viscosity, density, surface tensio

n, temperature, pressure, flow rate, etc.). etc.) may be different from each other. The multiph ase mixture passes from mixing zones 315, 325, 335 and 345 through non-apertured zones 3 16, 326, 336 and 346 to process microchannels 310, 320, 320, 348, respectively, as indicated by arrows 318, 328, 338 and 348, respectively. It flows out from 330 and 340. Heating or coo ling using heat exchange channels 370 and 380 may be an option. When heating or cooling is desired, heat exchange fluid flows through heat exchange channels 370 and 380, as indicated by arrows 371 and 372, and 381 and 382, and channels 310, 320, 330, 340, 360 and 360 he ats or cools the fluid in The degree of heating or cooling may vary over the length of each of t he channels. In sections with process channels and/or liquid channels may have negligible or no heating or cooling, and may be moderate or relatively large in other intervals. One advanta ge of this embodiment of the present invention is that the same equipment can be used to pr ovide for the formation and evaluation of multiple multiphase mixture products at the same ti me. This can be an advantage when it is desired to screen multiple formulations as new produ ct candidates.

In one embodiment, the process of the invention is suitable for making dual multiphase mixt ures . These dual multiphase mixtures are made using multiphase mixture forming unit 400, a n example of which is shown in FIG.
can be done. In FIG. 9, multiphase mixture forming unit 400 is positioned between centerlines 402 and 404 . Multiphase mixture forming unit 400 includes process microchannel 410 and liq uid channels 420 , 430 , 440 and 450 . Fluid flow channels 420 and 430 adjoin process microc hannel 410 . Fluid flow channel 440 is adjacent to fluid flow channel 420 and fluid flow channe l 450 is adjacent to fluid flow channel 430 . A common wall 412 containing a coarsely open se ction 415 separates the process microchannel 410 and the fluidic channel 420 . A common wa ll 422 containing a coarsely open section 425 separates the process microchannel 410 and the fluidic channel 430 . Aperture sections 415 and 425 include apertures 416 and 426, respective ly. Located between fluid flow channel 440 and fluid flow channel 420 is a micro-aperture secti on 435 including opening 436 to separate fluid flow channel 440 and fluid flow channel 420 . Between fluid flow channel 450 and fluid flow channel 430 is a micro-aperture section 445 incl uding opening 446 to separate fluid flow channel 450 and fluid flow channel 430 . Apertures 4 16 and 426 in coarsely apertured sections 415 and 425 are larger than apertures 436 and 446 in finely apertured sections 435 and 445 . Process microchannel 410 has a non-open or non-p orous region 411 and a mixing zone 413 . Non-apertured region 411 extends from the inlet to the process to the inlet to mixing zone 413 . Mixing section 413 is adjacent to open sections 4 15 and 425 . Optionally, heat exchange channels may be inserted at locations indicated by ce nterlines 402 and/or 404 to provide the desired heating or cooling to the fluid.
[0052]

Below centerline 402 lies a portion of adjacent multi-phase mixture forming unit 400a, an ex ample of which is also shown in FIG. Multiphase mixture forming unit 400a includes process m

icrochannel 410a, coarsely open sections 415a and 425a, fluid flow channel 430a and finely o pen section 445a. These are the same as the process microchannel 410, coarsely apertured s ections 415 and 425, fluid flow channel 430 and finely apertured section 445 discussed above. Also located above centerline 404 in FIG. 9 is a portion of another adjacent multiphase mixtur e forming unit 400b. Multiphase mixture formation 400b includes micro-opened section 435b and fluid flow channel 420b. These are the same as the micro-aperture section 435 and fluid f low channel 420 discussed above. The inclusion of portions of multiphase mixture forming uni ts 400a and 400b in FIG. 9 illustrates the repetitive nature of multiphase mixture forming unit 400 when used in a microchannel mixer for the process of the present invention. An example i s given.

[0053]

In operation, referring to FIG. 9, a first fluid stream enters the process microchannel 410 an d flows through the non-apertured region 411 into the mixing zone 413 as indicated by arrow 414 . A second fluid flow enters fluid flow channels 420 and 430, as indicated by arrows 423 a nd 433, respectively. A third fluid stream enters liquid channels 440 and 450, as indicated by arrows 442 and 452, respectively. A third fluid stream flows from fluid stream channel 440 thr ough open section 435 into fluid stream channel 420 and mixes with the second fluid stream t o form another multiphase mixture. A third fluid stream also enters fluid stream channel 430 f rom fluid stream channel 450 through open section 445 and mixes with the second fluid strea m to form another multiphase mixture. The third fluid stream forms the discontinuous phase and the second fluid stream forms the continuous phase in another multiphase mixture forme d in fluid flow channels 420 and 430 . Another multiphase mixture formed in fluid stream cha nnels 420 and 430 enters mixing zone 413 through open sections 415 and 425, respectively, and is mixed with the first fluid stream. Within the mixing zone 413, the additional multiphase mixture is dispersed as a discontinuous phase into the first fluid stream, and the first fluid str eam is brought into continuous phase form. The multiphase mixture formed in mixing zone 41 3 may be referred to as a dual multiphase mixture. Within the dual multiphase mixture, at lea st a portion of the third fluid stream can be encapsulated within the bubbles or microbodies (e g, microspheres) of the second fluid stream. Encapsulated bubbles or microbodies can be disp ersed as a discontinuous phase within the first fluid stream, which can be in the form of a con tinuous phase. A dual multiphase mixture is shown by arrow 418
, exit the process microchannel 410 . A dual multiphase mixture, which in one embodiment m ay be in the form schematically shown in FIG. It includes a third fluid stream 492 (ie, gas) enc apsulated within a fluid stream 494 (eg, liquid or microbody).

[0054]

In one embodiment, the process of the present invention can be used in an air blowing proce ss. An example of this is shown in FIGS. In this embodiment, the process is performed using an air-blown tank 500 containing a microchannel mixer 502 . In operation, air-blown fluid is c ontained within tank 500 and enters microchannel mixer 502 as a first fluid stream, as indicat

ed by arrow 504 . An example of a fluid that can be aerated is cell culture medium. A second f luid stream enters microchannel mixer 502 , as indicated by arrow 506 . The second fluid stre am may contain air or oxygen. A first fluid stream (e.g., cell culture medium) is mixed with a second fluid stream (e.g., air or oxygen) in the microchannel mixer, resulting in a multiphase mixture (e.g., air-blown cell culture medium). is formed. Microchannel mixer 502 may include multiple multiphase mixture forming units. The multiphase mixture forming unit 510 may be i n the form of a process microchannel 520, secondary fluid stream channels 530 and 540, ope n sections 550 and 560 which may be in the form of fine ceramic membranes, macroporous s upports. Includes open sections 570 and 580 and heat exchange channel 590 . In operation, a first fluid stream enters process microchannel 520 as indicated by arrow 522 . A second fluid stream enters second fluid stream channels 530 and 540, as indicated by arrows 532 and 54 2, respectively. The second fluid stream flows from second fluid stream channel 532 through o pen section 570 and then into process microchannel 520 through open section 550 . Similarly, another second fluid stream enters second fluid stream channel 540 , through open section 58 0 , and then through open section 560 and into process microchannel 520 , as indicated by ar row 542 . do. The first fluid stream and the second fluid stream are mixed in the process micr ochannel 520 to form a multiphase mixture. Polyphase The mixture exits process microchann el 520 as indicated by arrow 524 . Within the multiphase mixture, the first fluid stream may f orm the continuous phase and the second fluid stream may form the discontinuous phase. In one embodiment, the multiphasic mixture can comprise a cell culture medium having elevated levels of oxygen or air dispersed throughout the cell culture medium. The fluid can be heated or cooled by flowing the heat exchange fluid through the microchannel mixer 502, through th e heat exchange channels 590, and out of the microchannel mixer 502, as indicated by arrows 507. .

Although only one multiphase mixture forming unit is fully illustrated in each of FIGS. 3-9 an d 12, it may be used in a microchannel mixer to carry out the process of the present invention . There is virtually no upper limit to the number of multiphase mixture forming units. For exa mple, 1, 2, 3, 4, 5, 6, 8, 10, 20, 50, 100, hundreds, 1000, 1000, 10,000, tens of thousands, 100,000, 100,000, 1 million A multi-phase mixture forming unit as described above may also be used. In one embodiment, each multiphase mixture forming unit may be manifolded. Manif old connections may be accomplished by connecting macro-, pipe-, or duct-lines to each unit. Alternatively, multiple multiphase mixture forming units may be internally manifolded within a microchannel mixer containing the multiphase mixture forming units by creating relatively eq ual pressure drop circuits between each unit. On the other hand, the pressure drop need not be equal between each unit, as some flow imbalance may not affect product quality. In one e mbodiment, flow imbalances of up to about 50% are acceptable in forming multiphase mixtur es using the process of the present invention. The process microchannels, associated second and third fluid flow channels, and heat exchange channels may be arranged side-by-side or on

e above the other. For example, in multiphase mixture forming units 200 and 200A, process microchannels 210 may be arranged in a plane and parallel, and the second fluid
The flow channels 270 may be arranged parallel in adjacent planes on one side of the process microchannels 210 and the heat exchange channels 290 may be arranged parallel in another plane on the opposite side of the process microchannels 210 . For example, in multi-phase mi xture forming units 200B and 200C, process microchannels 210 may be arranged in one plane and parallel, and second fluid flow channels 270 and 270a are adjacent planes on each side of process microchannel 210. The heat exchange channels 290 may be arranged parallel in a pla ne adjacent to the second fluid flow channel 270a. In the multi-phase mixture forming unit 20 0D, the second fluid flow channels 270 may be arranged parallel in one plane and the process microchannels 210 and 210a are arranged parallel in adjacent planes on each side of the liqui d channel 270. The heat exchange channels 290 may be arranged parallel and in a plane adja cent to the process microchannels 210 . These multi-phase mixture forming units are not sho wn in FIGS. 3-9 and 12, but can be provided by those skilled in the art, with suitable headers, It may have footers, manifolds, valves, conduits, piping, control mechanisms, and the like. Fo r example, using slanted headers and footers to connect conduits or tubing at the inlets and o utlets to microchannel mixers containing multiphase mixture forming units to reduce unneces sary pressure drops associated with the size of the process microchannels. You can avoid it.
[0056]

In one embodiment, multiple multi-phase mixture forming units (200, 200A, 200B, 200C, 20 0D, 300, 400, 510) are stacked on top of each other to form the core of a scaled-up unit for la rge on-demand production capacity. may be formed. A scaled-up unit may have slanted head ers and footers not only for the multiphase mixture product, but also as manifolds for the liqui ds used to form the multiphase mixture. A more uniform flow distribution may be facilitated b y the addition of orifice plates or other open sections at the inlets of process channels, dispers ed phase channels or heat exchange channels. A frame section may be used to hold and seal t he multiphase mixture forming unit.
[0057]

Each of the process microchannels (210, 210a, 310, 320, 330, 340, 410, 520) may have any configuration, e.g., square, rectangular, circular, annular, elliptical, trapezoidal, etc. cross-secti on. . A process microchannel may be tubular. Process microchannels may be formed from par allel spaced apart sheets and/or plates that are placed side by side or stacked one on top of t he other. The term "sheet" refers to wall thicknesses up to about 5 mm. The term "plate" refe rs to a wall thickness of about 5 mm or greater. Sheets may be supplied to the user in the for m of rolls, while plates may be supplied to the user in the form of flat strips of material. Each of the process microchannels has internal dimensions (e.g., height, width or diameter). This di mension is about 0.05 to about 50 mm, in one embodiment about 0.05 to about 10 mm, in on e embodiment about 0.05 to about 5 mm, in one embodiment about 0.05 to about 2 mm, in o ne embodiment Embodiments may range from about 0.05 to about 1.5 mm, in one embodime

nt from about 0.05 to about 1 mm, and in one embodiment from about 0.05 to about 0.5 m m. Another internal dimension (e.g. height or width) perpendicular to the flow of liquid throug h the process microchannel may be any value, e.g. 01 cm to about 75 cm, in one embodiment from about 0.1 cm to about 50 cm, and in one embodiment from about 0.2 cm to about 25 c m.

[0058]

In one embodiment, the process microchannels (210, 210a, 310, 320, 330, 340, 410, 520) are mixed to provide uniform distribution of the first liquid flow within the process microchann els. non-open or non-porous regions (211, 211) in the inlet upstream of the zones (213, 213 a, 315, 325, 335, 345, 413)
a, 314, 324, 334, 344, 411). This can be useful when multiple process microchannels are arra nged side by side and/or on top of each other and the first liquid flow into the multiple proces s microchannels is not uniform. be. Providing these non-open areas may stabilize the flow of t he first fluid stream prior to reaching the mixing zone. The use of non-opened or non-porous r egions can be advantageous when the process microchannel has a circular cross-section (ie tu bular geometry). In one embodiment, the ratio of the length of the non-open area from the e ntrance to the process microchannel to the entrance to the mixing zone to the minimum inter nal dimension of the process microchannel within the non-open area or non-porous area is ab out It may range from 0.0001 to about 10000, in one embodiment from about 0.001 to about 1000.

[0059]

One or more of the interior walls of the process microchannels (210, 210a, 310, 320, 330, 3 40, 410, 520) may have surface features for altering flow within the process microchannels. . Examples of these surface features are shown in Figures 22-26. A surface feature may have t wo or more layers that are overlaid or intertwined with each other in a three-dimensional patt ern. The patterns in each separate layer may be the same or different. The flow may rotate or translate within each layer or within only one layer. Additional surface area may be created usi ng sublayers that may not be adjacent to the bulk flow channel. For example, these may be u sed to deposit a catalyst. The flow may rotate within the first level of surface features and mol ecularly diffuse into the second sublayer and beyond to facilitate reactions. Three-dimensional components may be made by metal casting or other processes. These methods also do not re quire the varying patterns to be decomposed into separate planes as if they were layered on t op of each other. A three-dimensionally varying surface feature can be placed adjacent to the bulk flow channel. These components have varying depths, shapes and locations, with sub-co mponents having patterns of varying depths, shapes and locations. Surface structures can be advantageous for chemical reactions that require additional surface area for catalyst depositio n, or for chemical separations such as distillation.

[0060]

FIG. 23 is a schematic plan view of a three-dimensional surface component structure. FIG. 2

4 shows an example of a back view of a three-dimensional surface element structure, with a r ecessed V at the adjacent interfaces of the bulk flow microchannels, and below the V is a bulk flow microchannel. There is a series of three-dimensional structures made up of structures of varying shapes, depths and locations that are connected to the passageway adjacent compon ents. It is further advantageous to create sub-layer passages that are not directly beneath op en surface features, but adjacent to bulk flow microchannels, but connected by one or more t ortuous two-dimensional or three-dimensional passages. Sometimes. This approach can be ad vantageous for creating a tailored residence time distribution in a reactor where it is desirable to have a broad residence time distribution rather than a narrow residence time distribution. FIG.

25 shows a three-dimensional surface feature in which a recessed V borders the bulk flow mi crochannel, behind the V is additional features of various shapes at varying depths and locatio ns. is a front view of the. The surface features may have a depth of less than about 2 mm, i n one embodiment less than about 1 mm, and in one embodiment in the range of about 0.01 mm to about 0.5 mm

.

The lateral width of the surface features should be sufficient to nearly reach the microchannel width (as shown in a fishbone design), but in one embodiment (such as fill features) is about 60% or less of the microchannel width. , in one embodiment about 40% or less, in one embo diment from about 0.1% to about 60%, and in one embodiment from about 0.1% to about 5 0%.

[0063]

The lateral width of the surface features ranges from about 0.05 mm to about 100 cm, and i n one embodiment is about 0 cm.

. It may range from 5 mm to about 5 cm, and in one embodiment from about 1 to about 2 c m.

[0064]

The length and width of the surface features may be defined similarly to the length and widt h of the microchannel. Depth may be the distance that a surface feature sinks into the microc hannel surface, in which case it is in the same direction as the microchannel height or the mic rochannel gap. This may correspond to the direction of stacking the laminated and bonded mi crochannel devices with surface features formed on or in the sheet surface. These dimensions of the surface feature refer to the maximum dimension of the surface feature. For example, th e depth of a groove with rounded corners may refer to the maximum depth, ie, the depth at t he bottom of the groove.

A microchannel

may contain multiple surface features or regions of surface features, including features that are recessed into one or more microchannel walls at varying depths. The spacing between the indentations may range from about 0.01 to about 10 mm, and in one embodiment from about

0.1 to about 1 mm. Surface features may be present throughout the length of the microchannel or may be present in portions or regions of the microchannel. Portions or regions having surface features may be intermittent so as to facilitate desired reactions or unit operations within specially tailored areas. For example, a 1 inch section of microchannel may have an array of dense surface features, followed by a 4 inch flat channel with no features, and a subsequent 2 inch section of sparse surface features. Sparsely spaced surface features refer to surface features having a pitch or inter-feature distance greater than five times the length of the surface features.

[0066]

In one embodiment, the surface features may extend substantially the entire axial length of the microchannel. In one embodiment, a microchannel may have surface features over about 50% or less of its axial length, and in one embodiment over about 20% or less of its axial length. In one embodiment, the surface features may extend over about 10% to about 100% of the axial length of the microchannel.

FIG.

26 shows several different patterns that can be used for surface features. These patterns are not meant to limit the invention, but merely to give examples of the possibilities. As with any surface feature, the pattern may be used in various axial or lateral sections of the microchannel.

[0068]

The second fluid flow channels (270, 270a, 350, 360, 420, 430, 530, 540) and the third fluid flow channels (440, 450) have dimensions too large to be characterized as microchannels. However, it is preferable that it is a microchannel. Each of these channels may have any configuration, eg, square, rectangular, circular, annular, elliptical, trapezoidal, etc. cross-section. These channels may include surface features, as described above. The second and third fluid flow channels may be tubular. The second and third fluid flow channels may be formed from parallel spaced apart sheets and/or plates arranged side-by-side or one above the other. Each second and third fluid flow channel ranges up to about 100 cm, in one embodiment from about 0.05 mm to about 100 cm, in one embodiment from about 0.05 mm to about 50 cm, in one embodiment about 0 cm. 0.05 mm to about 10 cm, in one embodiment about 0.05 mm to about 5 cm, in one embodiment about 0.05 mm to about 10 mm, in one embodiment about 0.05 mm to about 5 mm, in one embodiment about 0.05 mm to about 2 mm, and in one embodiment about 0.05 mm to about 1 mm, perpendicular to the fluid flow through the second and third fluid flow channels (eg, height, width or diameter). Another internal dimension (e.g., height or width) perpendicular to fluid flow through the second and third fluid flow channels is from about 0.01 cm to about 100 cm, in one embodiment from about 0.01 cm to about 75 cm. In embodiments it may range from about 0.1 cm to about 50 cm, and in one embodiment from about 0.2 cm to about 25 cm. The lengths of the second and third fluid flow channels are
Any value, such as from about 0.1 cm to about 500 cm, in one embodiment from about 0.1 c

m to about 250 cm, in one embodiment from about 1 cm to about 100 cm, in one embodimen t from about 1 cm to about 50 cm, in one embodiment It may range from about 2 cm to abou t 25 cm. The distance between each process microchannel and the next adjacent second fluid flow channel or adjacent second and third fluid flow channels is from about 0.05 mm to about 50 mm, in one embodiment about 0.1 to about 10 mm, and in one embodiment from about 0. 2 mm to about 2 mm.

[0069]

Heat sources and/or heat sinks may be used for cooling, heating, or both cooling and heatin g. A heat source and/or heat sink may include one or more heat exchange channels. The heat source may include one or more electrical heating elements or resistance heaters. The heat si nk may include one or more non-fluid cooling elements. These may be adjacent to process mi crochannels and/or second or third fluid flow channels. In one embodiment, the heat source a nd/or heat sink are not in contact with or adjacent to the process microchannels and/or the se cond and third fluid stream channels, and the process microchannels and/or the second and t hird fluid stream channels are away from either or both of the channels, but to transfer heat b etween the heat source and/or heat sink and the process microchannel and/or the second and third fluid stream channels. /or sufficiently close to the second and third fluid flow channels. p rocess microchannels (210, 310a, 310, 320, 330, 340, 410, 520), second fluid flow channels (270, 270a, 350, 360, 420, 430, 530, 540) and/or one or more walls of the third fluid flow ch annel (440, 450). Electric heating elements, resistive heaters and/or non-fluid cooling elemen ts may be constructed in one or more walls of the process microchannels, the second fluid flo w channels and/or the third fluid flow channels. The electric heating elements and/or resistive heaters may be thin sheets, rods, wires, discs or other shaped structures embedded within th e walls of the process microchannels and/or liquid channels. Electric heating elements and/or resistive heaters may be in the form of foils or wires adhered to the process microchannel wall s and/or liquid channel walls. Heating and/or cooling may be provided by Peltier-type thermoe lectric cooling and/or heating elements. It can also be implemented using a child. Multiple hea ting and/or cooling zones may be used along the length of the process microchannel, second f luid stream channel and/or third fluid stream channel. Similarly, along the length of the proce ss microchannel, the second fluid stream channel and/or the third fluid stream channel, using a heat transfer fluid of varying temperature in one or more heat exchange channels. good too. Heat sources and/or heat sinks may be used to provide precise temperature control within the process microchannels, second fluid stream channels and/or third fluid stream channels.

The heat exchange channels (290, 370 , 380, 590

) may be microchannels, but may have dimensions so large that they are not typically micro channels. Each of these channels may have any configuration, eg, square, rectangular, circula r, annular, elliptical, trapezoidal, etc. cross-section. The heat exchange channels may be tubul ar. The heat exchange channels are formed together with adjacent process microchannels or s econd and third fluid flow channels from parallel spaced apart sheets and/or plates arranged s

ide by side or one above the other. You may These channels may include the surface features described above. Each of the heat exchange channels has an internal dimension perpendicular to the heat exchange fluid flow through the heat exchange channels, such as a height, width o r diameter. This dimension is about 0.05 to about 50 mm, in one embodiment about 0.05 to a bout 10 mm, in one embodiment about 0.05 to about 5 mm, in one embodiment about 0.05 t o about 2 mm, in one embodiment Aspects may range from about 0.5 to about 1 mm. Anothe r internal dimension, such as height or width, perpendicular to the heat exchange fluid flow th rough the heat exchange chamber may be any value, such as from about 0.01 cm to about 10 0 cm, in one embodiment

may range from about 0.01 cm to about 75 cm, in one embodiment from about 0.1 cm to abo ut 50 cm, and in one embodiment from about 0.2 cm to about 25 cm. The length of the heat exchange channel is, for example, from about 0.1 cm to about 500 cm, in one embodiment fr om about 0.1 cm to about 250 cm, in one embodiment from about 1 cm to about 100 cm, in one embodiment from about 1 cm to about 50 cm. In embodiments, it may be any value in th e range of about 0.2 cm to about 25 cm. The distance between each process microchannel or second or third fluid stream channel and the next adjacent heat exchange channel is from abo ut 0.05 mm to about 50 mm, in one embodiment from about 0.1 to about 10 mm; Embodime nts may range from about 0.2 mm to about 2 mm. The heat exchange channels (290, 370, 380, 590) are arranged in a co-current direction parallel to the flow of fluid through the chann els through adjacent process microchannels or through the second and third fluid flow channel s

.

A heat exchange fluid may flow. Alternatively, the heat exchange fluid may flow through the h eat exchange channels in a direction countercurrent to fluid flow through the process microch annels or the second and third fluid flow channels. Alternatively, the heat exchange channel is in the process microchannel or the second and third fluid flow channels so as to provide heat exchange fluid flow in a cross-flow direction with respect to fluid flow through the process mic rochannel or the second and third fluid flow channels. It may be oriented with respect to the t hird fluid flow channel. The heat exchange channels may have a serpentine configuration to pr ovide a combination of cross-flow and co-flow or counter-flow.

[0072]

In one embodiment, a process microchannel (210, 210a, 310, 320, 330, 340, 410, 520), a s econd fluid flow channel (270, 270a, 350, 360, 420, 430, 530, 540), The third fluid flow chan nels (440, 450) and/or heat exchange channels (290, 370, 380, 590) have a square or rectan gular cross section and are formed from parallel spaced sheets or plates. The channels may b e arranged in vertically oriented alternating planes side by side or horizontally oriented altern ating planes stacked one above the other. These configurations, which may be referred to as p arallel plate configurations, have several advantages. For example, compared to a circular tub e, a parallel plate configuration experiences less pressure drop while achieving the same shea

r force for height, width or diameter at the same continuous phase material flux. For example, as the aspect ratio of a rectangular channel approaches about 10, i.e. approaching a parallel s heet or plate configuration, its pressure drop can be only about 50% of the pressure drop in a circular channel under the same conditions. . A process microchannel with a parallel plate conf iguration, a second fluid stream channel, a third fluid stream channel and a heat transfer chan nel can be easily arranged in a miniature device for scale-up. Higher throughput per unit volu me of the multiphase mixture formation process can also be achieved by using a parallel plate configuration as compared to circular tubes. An advantage of using parallel plate configuratio ns is that these configurations have a higher fluid/wall material ratio compared to circular tub es and are therefore more compact and have greater manufacturability or output potential

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It is a point.

[0074]

In one embodiment, a process microchannel (210, 210a, 310, 320, 330, 340, 410, 520), a s econd fluid flow channel (270, 270a, 350, 360, 420, 430, 530, 540), The third fluid flow chan nels (440, 450) and/or heat exchange channels (290, 370, 380, 590) may be in the form of c oncentrically arranged circular tubes. The process microchannel and the second fluid stream c hannel may be adjacent to each other, one channel in the annular space and the other channe l in the central space or the adjacent annular space. In one embodiment, a microchannel mixe r useful in the process of the present invention comprises a plurality of interleaved concentric tube process microchannels, a second fluid flow channel, and optionally a third fluid flow chan nel. , the microchannel mixer may be cylindrical in shape.

The apertures (244, 244a, 313, 323, 333 , 343, 416, 426, 436, 446

) may be of sufficient size to permit the indicated fluid flow through the apertured section. A pertures may be referred to as pores. The opening section (240, 240a, 311, 321, 331, 341, 4 15, 425, 435, 445, 550, 560, 570, 580) is about 0.01 to about 50 mm, in one embodiment ab out 0.05 to It may have a thickness in the range of about 10 mm, and in one embodiment ab out 0.1 to about 2 mm. Apertures range up to about 50 microns, in one embodiment from ab out 0.001 to about 50 microns, in one embodiment from about 0.05 to about 50 microns, in o ne embodiment from about 0.1 to about 50 microns. should have an average diameter of In o ne embodiment, the apertures may have an average diameter ranging from about 0.5 to abou t 10 nanometers (nm), in one embodiment from about 1 to about 10 nm, and in one embodi ment from about 5 to about 10 nm. The number of openings in the aperture section is from a bout 10 to about 5×10^{8} openings per square centimeter, in one embodiment from about 1 to about 1×10^{6} openings per square centimeter. It should be within the range of the opening. The openi ngs may or may not be isolated from each other. Some or all of the apertures may be in fluid communication with other apertures within the aperture section. The ratio of the thickness of the open section to the length of the open section along the flow path of the fluid flowing thro

ugh the process microchannel (210, 210a, 310, 320, 330, 340, 410, 520) is about 0 .001 to a bout 100, in one embodiment about 0.01 to about 50, in one embodiment about 0.03 to abou t 25, in one embodiment about 0.05 to about 10, in one embodiment about 0.08 to about 5, a nd in one embodiment from about 0.1 to about 1. The open section may be constructed of an y material that provides sufficient strength and dimensional stability to allow operation of the process of the present invention. These materials include steel (e.g. stainless steel, carbon ste el and the like), monel, inconel, aluminum, titanium, nickel, platinum, rhodium, copper, chrom ium, brass, alloys of any of the above metals, polymers (e.g. thermosets), ceramics, glasses, composites containing one or more polymers (e.g. thermosets) and glass fibers, quartz, silico n, microporous carbon containing carbon nanotubes or carbon molecular sieves, zeolites or th eir Including combinations of two or more. Apertures may be made using known techniques s uch as laser drilling, microelectromachining systems (MEMS), lithographic electrodeposition an d molding (LIGA), electrosparkling or electrochemical etching. The apertures may be made usi ng techniques used to make structured plastics, such as extrusion, or techniques used to mak e films, such as aligned carbon nanotube (CNT) films. Apertures may be made using techniqu es such as sintering or compacting metal powders or particles to form tortuous and interconne cted capillary channels, and techniques of membrane fabrication. Apertures may vary from th e size provided by any of these methods to the inner sidewalls of the aperture that partially fil l the aperture. The size may be reduced by the application of ting. Selective coatings may for m a thin layer on the outside of the porous body and provide minimal pore sizes adjacent to t he continuous flow paths. The minimum average pore opening may range from about 1 nano meter to about several hundred microns, depending on the desired droplet size for the multip hase mixture. Apertures may be reduced in size by heat treatment and by methods that caus e an oxide scale or coating to form on the inner sidewalls of the aperture. These techniques m ay be used to partially occlude the apertures to reduce the size of the apertures exposed to fl ow. Figures 13 and 14 show a comparison of the SEM surface structure of the stainless steel p orous substrate at the same position at the same magnification before and after heat treatme nt. FIG. 13 shows the surface before heat treatment and FIG. 14 shows the surface after heat treatment. The surface of the porous material after heat treatment has significantly smaller g aps and opening sizes. Correspondingly, the average distance between apertures increases.

The open section (240, 240a, 311, 321, 331, 341, 415, 425, 435, 445, 550, 560, 570, 580) has average pores ranging from about 0.01 to about 200 microns . It may be made from a m etallic or non-metallic porous material with sized interconnecting channels or pores. These por es have openings (244, 244a, 313, 323, 3
33, 343, 416, 426, 436, 446). Porous materials may be made from powders or particulates su ch that the average interpore distance is similar to the average pore diameter. When very sma ll pore sizes are used, the pore-to-pore distance can also be very small, and the droplets are e ither in the process microchannels (210, 210a, 310, 320, 330, 410, 520) or in the second Und

esirably large droplets may coalesce at the surfaces on the sides of the fluid flow channels (420, 430). The porous material is formed by oxidation at elevated temperatures in the range of about 300° C. to about 1000° C. for a length of about 1 hour to about 20 days, or by sol coating alumina or another material such as nickel using chemical vapor deposition. A thin layer may be coated on the surface and inside the pores to close the small pores and reduce the pore size of the large pores, thus increasing the interpore distance. . As such, droplet coalescence may be reduced or eliminated, allowing the production of smaller droplets. An SEM image of the conditioned substrate or aperture section is shown in FIG.

[0077]

The openings (244, 244a, 313, 323, 333, 343, 416, 426, 436, 446) are regularly spaced throughout the mixing zone (213, 213a, 315, 325, 335, 345, 413). good. The openings may be preferentially spaced so that smaller openings or larger openings are used closer to either the front or back of the mixing zone. Together, the openings may be closer together at the beginning of the mixing zone and farther apart near the end of the mixing zone to help suppress droplet coalescence. Microscale openings or pores (244, 244a, 313, 323, 333, 343, 416, 426, 436, 446) small enough to provide multiphase mixtures with bubble or microsphere sizes smaller than about 1 micron Fabrication of substrates used as open sections (240, 240a, 311, 321, 331, 341, 415, 425, 435, 445, 550, 560, 570, 580) with One of the reasons for this lies in the fact that untreated ordinary porous materials, such as metallic porous substrates made from powders/particles by compaction and/or sintering, produce a relatively large surface roughness. . In general, these metallic porous substrates do not have the required pore size in the surface region when a given nominal pore size is below a certain value. Although the bulk of the porous material has a specified nominal pore size, the surface region is often characterized by much larger sized fused pores and cavities. This problem can be overcome by tailoring these substrates to provide the desired pore size and interpore distance in the surface area. This may be done by removing a surface layer from the porous substrate to expose or add a smooth new surface with smaller openings. The bubble or microsphere size in multiphase mixtures formed using these tailored substrates can be reduced without increasing the pressure drop across the substrate. Direct polishing or machining of porous surfaces results in smearing of the surface structure and removal of pores. Filling the porous structure with a liquid filler may be followed by solidification and mechanical grinding/polishing, as this may cause clogging. The filler is then removed to regain the porous structure of the material. The filler may be a metal with a low melting point such as zinc or tin or a precursor of a polymer such as an epoxy. Liquid filling and removal processes may be assisted by the use of vacuum. Grinding/polishing may be performed using a grinder and grinding powder. Metal filler removal may be accomplished by fusing and vacuuming or by acid etching. Epoxies or other polymers may be removed by solvent dissolution or by burning off in air.

Referring to FIGS. 16-19, in one embodiment the apertured sections (240, 240a, 311, 321,

331, 341, 415, 425, 435, 445, 550, 560, 570, 580) are It may be constructed of a relatively t hin sheet 600 containing relatively small openings 602 and a relatively thick sheet or plate 61 0 containing an array of relatively large openings 612 coaxially arranged or connected to the o penings 600 . A relatively thin sheet 600 is bonded over a relatively thick sheet 610, and the r elatively thin sheet 600 is bonded to the process microchannels (210, 210a, 310, 320, 330, 3 40, 410) or the second

The relatively thick sheet 610 faces the interior of the fluid flow channels (420, 430) of the se cond fluid flow channel (270, 270a, 350, 360, 420, 430, 530, 540) or the third fluid flow chan nel (270, 270a, 350, 360, 420, 430, 530, 540). Facing the interior of the flow channels (440, 450). The relatively thin sheet 600 can be bonded to the relatively thick sheet 610 using any suitable procedure (eg, diffusion bonding) to provide a composite structure 620 with increase d mechanical strength. A relatively thin sheet 600 may have a thickness in the range of about 0.001 to about 0.5 mm, and in one embodiment about 0.05 to about 0.2 mm. Relatively small openings 602 may have any shape, such as circular, triangular, or rectangular. Relatively small openings 602 may have an average diameter in the range of about 0.05 to about 50 microns, and in one embodiment about 0.05 to about 20 microns. A relatively thick sheet or plate 610 may have a thickness in the range of about 0.1 to about 5 mm, and in one embodiment about 0.1 to about 2 mm. Relatively large opening 612 may have any shape, such as circular, triang ular, or rectangular. The relatively large openings 612 may have an average diameter ranging from about 0.1 to about 4000 microns, in one embodiment from about 1 to about 2000 micro ns, and in one embodiment from about 10 to about 1000 microns. The number of openings 60 2 in sheet 600 and the number of openings 612 in sheet or plate 610 are each in the range of about 2 to about 10,000 openings per square centimeter, and in one embodiment about 2 to a bout 1,000 openings per square centimeter. good. Sheet 600 and sheet or plate 610 are descr ibed above as being useful for constructing apertured sections (240, 240a, 311, 321, 331, 34 1, 415, 425, 435, 445, 550, 560, 570, 580). may be constructed from any of the materials de scribed in . Apertures 602 and 612 are coaxial such that liquid flowing through the apertured section first flows through aperture 612 and then through aperture 602 . may be arranged or connected. The relatively short path for liquid to flow through the relatively small opening 602 is the pressure drop that would occur if the path through the opening had a length equal to th e length of the openings 602 and 612 combined. allows liquid to flow through opening 602 wit h a relatively low pressure drop compared to .

In the embodiment illustrated in FIG. 19, composite structure 620a is similar to that illustrate d in FIG .

18, except that convex portion 604 of relatively thin sheet 600 covering opening 612 is provi ded. have the same design as Convex portions 604 provide increased local shear forces in adj acent channels. Directional arrows 630 in FIG. 19 indicate fluid flow in channels adjacent to o penings 602 . Due to the greater shear forces, fluid flowing through openings 602 has a small er bubble or microsphere size. In the embodiment illustrated in FIG. 20, a surface coating 64

2 is deposited over the surface of sheet or plate 640 and interior sidewalls 644 of opening 646 .

This coating provides an easier way to reduce the diameter of the apertures (244, 244a, 313, 323, 333, 343, 416, 426, 436, 446). Coating materials used to form coating 642 may include alumina, nickel, gold, or polymeric materials (eg, Teflon®). Coating 642 may be applied to sh eet or plate 640 using known techniques including chemical vapor deposition, metal sputterin g, metal plating, sintering, sol coating, polymer coating and similar methods. The diameter of the opening may be controlled by adjusting the thickness of coating 642 .

[0081]

In one embodiment, the open section (240, 240a, 311, 321, 331, 341, 415, 425, 435, 445, 550, 560, 570, 580) is an asymmetric porous material, such as a plurality of sintered particle s. It may be formed of a porous material having a layer of The number of layers may be 2, 3 or 4 or more. The advantage of these multilayer substrates is that they provide increased dur ability and bond strength. Examples include sintered ceramics with relatively large pores on o ne side and relatively small pores on the other side. Relatively small pores range from about 2 to about 10 nm.

diameter. Relatively small pores may be located in relatively thin layers of the multilayer subst rate. A relatively thin layer may have a thickness in the range of about 1 to about 10 microns. The side with the smaller pores faces the interior of the process microchannel (210, 210a, 31 0, 320, 330, 340, 410, 520) or the second fluid flow channel (420, 430). , relatively high shea r forces may be used to remove relatively small multiphase mixture bubbles or microspheres as they form. Process microchannels (210, 210a, 310, 320, 330, 340, 410, 520), second flui d flow channels (270, 270a, 350, 360, 420, 430, 530, 540),

third

The fluid flow channels (440, 450) and heat exchange channels (290, 370, 380, 590) of, alon g with associated headers, footers, manifolds, etc., are of sufficient strength to enable operati on of the process of the present invention, It may be made of any material that provides dime nsional stability, corrosion resistance and heat transfer properties. These materials include ste el (e.g. stainless steel, carbon steel and the like), monel, inconel, aluminum, titanium, nickel, platinum, rhodium, copper, chromium, brass, alloys of any of the aforementioned metals, poly mers (thermosets), ceramics, glasses, composites comprising one or more polymers (eg, the rmosets) and glass fibers, quartz, silicon, or combinations of two or more thereof.

[0083]

The first fluid stream may comprise a gas or a liquid. The second fluid stream may contain a gas or microbody-forming material. The third fluid stream may contain gas.

[0084]

Gases may include any gas. In one embodiment, the gas may include one or more of air, oxy gen, nitrogen, carbon dioxide, water vapor, ammonia, ozone, chlorine gas, hydrogen and the l ike. The gas may include one or more gaseous hydrocarbons, such as hydrocarbons containin

g from 1 to about 5 carbon atoms. These include saturated and unsaturated hydrocarbons. Hydrocarbons include methane, ethane, ethylene, propane, isopropane, propylene, butanes, butylenes, pentanes, cyclopentane, pentylenes, cyclopentylene and the like.

[0085]

The liquid may include any liquid. Liquids may include water, organic liquids, or combinations thereof. The liquid may contain one or more liquid hydrocarbons. They have from 1 to about 24 carbon atoms, in one embodiment from about 5 to about 24 carbon atoms, in one embodiment from about 6 to about 18 carbon atoms, in one embodiment about 6 to about 12 carbon atoms. The term "hydrocarbon" denotes a compound having a hydrocarbon or predominantly hydrocarbon character. These hydrocarbon compounds include:

(1) Pure hydrocarbon compounds, i.e. aliphatic compounds (e.g. alkanes or alkylenes), cycloaliphatic compounds (e.g. cycloalkanes, cycloalkylenes), aromatic compounds, aliphatic and alicyclic substituted aromatic compounds, aromatics Substituted Aliphatic Compounds and Aromatically Substituted Alicyclic Compounds and the like. Examples include hexane, 1-hexene, dodecane, cyclohexene, cyclohexane, ethylcyclohexane, benzene, toluene, xylenes, ethylbenzene, styrene, and the like.

(2) Substituted hydrocarbon compounds, i.e., hydrocarbon compounds containing non-hydrocarbon substituents that do not alter the predominantly hydrocarbon character of the compound. Examples of non-hydrocarbon substituents include hydroxy, acyl, nitro, halo, and the like.

(3) Heterosubstituted hydrocarbon compounds, i.e., hydrocarbon compounds that are predominantly hydrocarbon in nature but contain atoms other than carbon in chains or rings that are normally composed of carbon atoms. For example, heteroatoms include nitrogen, oxygen and sulfur. The liquid may contain natural oils, synthetic oils or mixtures thereof

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Natural oils include animal and vegetable oils (eg castor oil, lard oil) and liquid petroleum oils. and mineral oils such as solvent-treated or acid-treated mineral oils of the paraffinic, naphthenic or mixed paraffinic-naphthenic type. Natural oils include oils derived from coal or shale. The oil may be a saponifiable oil from the triglyceride family, such as soybean oil, sesame seed oil, cottonseed oil, safflower oil and the like. The oil may be a silicone oil (eg, cyclomethicone, silicone methicones, etc.). The oil may be an aliphatic or naphthenic hydrocarbon such as petrolatum, squalane, squalene or one or more dialkylcyclohexanes, or mixtures of two or more thereof. Synthetic oils include polymerized and intermolecularly reacted olefins (e.g. polybutylenes, polypropylenes, propylene isobutylene copolymers, etc.), poly(1-hexenes), poly(1-octenes), poly(1-decenes).) and mixtures thereof, alkylbenzenes (e.g. dodecylbenzenes, tetradecylbenzenes, dinonylbenzenes, di-(2-ethylhexyl)benzenes, etc.), polyphenyls (e.g. biphenyls, terphenyls, alkylated polyphenyls, etc.), alkylated diphenyl ethers and alkylated diphenyl sulfides and their derivatives, analogs and homologues and likes. Alkylene oxide polymers and copolymers and derivatives thereof in which the terminal hydroxyl groups have been modified by esterification, etherification, etc. are synthetic oils that can be used. Synthetic oils may include p

oly-alpha-olefins or Fischer-Tropsch synthetic hydrocarbons.

The liquid

may comprise a normally liquid hydrocarbon fuel, for example a distillate fuel such as motor gasoline as defined in ASTM standard D439, or a diesel fuel or heavy oil as defined in ASTM st andard D396.

[0088]

The liquid may comprise fatty alcohols, fatty acid esters or mixtures thereof. The fatty alcoh ol may be Guerbet alcohol. The fatty alcohol may contain from about 6 to about 22 carbon ato ms, in one embodiment from about 6 to about 18 carbon atoms, and in one embodiment from about 8 to about 12 carbon atoms. Fatty acid esters are esters of straight chain fatty acids of about 6 to about 22 carbon atoms with straight or branched chain fatty alcohols of about 6 to about 22 carbon atoms; It can also be an ester of a branched carboxylic acid of 1 atom with a straight or branched chain fatty alcohol of from about 6 to about 22 carbon atoms, or mixture s thereof. Examples are myristyl myristate, myristyl palmitate, myristyl stearate, myristyl isos tearate, myristyl oleate, myristyl behenate, myristyl erucate, cetyl myristate, cetyl palmitate, cetyl stearate, cetyl isostearate, cetyl oleate. , cetyl behenate, cetyl erucate, stearyl myristat e, stearyl palmitate, stearyl stearate, stearyl isostearate, stearyl oleate, stearyl behenate, ste aryl erucinate, isostearyl myristate, isostearyl palmitate, iso-stearate Stearyl, isostearyl isoste arate, isostearyl oleate, isostearyl behenate, isostearyl oleate, oleyl myristate, oleyl palmitate, oleyl stearate, oleyl isostearate, oleyl oleate, oleyl behenate, oleyl erucate, behenyl myristate, behenyl palmitate, behenyl stearate, behenyl isostearate, behenyl oleate, behenyl behenate, behenyl erucate, erucyl myristate, erucyl palmitate, erucyl stearate, erucyl isostearate, erucyl oleate, behenic acid Includes erucyl and erucyl erucate. fatty acid
mixtures of mono-, di-, and/or triglycerides made up of one or more fatty acids of about 18 c arbon atoms; one with one or more fatty alcohols and/or Guerbet alcohols of about 6 to about 22 carbon atoms; esters with one or more aromatic carboxylic acids (e.g., benzoic acid); one or more dicarboxylic acids of 2 to about 12 carbon atoms and one or more linear chains of 1 t o about 22 carbon atoms; or esters with branched alcohols, one or more polyols containing 2 to about 10 carbon atoms and 2 to about 6 hydroxyl groups, or mixtures of such alcohols and polyols, 2 to about 12 esters of one or more dicarboxylic acids (e.g. phthalic acid) of 1 to 22 c arbon atoms with one or more alcohols (e.g. butyl alcohol, hexyl alcohol) of 1 to 22 carbon at oms, benzoic acid and from about 6 It may also include esters with linear and/or branched alc ohols of about 22 carbon atoms, or mixtures of two or more thereof. The liquid is one or mor e branched primary alcohols of about 6 to about 22 carbon atoms, one or more linear and/or branched aliphatic alcohols of about 6 to about 22 carbon atoms

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carbonates, one or more Guerbet carbonates made from one or more aliphatic alcohols of fro m about 6 to about 22 carbon atoms, one or more of which each alkyl group contains from 1 t o about 12 carbon atoms; dialkyl (e.g. diethylhexyl) naphthalate, one or more linear or branc

hed, symmetrical or asymmetrical dialkyl ethers containing from about 6 to about 22 carbon a toms per alkyl group, from about 6 to about 22 carbon atoms Epoxidized fatty acid esters and one or more ring-opening products of polyols containing 2 to 10 carbon atoms and 2 to 6 hydr oxyl groups, or mixtures of two or more thereof. good.

[0090]

Water may be obtained from any convenient source. Water may be deionized or purified usin g osmotic or distillation methods. The microbody-forming material may include any microbod y-forming material

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The microbody-forming material may be in the form of a liquid or solid melt. Microbody-formi ng materials may include glass, eg, glass microbody (eg, microsphere)-forming materials, pol ymeric, eg, polymeric microbody (eg, polymeric microsphere)-forming materials. The polymer ic microbody-forming material is one or more of acrylic resins, silicone resins, urethane resin s, vinyl acetate resins, Teflon resins, polyamide resins, vinyl chloride resins, styrene-based res ins, phenolic resins, epoxy resins, styrene resins. -butadiene-styrene block copolymer resin, s tyrene-ethylene-butylene-styrene block copolymer resin, styrene-isoprene-styrene block copol ymer resin, n-butyl rubber, chloroprene rubber, natural rubber or two or more thereof It may also include combinations. In one embodiment, the polymeric microbody-forming material ma y comprise (meth)acrylic acid esters of alcohols of 1 to about 14 carbon atoms. In one embod iment, the polymeric microbody-forming material may comprise at least one alkyl (meth)acryl ate.

[0092]

In one or more embodiments of the present invention, emulsifiers and/or surfactants are not required, although one or more emulsifiers and/or surfactants may be used in forming the mu ltiphase mixture prepared by the process of the present invention. may be used. Emulsifiers a nd/or surfactants may be premixed with the liquid. The emulsifiers and/or surfactants are ioni c or non-ionic with a Hydrophilic-Lipophilic Balance (HLB) in the Griffin system ranging from 0 to about 18, in one embodiment from about 0.01 to about 18. may contain a chemical compo und. Ionic compounds may be cationic or amphoteric compounds. Examples include those disc losed in "McCutcheons Surfactants and Detergents", 1998 Edition, North American and Intern ational Editions. Pages 1-235 of the North American version and pages 1-199 of the Internatio nal version are hereby incorporated by reference in part for their disclosure of such emulsifier s. Emulsifiers and/or surfactants that can be used are

, alkylene oxide repeat units, carboxylated alcohol ethoxylates, ethoxylated alcohols, ethoxyla ted alkylphenols, ethoxylated amines and amides, ethoxylated fatty acids, ethoxylated fatty a cid esters and oils, fatty acid esters, fatty acid amides, glycerol esters , glycol esters, sorbitan esters, imidazoline derivatives, lecithin and derivatives, lignin and derivatives, monoglycerides and derivatives, olefin sulfonate esters, phosphate esters and derivatives, propoxylated and et hoxylated fatty acids or alcohols or alkylphenols, sorbitan derivatives, Sucrose esters and deri

vatives, sulfates or alcohols or ethoxylated alcohols or fatty acid esters, dodecylbenzenes and tridecylbenzenes or condensed naphthalenes or petroleum sulfonates, sulfosuccinates and der ivatives, tridecylbenzene and dodecyl Contains benzenesulfonic acid. Emulsifiers and/or surfac tants include one or more polyalkylene glycols, glycerol or sorbitan and one or more partial es ters of fatty acids containing from about 12 to about 22 carbon atoms, or mixtures thereof. m ay contain. Emulsifying agents and/or surfactants may include pharmaceutically acceptable m aterials such as lecithin. The concentration of these emulsifiers and/or surfactants in the multi phasic mixture made by the process of the present invention is up to about 20% by weight of the multiphasic mixture, and in one embodiment from about 0.01 to about 5% by weight. It may be in the range, in one embodiment from about 0.01 to about 2% by weight. In one emb odiment, this concentration may be up to about 2% by weight, in one embodiment up to abou t 1% by weight, and in one embodiment up to about 0.5% by weight.

[0093]

In one embodiment, the first fluid stream comprises a liquid stream and the second fluid str eam comprises air.

[0094]

In one embodiment, the first fluid stream comprises a liquid waste stream and the second fl uid stream comprises air. In one embodiment, the first fluid stream contains the hazardous li quid waste stream and the second fluid stream contains air

. In one embodiment, the first fluid stream contains salad dressing or mustard and the seco nd fluid stream contains nitrogen . [0097] In one embodiment, the first fluid stream compris es a liquid beverage or beer and the second fluid stream comprises carbon dioxide. In one e mbodiment, the first fluid stream contains bleached pulp used in paper manufacture and the s econd fluid stream contains chlorine . [0099] In one embodiment, the first fluid stream com prises a dispersion of coal in water and the second fluid stream comprises air. In one embodi ment, the first fluid stream comprises motor oil with entrained water and the second fluid stre am comprises nitrogen . [0101] In one embodiment, the first fluid stream contains the cells for the culture reaction and the second fluid stream contains oxygen or air. In one embodime nt, the first fluid stream contains the liquid reaction medium and the second fluid stream cont ains air or oxygen . In one embodiment, the first fluid stream contains the reaction medium for carrying out the hydrogenation reaction and the second fluid stream contains hydrogen .

[0104]

In one embodiment, the first fluid stream comprises a mixture of oil and water and the seco nd fluid stream comprises air or natural gas. In one embodiment, the first fluid stream conta ins bleached pulp used in paper manufacture and the second fluid stream contains oxygen . In one embodiment, the first fluid stream contains edible oil, wine or juice and the second f luid stream contains nitrogen . In one embodiment, the first fluid stream contains water use d in fish farming and the second fluid stream contains oxygen . In one embodiment, the first fluid stream contains water and the second fluid stream contains ozone . [0109] In one emb odiment, the first fluid stream comprises a waste or process stream and the second fluid strea m comprises carbon dioxide or ammonia. In one embodiment, the first fluid stream contains air and the second fluid stream contains water vapor . In one embodiment, the first fluid stre am comprises a waste or process stream containing volatile organic compounds and the secon d fluid stream comprises air . [0112] In one embodiment, the first fluid stream comprises a gas or liquid and the second fluid stream comprises the microbody-forming material. In one embodiment, the first fluid stream contains the water-based composition and the second fluid stream contains hydrogen and/or oxygen . This may be used for direct combination for hydrog en peroxide production. [0114]

In one embodiment, the first fluid stream contains the 2-alkylanthraquinone and the second stream contains hydrogen. It may be used to generate hydrogen peroxide. The first fluid str eam material comprises about 0.1 to about 80 weight percent, in one embodiment about 1 to about 50 weight percent, in one embodiment about 0.1 to about 80 weight percent, in the mu ltiphase mixture made by the process of the present invention

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may be present in concentrations ranging from about 1 to about 20% by weight. The second f luid stream material comprises from about 1 to about 95 weight percent, in one embodiment f rom about 10 to about 50 weight percent, in one embodiment from about 10 to about It may be present at a concentration in the range of 25% by weight. The third fluid stream material c omprises up to about 0.01% to about 50% by weight, in one embodiment about 1 to about 1 5% by weight, in one embodiment It may be present in concentrations ranging from about 0. 1 to about 1% by weight.

[0116]

In one embodiment, the second fluid may dissolve in the first fluid. This may occur within th e process microchannel or after the multiphase mixture exits the process microchannel. In on e embodiment, the second fluid is mixed with the first fluid within a period of up to about 10 h ours, in one embodiment up to about 1 hour, into the first fluid. It should dissolve.

[0117]

The multiphase mixture of the present invention may contain more than one type of solid pa rticles. These may be premixed with the first, second and/or third liquid. Solid particles may b e organic, inorganic, or a combination thereof. The solid particles are catalysts (e.g. CeO2 / Ba Al12O19 , Pt / Al Combustion catalysts such as 2O3 , polymerization catalysts and the like) , pigments (e. g.

TiO 2 , carbon black, iron oxide, etc.), fillers (eg, mica, silica, talc, barium sulfate, polyethylen es, polytetrafluoroethylene, nylon powder, methyl methacrylate powder) and the like. Solid pa rticles may include nano-sized particles. The solid particles may have an average particle diam eter ranging from about 0.001 to about 10 microns, and in one embodiment from about 0.01 to about 1 micron. The concentration of solid particles in the multiphase mixture may range u p to about 70% by weight, and in one embodiment from about 0.1 to about 30% by weight, b ased on the weight of the multiphase mixture.

[0118]

In one embodiment, the multiphase mixture made by the process of the present invention c

omprises a discontinuous phase dispersed within a continuous phase. The discontinuous phas e is up to about 200 microns, in one embodiment about 0.01 to about 200 microns, in one em bodiment about 0.01 to about 100 microns, in one embodiment about 0.01 to about 50 micro ns, one In embodiments from about 0.01 to about 25 microns, in one embodiment from about 0.01 to about 10 microns, in one embodiment from about 0.01 to about 5 microns, in one em bodiment from about 0.01 to about 2 microns. , in one embodiment about 0.01 to about 1 mi cron, in one embodiment about 0.01 to about 0.5 micron, in one embodiment about 0.01 to a bout 0.2 micron, in one embodiment about 0 .01 to about 0.1 microns, in one embodiment ab out 0.01 to about 0.08 microns, in one embodiment about 0.01 to about 0.05 microns, in one embodiment about 0.01 to about 0 It may contain bubbles or microbodies having volume-bas ed average dimensions (eg, diameter, height, width, length) in the range of 0.03 microns. On e advantage of the process of the present invention is that, in at least one embodiment, the b ubbles or microbodies are characterized by having a relatively narrow average diameter (or h eight, width or length) distribution.

[0119]

A "relative span" is often referred to as a "span". Relative span is a dimensionless parameter calculated from the volume distribution. As with the volume median foam or microbody size (VMD), D[v, 0.1] and D[v, 0.9] correspond to 10% and 90% of the dispersed foam or microbo dy volume, respectively. A diameter (or height, width or length) representing a point within a smaller diameter bubble or microbody. The span may be defined as the quotient of D[v,0.9] m inus D[v,0.1] divided by VMD(D[v,0.5]). In one embodiment, the span of bubbles or microbod ies in the multiphase mixture made by the process of the present invention ranges from about 1.3 to about 5, in one embodiment from about 1.8 to about 2.5. Good to have. In one embodi ment, the process of the invention is carried out in a single process microchannel and the spa n may range from about 1.3 to about 2.5. In one embodiment, the process of the present inv ention is carried out in a scaled-up multiphase mixing process using multiple process microch annels and spans may range from about 1.3 to about 5. In one embodiment, the volume-ba sed average diameter (or height, width or length) of the bubbles or microbodies in the multip hase mixture made by the process of the present invention is from about 0.1 to about
100
It may be in the micron range and the span may be in the range of about 1 to about 25. In on e embodiment, the volumetric average diameter (or height, width or length) may range from about 1 to about 10 microns and the span may range from about 1.8 to about 2.5. Good to ha ve.

[0121]

In one embodiment, cells are formed, the cells having a volume-based average diameter in t he range of up to about 25 microns and a span in the range of about 1.9 to about 2.5.

[0122]

In one embodiment, microbodies are formed having a volumetric average diameter (or heigh

t, width or length) in the range of up to about 5 microns and a diameter in the range of about 1.8 to about 2.5. span. Microbodies formed by the process of the invention have numerous u ses

.

these

includes glass microspheres for density-reducing cast filings, glass microspheres for selective species immobilization in fluid bed reactors, and the like. Other examples include microsphere polymer, gel or colloidal suspension generation used for immunoassays and treatments. Micro bodies (e.g. microspheres) are processed in secondary processes to form aggregates, catalyti c fluidized or packed beds, drug delivery systems (e.g. protein-enzymatic reactions), and mod ern separation and fluidized bed applications (e.g. magnetic vibration Encapsulated solids may be formed for some applications, including coated magnetic carriers that can be advantageous ly separated or excited by In at least one embodiment, one advantage of the process of the present invention is that whether the process is for laboratory, pilot plant scale, or commercial scale, the process microchannel,

first

The gap distance between the two fluid flow channels, optionally the third fluid flow channel, and/or the heat exchange channel may be the same. As a result, whether the microchannel m ixer is built at laboratory or pilot plant scale, or as a commercial scale plant unit, the particle s ize distribution of the multiphase mixture produced by the microchannel mixer used in the pro cess of the present invention is , can be substantially the same. The shear force in the direct ion of velocity u for a fluid control element (discrete) is given by the formula F

$X = mu^{*}$

It can be calculated by du/dy. where mu is the viscosity and du/dy is the velocity gradient of the liquid flow perpendicular to the aperture section. However, as with liquid position (represe nted by a control element), velocity generally has three components, and shear force also has three components. For near-surface and surface-channel flow, one-dimensional assumptions c an be made and the net shear force of the liquid at the element surface can be approximated by Fx . Computational fluid dynamics, including commercially available software packages such as Fluent or FEMLAB, can be used to solve the necessary transport equations and consequentl y to calculate surface shear forces. Surface shear forces parallel to the direction of flow along the channel length can be calculated. Shear forces between parallel channels can also be calc ulated, incorporating flow distribution effects to determine the mass flux into each parallel cha nnel as a function of detailed channel and manifold geometry. For example, "Fundamentals of Fluid Mechanics", 3rd Edition, BR Munson, D.F. Young and T.H. Okiishi (T. H. Okiishi), John Wil ey & Sons, Inc., Weinheim, 1998, for more detailed calculations.

In one embodiment, the shear force deviation

factor (SFDF) for a process using a single process microchannel is within about 50% of the S FDF for a scaled-up process containing multiple process microchannels. can do. The SFDF is c

alculated by the formula

$SFDF=(F_{max}-F_{min})/(2F_{mean})$

. where F_{max} is the maximum shear force in the process microchannel for a particular liquid, F_{min} is the minimum shear force in the process microchannel for the same liquid, F_{mean} is th e open section in the process microchannel (240, 240a, 311, 321, 331, 341, 415, 425, 435, 4 45, 550, 560, 570, 580) are the arithmetic mean shear forces for the same liquid at the surfa ce. Within a single process microchannel operated by the process of the present invention, the SFDF is less than about 2, in one embodiment less than about 1, in one embodiment less than about 0.5, in one embodiment about 0.5. Should be less than 2. In one embodiment, the pr ocess of the present invention can provide relatively uniform shear forces while using multiple process microchannels

.

of multiple process microchannels

To measure the inter-channel shear force uniformity, the average shear force for each channel is calculated and compared. F_{max} is the maximum average channel shear force and F_{min} is t he minimum average shear force. F_{mean} is the mean value of the mean shear force of all cha nnels. SFDF can be calculated from these values. Among the plurality of process microchannel s, in at least one embodiment of the process of the invention, the SFDF is less than about 2, i n one embodiment less than about 1, in one embodiment less than about 0.5, in one embodi ment In embodiments it can be less than about 0.2.

[0128]

The heat exchange fluid may comprise any fluid. These include air, steam, liquid water, gase ous nitrogen, liquid nitrogen, other gases including inert gases, carbon monoxide, carbon diox ide, molten salts, oils such as mineral oil, gaseous hydrocarbons, liquid hydrocarbons and Do w. - including heat exchange fluids such as Dowtherm A and Therminol available from Dow-Un ion Carbide.

Heat

exchange fluids may include first, second and/or third fluids used to create a multiphase mix ture. This can provide process preheating or precooling to increase the overall thermal efficien cy of the process.

[0130]

In one embodiment, the heat exchange channels include process channels in which endother mic or exothermic processes are performed. These heat exchange process channels may be m icrochannels. Examples of endothermic processes that can be carried out in heat exchange ch annels include steam reforming and dehydrogenation reactions. In one embodiment, the incor poration of simultaneous endothermic reactions that provide heat sink enhancement typically allows for heat fluxes approximately an order of magnitude greater than convective cooling he at fluxes. Examples of exothermic processes that can be carried out in heat exchange channel s include water gas shift reactions, methanol synthesis reactions and ammonia synthesis react

ions.

In one embodiment

, the heat exchange fluid undergoes a phase change within the heat exchange channels. This phase change provides additional heating or removal of heat from the process microchannels or liquid channels beyond the heat supplied by convective heating or cooling. In the case of a n evaporating liquid heat exchange fluid, this additional heat transferred from the process mic rochannels can come from the latent heat of vaporization required by the heat exchange fluid. Examples of such phase changes are nucleate boiling oil or water. In one embodiment, the va por mass fraction quality of boiling of the phase change fluid can be up to about 100%, in one embodiment up to about 75%, and in one embodiment up to about 50%. The use of phase c hange or chemical reaction enhancement heat transfer can be made even more advantageous when multiphase mixture generation occurs in concert with the chemical reaction in the proce ss channel

.

In one embodiment, for example, the multiphase mixture may require reactive monomers or other additional heat exchange for the polymerization reaction.

[0133]

The heat flux of convective heating or cooling in the microchannel mixer is about 0.01 to abo ut 125 watts per square centimeter of surface area of the process microchannel in the microc hannel mixer (W/cm 2), in one embodiment about ^{0} . .1 to about 50 W/cm ^{2} , in one embodi ment about 1 to about 25 W/cm ^{2} , in one embodiment about 1 to about 10 W/cm ^{2} . The he at flux of the heating or cooling phase is in the range of about 1 to about 250 W/cm ^{2} , in one embodiment about 1 to about 100 W/cm ^{2} , in one embodiment about 1 to about 50 W/cm ^{2} , in one embodiment Embodiments may range from about 1 to about 25 W/cm ^{2} , and in one embodiment from about 1 to about 10 W/cm ^{2} .

Heat

exchange channels can be used to provide aseptic conditions during the preparation of multi phase mixtures using the process of the present invention. Unlike batch mixers, the process o f the present invention is closed to the environment.

and does not need to be blanketed with an inert gas to isolate it from the environment. Since the heat exchange channels are adjacent to the process microchannels or liquid channels, the y provide relatively short heat transport and diffusion distances to rapidly heat and cool the liq uid in the microchannel mixer and reduce temperature gradients. can be done. As a result, th e process of the present invention can be used to prepare multiphase mixtures that are unsuit able for prolonged heating or that may degrade under large temperature gradients. In one em bodiment, the temperature gradient between the process microchannel wall at the same axial location within the process microchannel and the bulk flow within the process microchannel is

less than about 5°C, and in one embodiment about 2°C. It can be less, and in one embodiment less than about 1°C. Process microchannels with controlled heating and/or cooling and/or heat exchange channels in intimate contact with the second or third fluid stream channels provide a uniform temperature profile among the plurality of process microchannels

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can provide. This allows for uniform heating and cooling at faster rates than can be obtained using conventional processing equipment such as mixing tanks. a temperature difference between the process microchannels of less than about 5°C, in one embodiment less than about 2°C, at least in some axial locations along the length of the process stream in the multichannel microchannel mixer; In one embodiment, it can be less than about 1°C.

[0136]

Heat exchange channels adjacent to either the process microchannels and/or the second or third fluid stream liquid channels can employ temperature zones along the length of such channels. In one embodiment, the temperature in the first zone near the entrance to the process microchannel is maintained at a higher temperature than the second temperature in the second zone near the end of the process microchannel. A cooling or quench zone may be incorporated into the process microchannels to rapidly cool and stabilize the multiphase mixture. Optimal along the length of the process microchannel, including the possibility of sections both before and/or after the mixing zone within the process microchannel that heat and/or cool the feedstock and/or the multiphase mixture product A large number of combinations of heat profiles are possible that allow for a wide range of heat profiles.

Fluid flow rates through the process microchannels (210, 210a, 310, 320, 330 , 340,

410, 520) are from about 0.01 to about 50 lpm, in one embodiment from about 0.01 to about 10 lpm. should be in range. The velocity of fluid flowing through the process microchannels may range from about 0.1 to about 100 m/s, and in one embodiment from about 0.1 to about 10 m/s. The Reynolds number of the fluid flowing through the process microchannels may range from about 25 to about 10,000, and in one embodiment from about 250 to about 5000. The temperature of the fluid entering the process microchannels may range from about 10°C to about 550°C, and in one embodiment from about 25°C to about 400°C. The absolute pressure within the process microchannels may range from about 1 to about 20 atmospheres, and in one embodiment from about 1 to about 5 atmospheres.

[0138]

of the second fluid flow through the second fluid flow channels (270, 270a, 350, 360, 420, 430, 530, 540) and the third fluid flow through the third fluid flow channels (440, 450) Flow rates may range from about 0.01 to about 10 ml/s, in one embodiment from about 0.1 to about 2 ml/s. The velocities of the second and third fluid streams may range from about 0.1 to about 100 m/s, and in one embodiment from about 0.1 m/s to about 10 m/s. The Reynolds number of the second and third fluid streams may range from about 50 to about 5000, and in one embodiment from about 50 to about 500. The temperature of the second fluid stream entering

the second fluid stream channel and the third fluid stream entering the third fluid stream chan nel are from about -10°C to about 650°C, in one embodiment from about 25°C to about 450° C. °C. The absolute pressure within the second and third fluid flow channels may range from a bout 1 to about 25 atmospheres, and in one embodiment from about 1 to about 5 atmosphere s. Apertures (244, 244a, 313, 323, 333, 34
3, 416, 426, 436, 446) is in the range of about 0.005 to about 0.5 atmospheres, and in one e mbodiment about 0.05 to about 0.1 atmospheres. good. A schematic of the formation of bub bles or microbodies by the process of the present invention is shown in FIG
.
Referring to FIG. 21, gas bubbles or microbodies 650 emerge from openings 652 in microchan nels 654 and disperse into first fluid stream 656 . The bubble or microbody may grow in size while attached to the gas or microbody-forming material base 658 within the opening 652, for example, about ten times the size of the opening or more. Ultimately, shear forces at the bas e of the gas or microbody-forming material base 658 separate the bubbles or microbodies fro m the openings, dispersing the bubbles or microbodies into the first fluid stream 656 . In one embodiment, a relatively high open section pressure drop or, correspondingly, a high flow velo city of the second fluid stream through the second fluid stream channel results in a second flui d stream within the first fluid stream. may not be necessary to achieve the distribution of The lower pressure drop or lower flow velocity results in a lower inertia of the second fluid stream flowing through the apertured section, reducing bubble or microbody growth before the bubbl e or microbody separates from the aperture. can give rise to smaller bubbles or microbodies.
The multiphase mixture exiting the process microchannels (210, 210a, 310, 320, 330, 340, 410, 520) has a temperature of about 10°C to about 600°C, in one embodiment about 25°C t o about 450°C
.
It should be within the temperature range.
[0141]
The heat exchange fluid entering the heat exchange channels (290, 370, 380, 590) may be at a temperature ranging from about -40°C to about 300°C, and in one embodiment from abo ut 25°C to about 100°C. The heat exchange fluid exiting the heat transfer channels may have a temperature in the range of about -30°C to about 550°C, and in one embodiment about 30° C to about 200°C. The pressure drop of the heat exchange fluid as it flows through the heat e xchange channels may range from about 0.005 to about 5 atmospheres, and in one embodim ent from about 0.05 to about 1 atmosphere. The Reynolds number of the heat exchange fluid stream flowing through the heat exchange channels is up to about 10,000, in one embodimen t up to about 5000, in one embodiment in the range of about 100 to about 5000, in one embo diment from about 500 to about It should be in the range of 2000. The fluid stream may be preheated in the microchannel mixer or prior to entering the microchannel mixer using any ty pe of heat transfer device including microchannel heaters or heat pipes

.

In one embodiment, the first fluid stream may be preheated in a non-apertured region of the process microchannel upstream of the mixing zone. The multiphase mixture produced in the microchannel mixer is cooled in the microchannel mixer or after exiting the microchannel mix er using any type of heat exchange device including a microchannel heat exchanger. good too. In one embodiment, the multiphase mixture may be quenched to stabilize or remain stable. I n one embodiment, the multiphase mixture may be quenched in non-apertured regions of the process microchannel downstream of the mixing zone. In one embodiment, the multiphase mi xture may be cooled to room temperature or quenched within a time period ranging from abo ut 0.01 to about 100 seconds, in one embodiment from about 0.01 to about 10 seconds. goo d.

[0143]

Using the process of the present invention, a multiphase mixture can be produced at a rate of at least about 0.01 liter per minute, and in one embodiment at least about 1 liter per minut e. In one embodiment, the process can be used to create a multiphase mixture at a rate of at least about 10 liters per second. In one embodiment, optical or thermo-optical properties ma y be adjusted within the process microchannel

.

Examples of techniques for measuring and/or adjusting these optical or thermo-optical proper ties are in-line LSD (laser scattering diffraction) detection for multiphase mixture quality contr ol and analysis, including mean droplet size and span; Viscosity to assess product viscosity an d solids content

holographic imaging and similar methods including interferometry by modulating the propertie s of multiphase mixtures, optical measurements using photometry for bubble or microsphere size measurement.

Example 1 A multiphase microchannel containing an acrylic process microchannel having a r ectangular cross section and internal dimensions of 0.040 x 1.25 x 3 inches (1.02 x 31.75 x 7 6.2 mm)

.

A mixing device is constructed. A process microchannel has an open section in one of its side walls. The open section has a nominal aperture or pore size of 0.1 microns and dimensions of 0.010 x 1 x 1.5 inches (0.254 x 25.4 x 38.1 mm). The aperture section is constructed of stain less steel 316L and is supplied by Mott Corporation of Farmington, Conn. under catalog numb er 1110-12-12-018-01-A. The open section is connected to a gas distribution plenum and tubi ng to allow gas flow through the open section and into the process microchannel. The process microchannels are connected to plumbing to allow liquid flow through the process microchann els. Gas enters the process microchannel through the open section and contacts the liquid flo wing through the process microchannel. Bubbles form in the process microchannel as the gas flows through the openings in the open section. The process is carried out using air as the gas

and deionized water as the liquid. The air flow rate varies between 2 and 20 standard cubic ce ntimeters per minute (SCCM) and the water flow rate varies between 10 and 80 milliliters per minute (ml/min). Bubbles are formed with diameters in the range of 5 to 15 microns.

Example

2

The process described in Example 1 is carried out using a gas flow rate of 2 SCCM and a liqui d flow rate of 60 ml/min.

EXAMPLE 3 The process described in Example 1 is carried out using hydrogen as the gas and 1-hexene as the liquid

. Example 4 A high velocity gas (flow rate greater than 1 SLPM) and liquid (flow rate greater than 0.1 liters per minute) are mixed near the inlet of a process microchannel and then subje cted to surface feature regions. flows through The surface feature area has features with a de pth of 0.01 inch and an angle of 45 degrees on one side of the wall. The bulk flow path within the surface features is 0.0065 inches. A foam is produced having uniform cells with an averag e diameter of less than 25 microns. The stream length is 1.5 inches and the channel width or span is 0.5 inches. The process microchannels are near room temperature and ambient press ure. Very small bubbles are observed on and throughout the surface feature area. Example 5

The addition of surface features to the two sides of a microchannel that induces a change fro m laminar flow in the channel to strongly mixed flow in the channel was performed using Flue nt™ . studied by dynamics (CFD) simulations. For the simulation, the properties of the fluid w ere assumed constant, with a density of 5.067 kg/m ^{3} and a viscosity of 3.62e $^{-5}$

kg/m-sec. Boundary conditions were a uniform inlet velocity of 12.13 m/sec and no slip flow on all walls. A grid size of 315,174 cells is used. The geometry assumed is 4.06 mm wide, 0. 318 mm high and 63.5

mm

Rectangular cross-section of a continuous channel with a length of . The section 0 to 3.5 mm downstream of the inlet and the section 0 to 5.0 mm upstream of the outlet contain no mixing surface features (simple rectangular microchannels). Mixing surface features (or grooves) are cut into two opposing walls, each feature being generally rectangular in cross section. The mid dle section of the microchannel (3.5 mm to 58.5 mm downstream of the inlet) contains a mixi ng surface feature. A surface feature diagonally spans one of the channel walls at an angle of 63° from the direction of the mean bulk laminar flow, as shown in FIGS. Each surface feature

is approximately 0.25 mm deep, 0.48 mm wide and 9 mm long. The surface features are arra nged parallel to each other with a spacing of 0.48 mm between the features. The surface feat ures on the opposite wall are the same as the surface features on the first wall, rotated 180° around the channel centerline (the channel geometry is the center point of the inlet face is sy mmetrical about the axis of flow extending from to the center point of the exit face).

[0151]

FIG. 27 shows a plan view of the geometry of surface features simulated by CFD. Both the t op wall and bottom wall mixing components are superimposed. FIG. 28 is an isometric view of a microchannel with mixing components simulated by CFD, showing the direction of flow enter ing the channel. FIG. 29 shows a typical flow path line initiated along the horizontal centerline of the inlet face (drawn between arrows), looking down the flow axis from the inlet face. In cl assical laminar flow, the path line runs in a straight line between the inlet and outlet planes (i n the diagram shown in FIG. 29, the classical laminar flow path line deviates from the center li ne between the arrows). considered not to). In FIG. 30 a side view of the same path line of fl ow initiated along the horizontal centerline of the inlet face is shown (arrows indicate direction of flow). In FIG. 30, the divergence of the flow path lines from the centerline and swirling mot ion among the surface features show improved mixing and reduced heat and mass transport r esistance compared to laminar flow. FIG. 31 shows the flow path line initiated along the vertic al centerline of the inlet face (drawn between the arrows), looking down the flow axis from th e inlet face. In FIG. 31, the swirling motion of the flow suggests improved mixing and reduced heat and mass transfer resistance compared to classical laminar flow. Results from CFD simu lations show that, unlike laminar flow in microchannels, the mixing surface features twist and swirl the flow path in continuous channels, which is expected for laminar flow

.

Push outwards toward the wall faster than you can. The calculated pressure drop is 5.2 kPa.

[0153]

Addition of a gas or a second fluid stream to a microchannel containing surface features crea tes a flow pattern whereby the multiphase mixture is expected to approach laminar flow and b ubbles to be small and well dispersed. A small bubble may be defined as less than 25% of the microchannel gap. Although the invention has been described in connection with specific em bodiments, it is understood that various modifications of these embodiments will become app arent to those skilled in the art upon reading the specification

.

It is therefore intended that the invention disclosed herein encompass such modifications as f all within the scope of the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0155]

FIG. 1 is a schematic representation of a microchannel that can be useful in the process of the invention.

FIG. 2 is a flowsheet showing an example of a particular form of the process of the invention i n which a microchannel mixer is used to form a multiphase mixture;

FIG. 3 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention; A first fluid stream flows through the process microchannel and from an adjacent second fluid stream channel through an open section in the process microchannel to the process microchannel.

It mixes with the second fluid stream entering the channel.

FIG. 4 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 5 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 6 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 7 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 8 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 9 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 10 is a schematic representation of a dual multiphase mixture;

FIG. 11 is a schematic diagram of a microchannel air blowing unit that can be used in accorda nce with the process of the present invention;

12 is a schematic diagram of a microchannel multiphase mixture forming unit that can be use d in the air blowing unit illustrated in FIG. 11; FIG.

FIG. 13 is an SEM image of a porous stainless steel substrate before heat treatment;

14 is a SEM image of the substrate shown in FIG. 8 after being heat treated; FIG.

FIG. 15 is an SEM image of a specialized porous substrate useful in the process of the inventio n;

FIG. 16 is a plan view of an apertured sheet useful in making the apertured sections of proces s microchannels used in the process of the present invention;

FIG. 17 is a plan view of an apertured sheet or plate useful in making the apertured section of the process microchannels used in the process of the invention;

FIG. 18 is an illustration of a relatively thin apertured sheet overlying a relatively thick apertur ed sheet or plate useful in creating the apertured section of the process microchannels used in the process of the present invention;

FIG. 19 shows an example of a relatively thin apertured sheet overlying a relatively thick aper tured sheet or plate useful in creating the apertured sections of process microchannels used in the process of the present invention.

FIG. 20 shows examples of alternative embodiments of apertures that can be used in the aper

tured section of process microchannels used in the process of the present invention; The aperture has a coating partially filling the aperture and overlying the sidewalls of the aperture.

FIG. 21 is a schematic diagram showing the formation of gas bubbles or microbodies during operation of the process of the invention;

FIG. 22 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 23 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 24 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 25 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 26 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 27 is a plan view of the surface feature geometry simulated by computational fluid dynamics (CFD) as described in Example 5; The surface elements above the upper and lower walls are visible.

FIG. 28 shows surface elements simulated by CFD as described in Example 5;

1 is an isometric view of a microchannel with

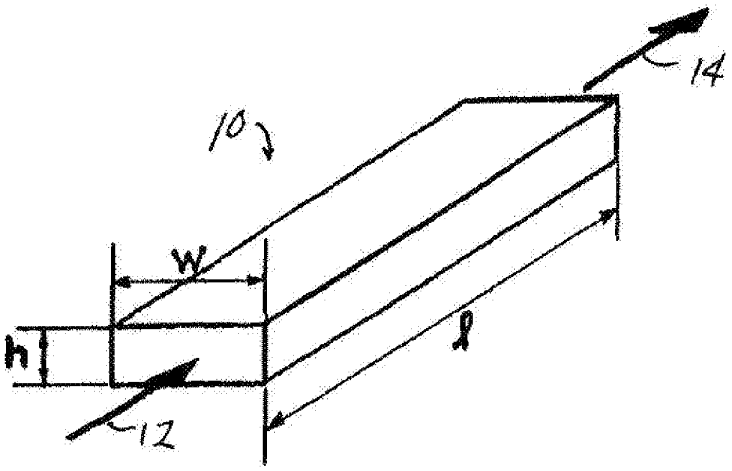
FIG. 29 shows examples of flow pathlines in microchannels initiated along the horizontal centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

FIG. 30 shows flow pathlines (arrows indicate direction of flow) in microchannels initiated along the horizontal centerline of the inlet face. Viewed from the side, as described in Example 5.

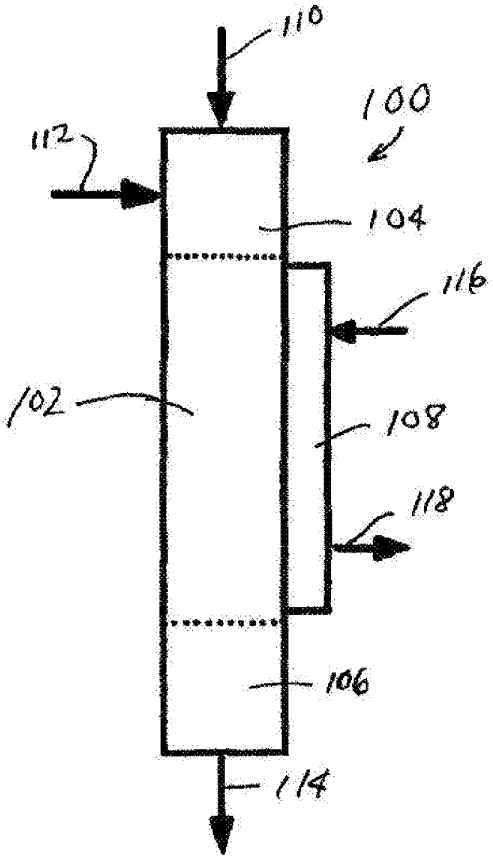
Figure 31 shows flow pathlines in the microchannel initiated along the vertical centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

drawing open —

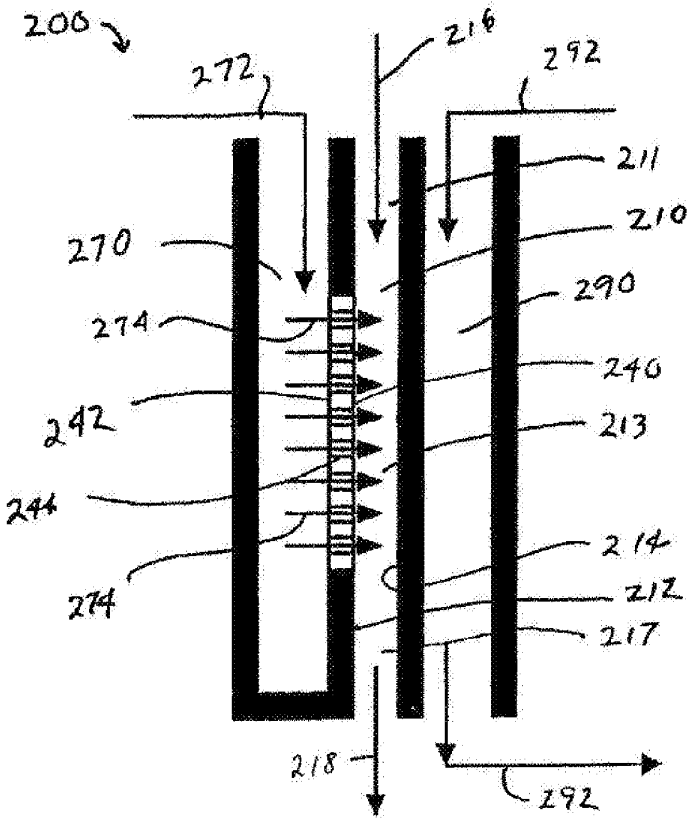
[Fig. 1]



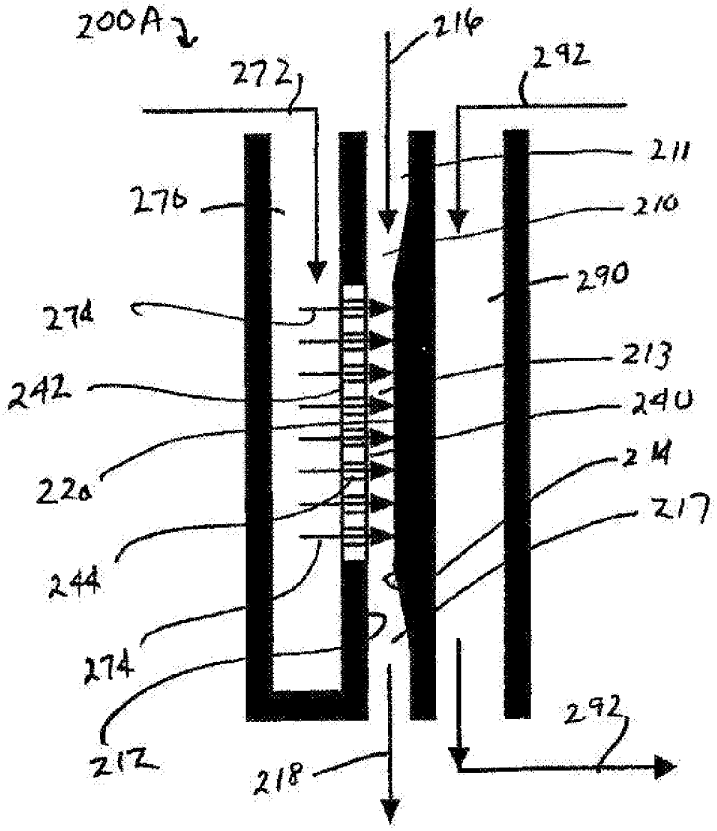
[Figure 2]



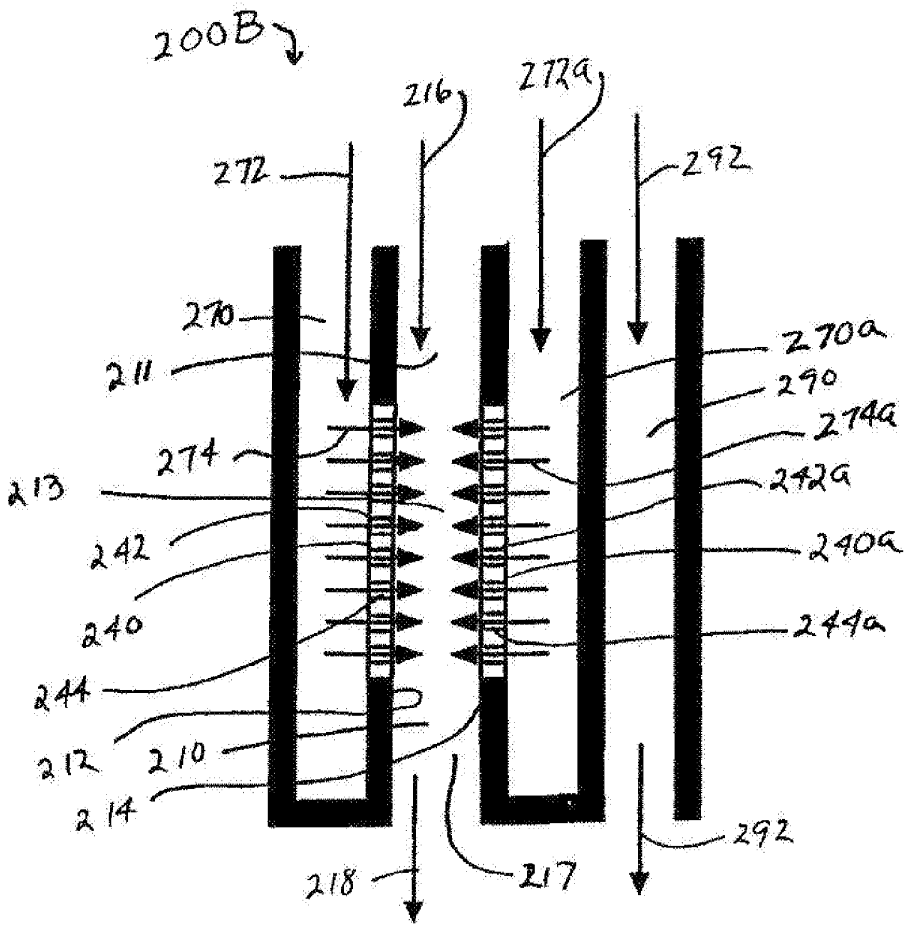
[Figure 3]


200
272
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218
292

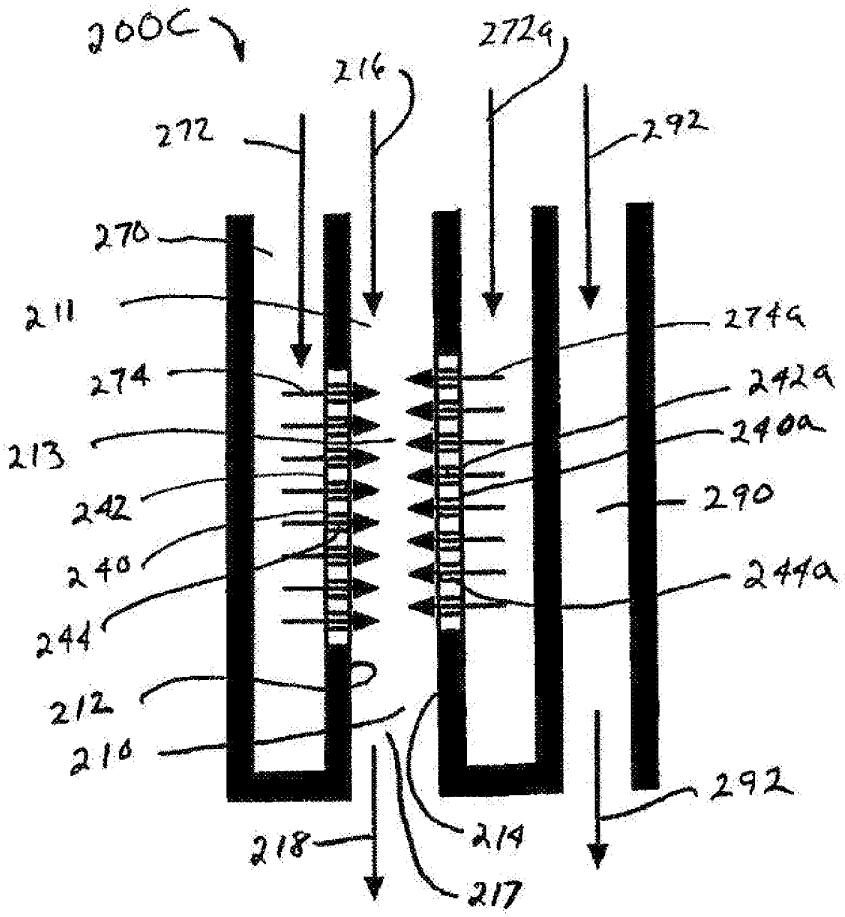
[Figure 4]


200A
272
216
292
211
276
210
290
274
213
242
240
220
214
244
217
274
212
218
292

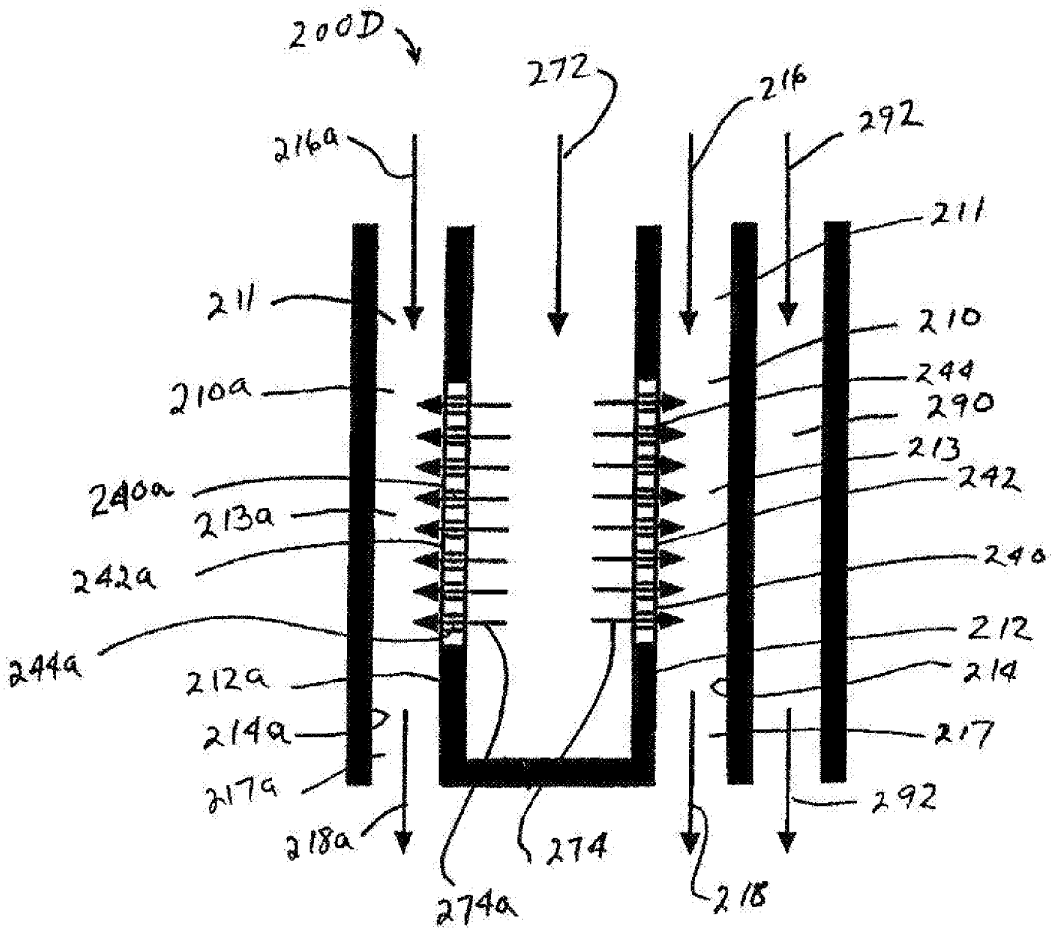
[Figure 5]


200B
216
272a
272
292
270
270a
211
290
274a
274
213
242a
242
240a
240
244a
244
212
210
214
292
218
217

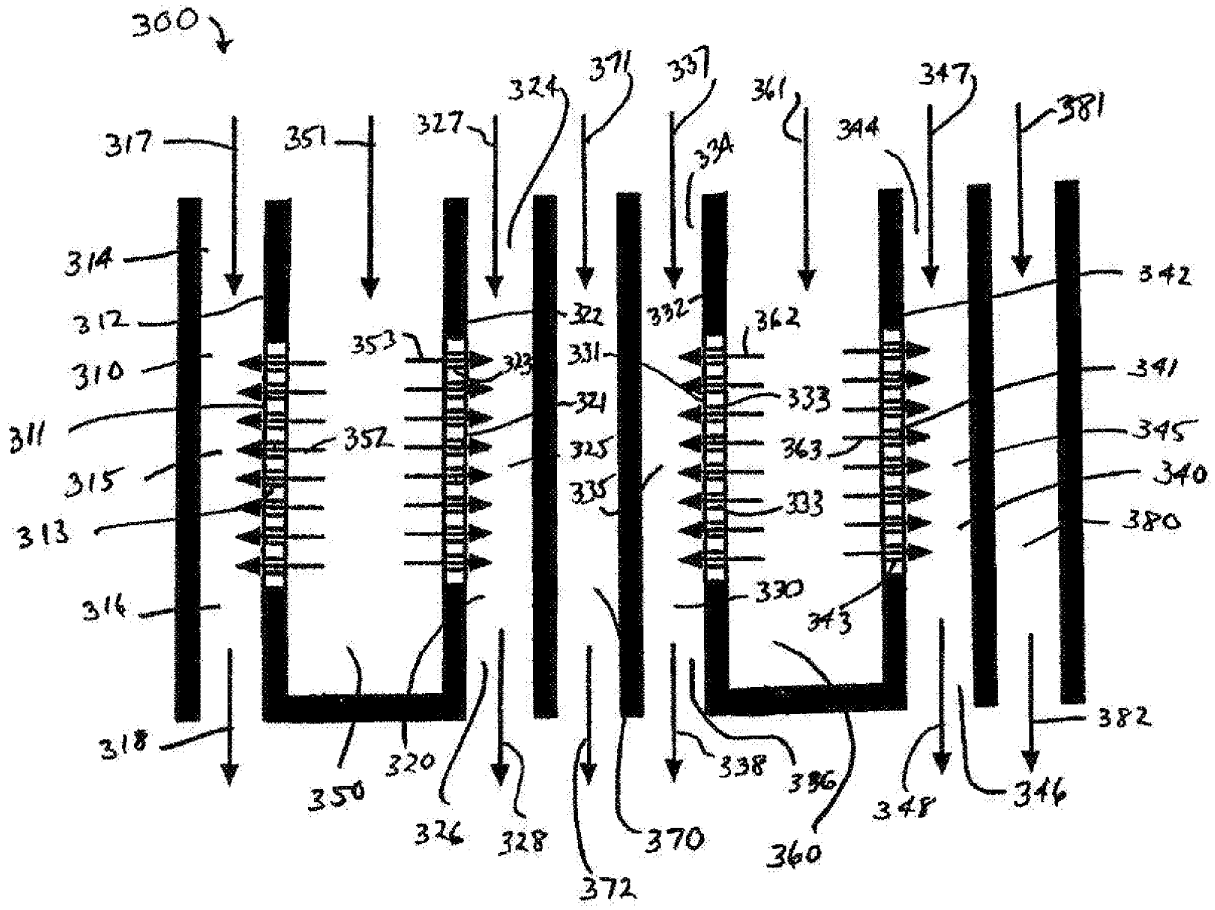
[Fig. 6]


200C
216
272a
292
272
270
211
274a
274
242a
213
240a
242
290
240
244a
244
212
210
292
218
214
217

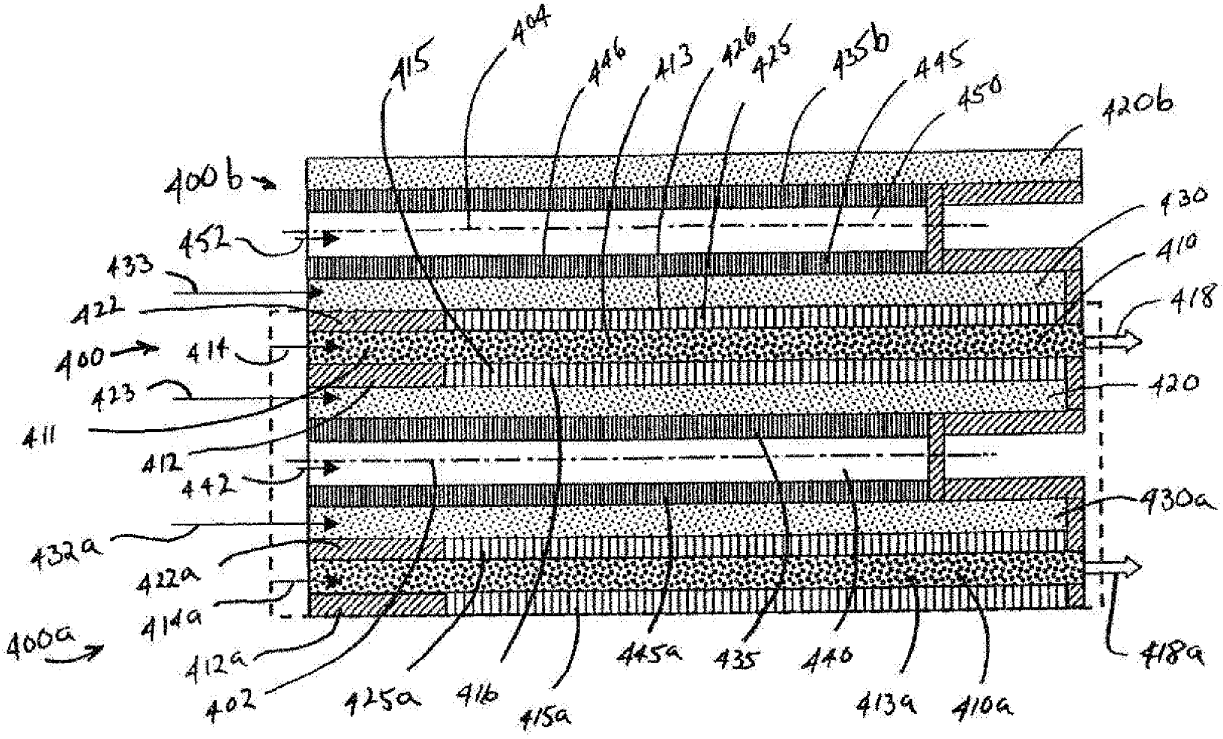
[Fig. 7]


200D
272
216
292
216a
211
211
210
210a
244
290
240a
213
213a
242
242a
240
244a
212
212a
214
214a
217
217a
292
218a
274
274a
218

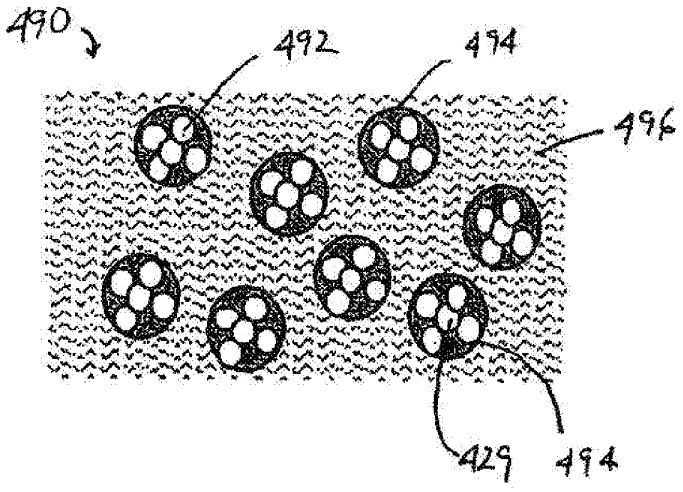
[Fig. 8]


300
317
351
327
324
371
337
361
347
381
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314
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316
318
353
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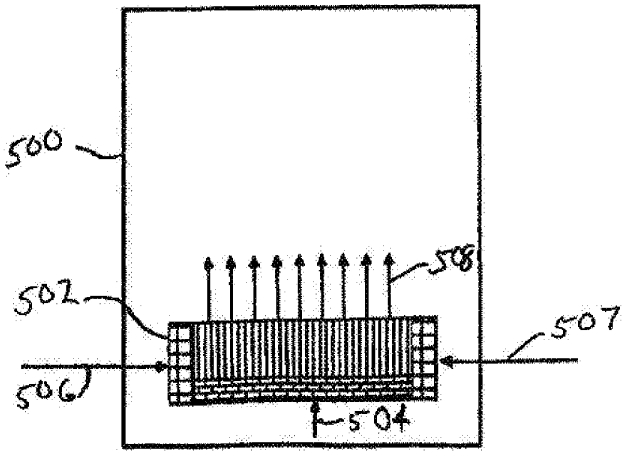
[Fig. 9]


415
404
446
413
426
425
435b
445
450
420b
400b
452
430
433
410
422
418
400
414
423
420
411
412
442
430a
432a
422a
414a
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412a
402
425a
416
415a
445a
435
440
413a
410a
418a

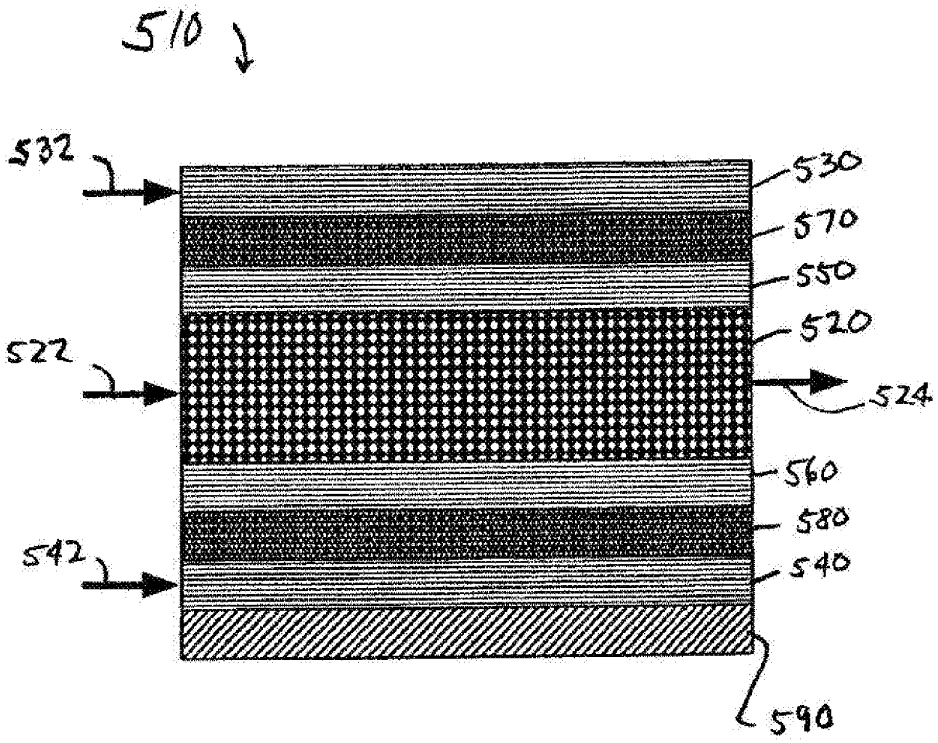
[Fig. 10]



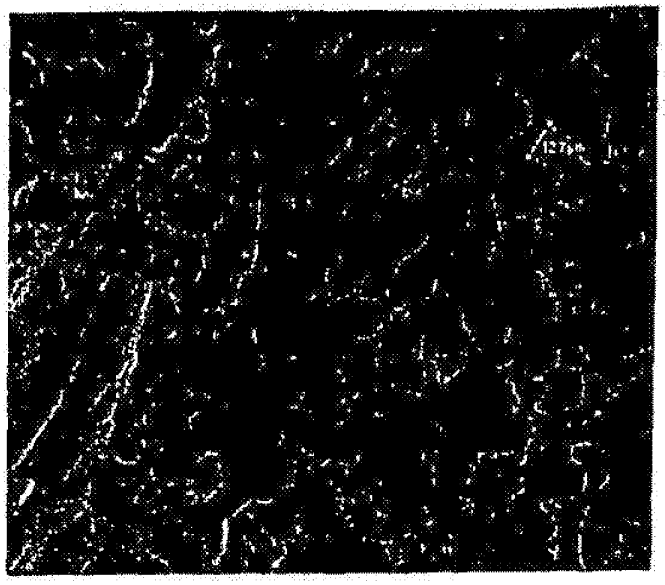
[Fig. 11]



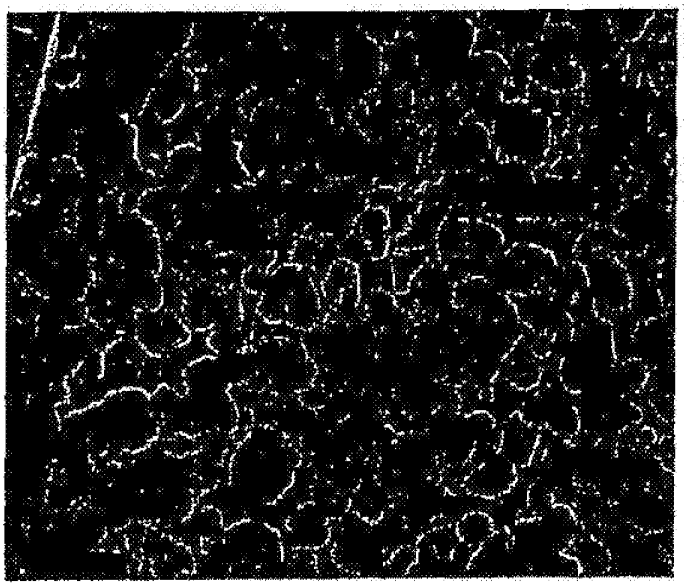
[Fig. 12]



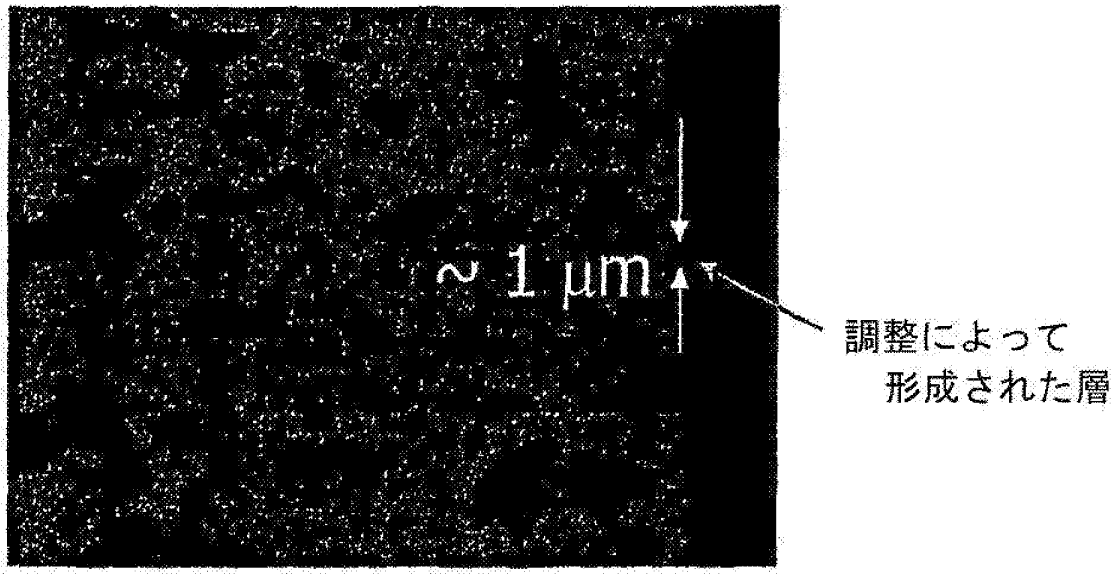
[Fig. 13]



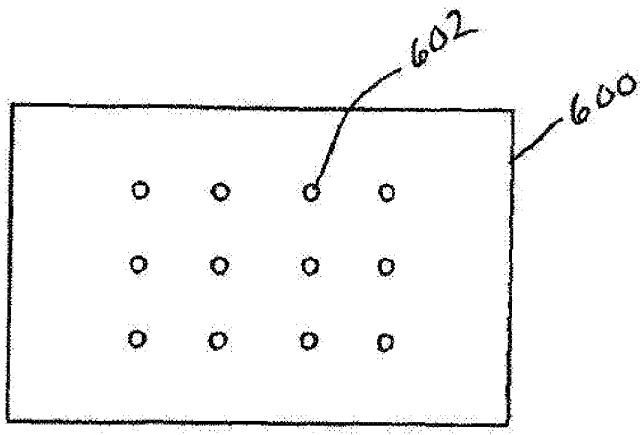
[Fig. 14]



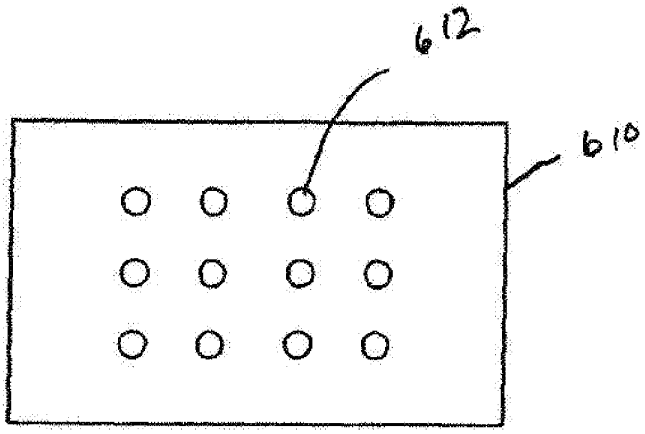
[Fig. 15]



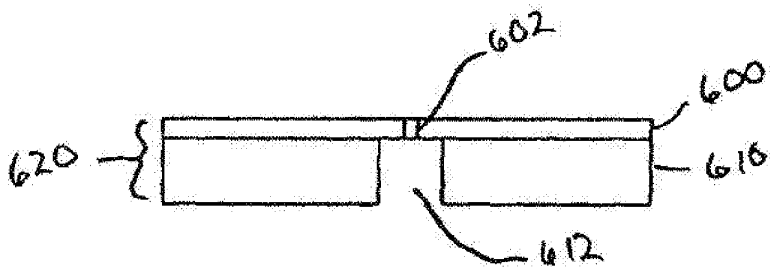
[Fig. 16]



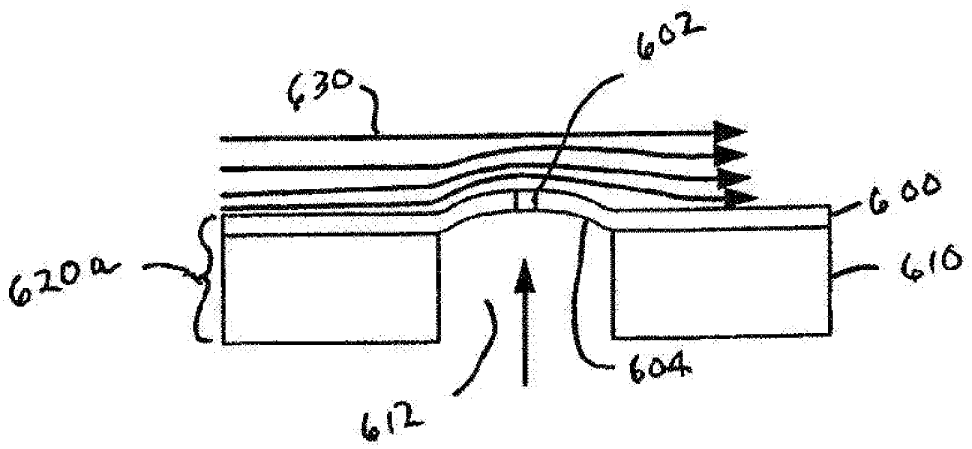
[Fig. 17]



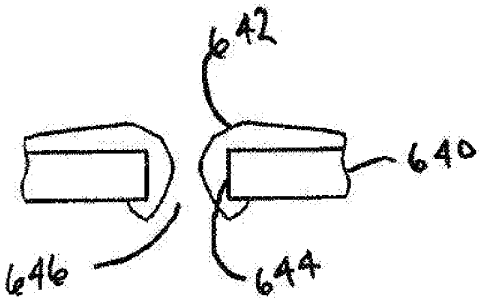
[Fig. 18]



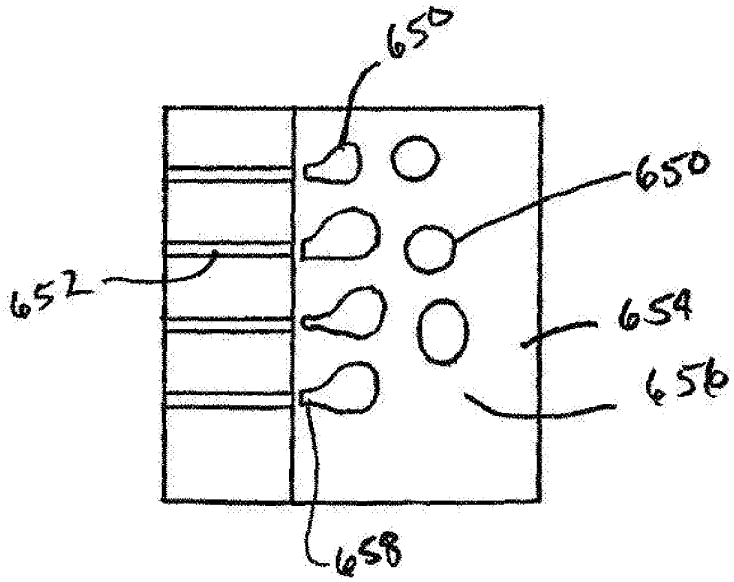
[Fig. 19]



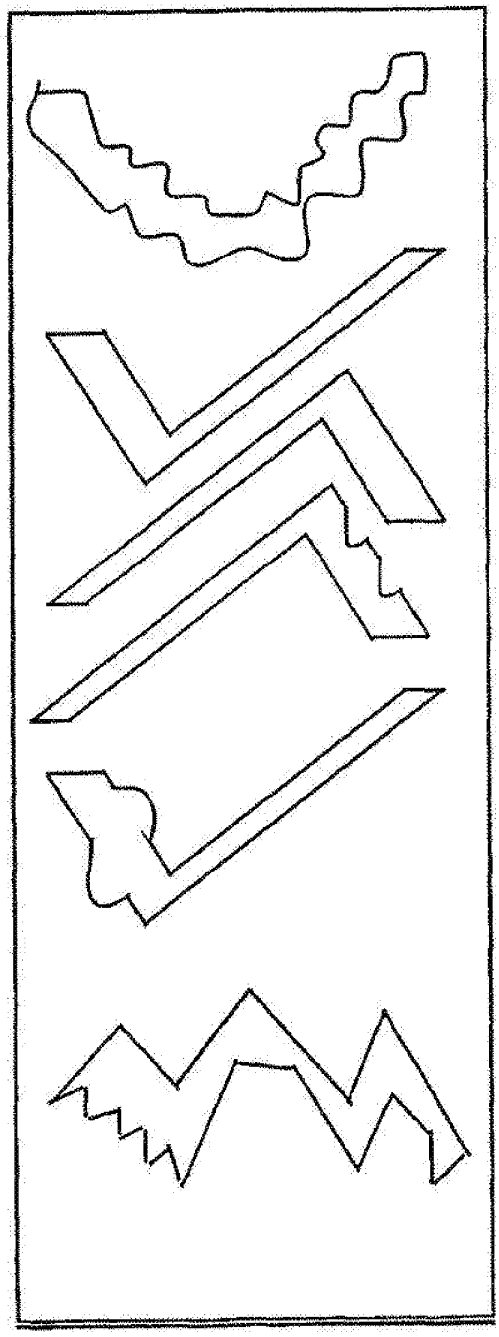
[Fig. 20]



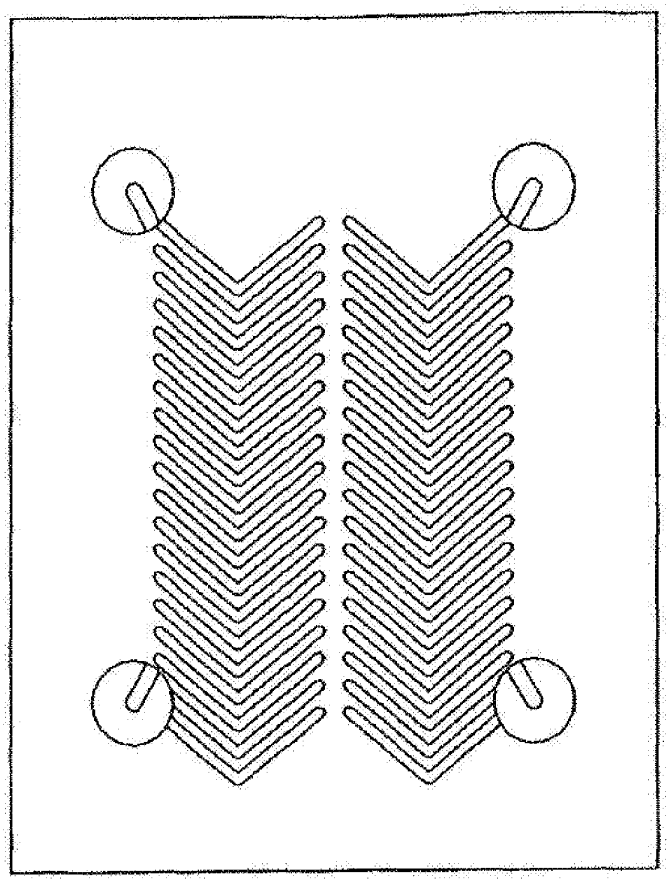
[Fig. 21]



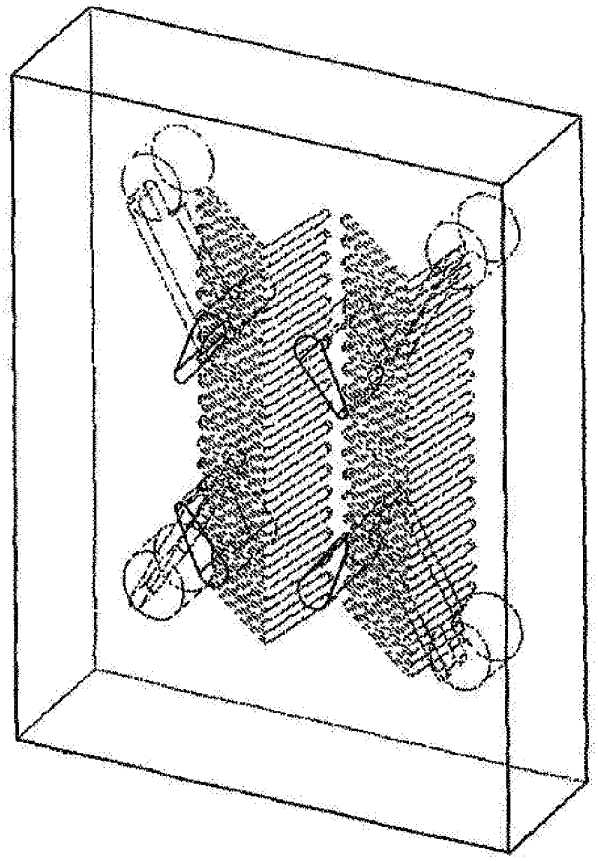
[Fig. 22]



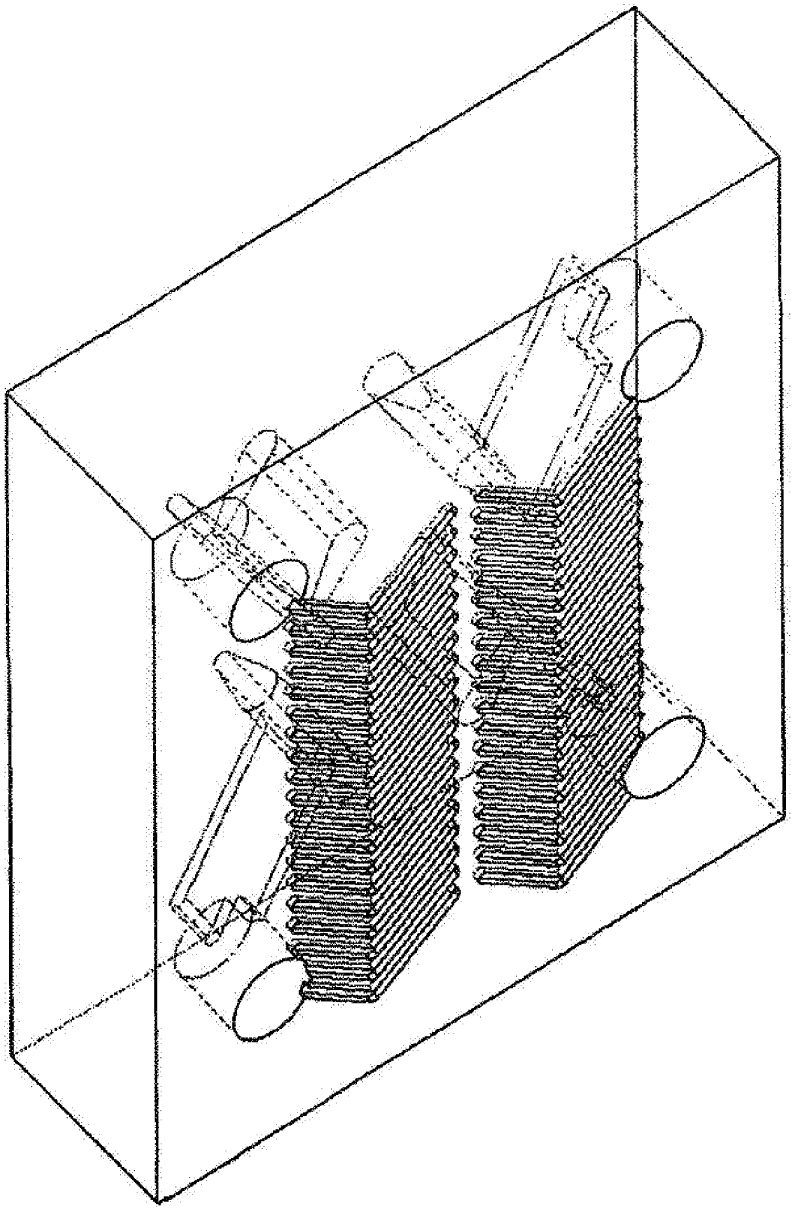
[Fig.23]



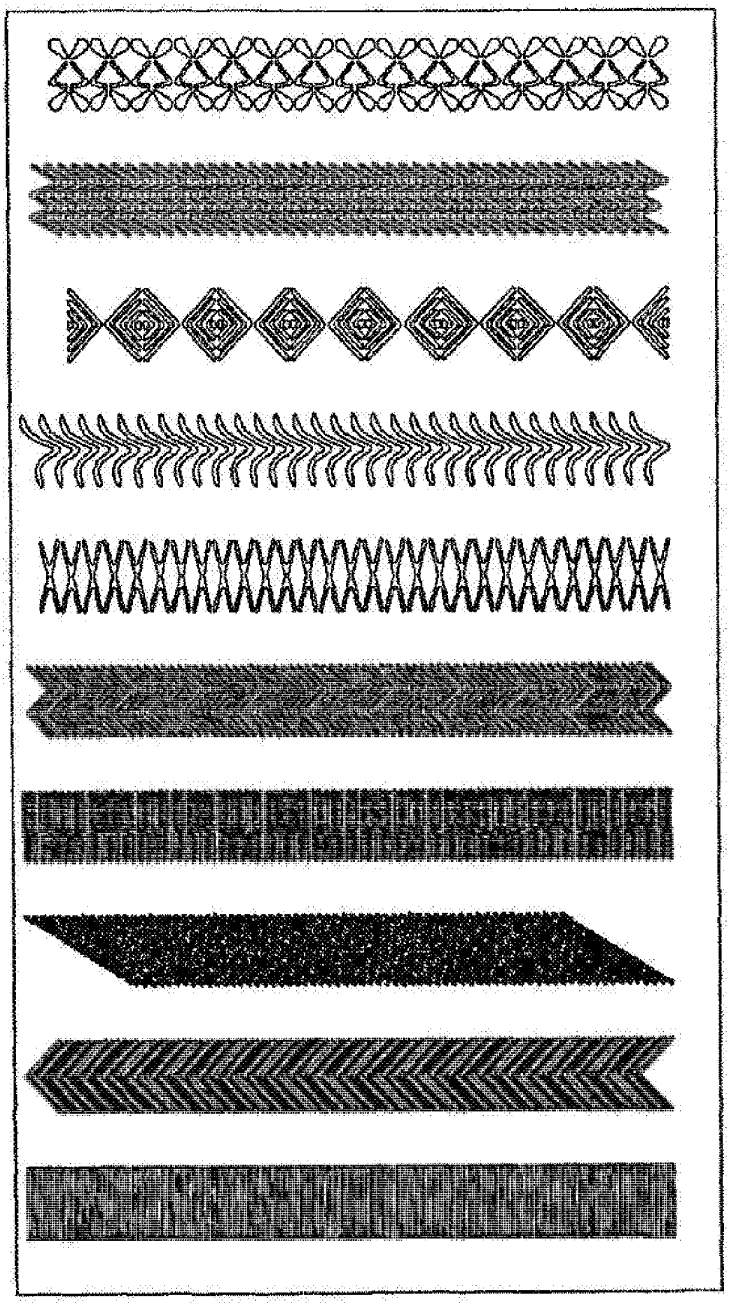
[Fig.24]



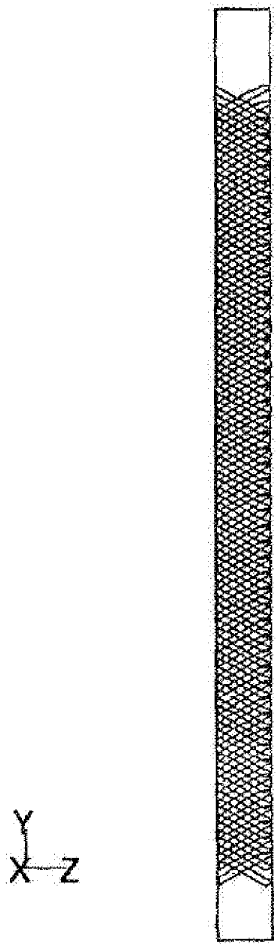
[Fig.25]



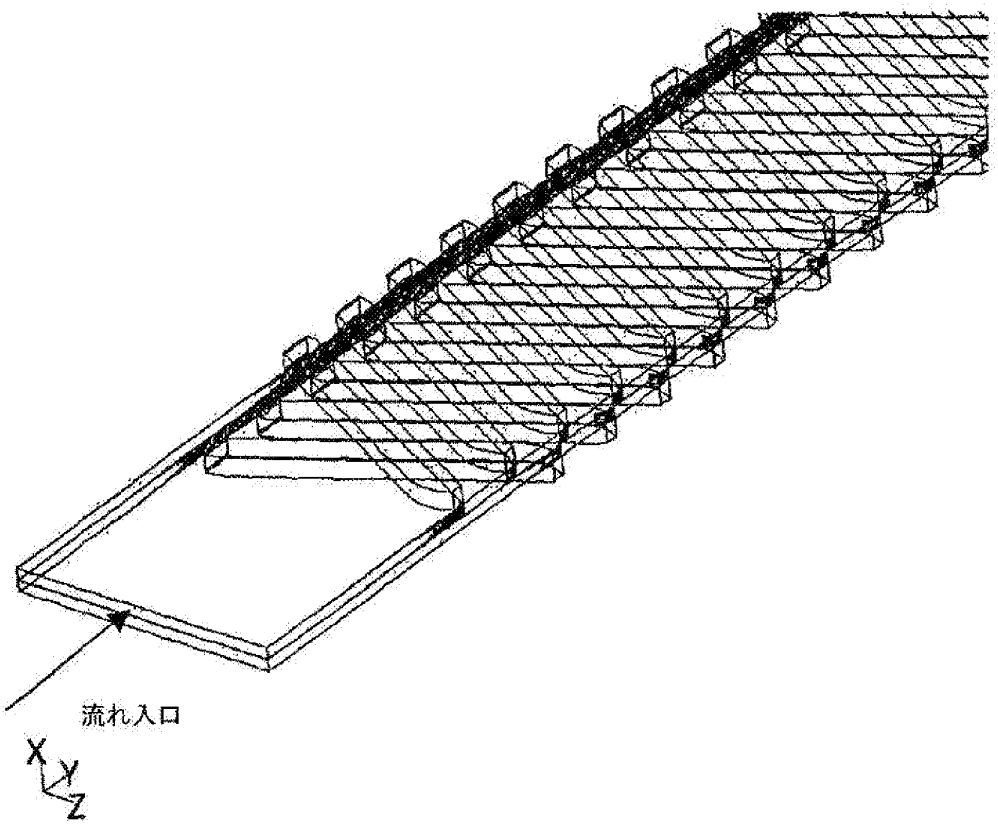
[Fig.26]



[Fig.27]



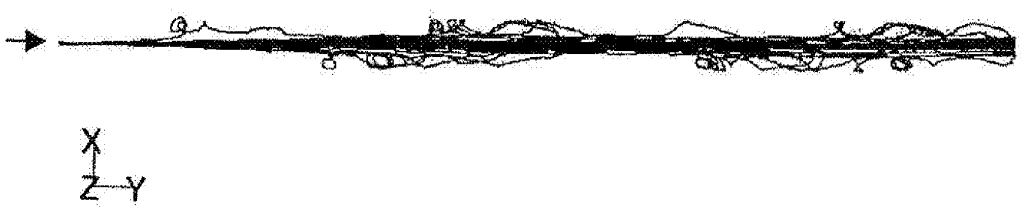
[Fig.28]



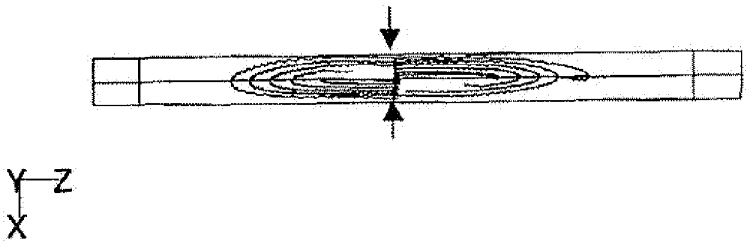
[Fig.29]



[Fig. 30]



[Fig. 31]



drawing open —

1 2 3 Four Five 6 7 8 9 Ten ...

Magnify and Rotate

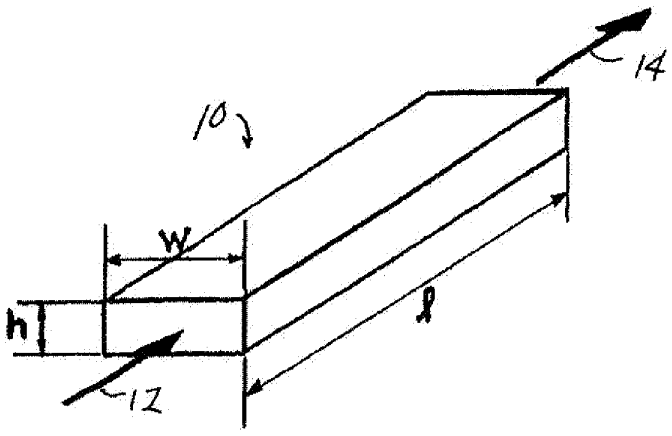


Figure 1

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Bibliographic data: JP5643474 (B2) — 2014-12-17

MULTIPHASE MIXING PROCESS USING MICROCHANNEL PROCESS TECHNOLOGY

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Applicant(s): ヴェロシス，インク ．

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Application number: JP20070534825 20050930 Global Dossier

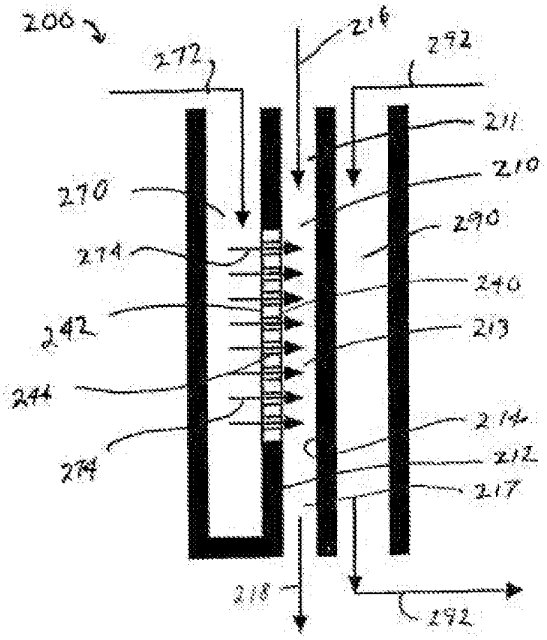
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Abstract not available for JP5643474 (B2)
Abstract of corresponding document: WO2006039568 (A1)

The disclosed invention relates to a process for making a multiphase mixture, comprising: flowing a first fluid stream (216) through a process microchannel (210), the first fluid stream (216) comprising at least one liquid and/or at least one gas, the process microchannel (210) having an apertured section (244); flowing a second fluid

stream (272) through the apertured section (244) into the process microchannel (210) in contact with the first fluid stream (216) to form the multiphase mixture (218), the second fluid stream (272) comprising at least one gas and/or at least one microbody-forming material, the first fluid stream (272) forming a discontinuous phase dispersed in the continuous phase. Heat exchange may also take place between the process microchannel (210) and a heat source or heat sink (290).



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(54)【発明の名称】マイクロチャネルプロセス技術を用いる多相混合プロセス

(57)【特許請求の範囲】
【請求項１】
多相混合物を作るためのプロセスであって、
第一の流体流をプロセスマイクロチャネルの中に流す工程であって、前記第一の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、複数の開口を含む開口区間を有する工程であって、前記開口区間は前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に沿った長さと前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に垂直な厚さ寸法を有し、
前記厚さを有する前記開口区間を通して第二の流体流を前記プロセスマイクロチャネルの中に流し、前記第一の流体流と接触させて前記多相混合物を形成させる工程であって、前記第二の流体流は、少なくとも一種類の気体を含む気体流であり、前記第一の流体流は、前記多相混合物の中の連続相を形成し、前記第二の流体流は、前記連続相の中の分散した不連続相を形成する工程、
を含み、
前記第二の流体流は、前記プロセスマイクロチャネルに隣接する第二の流体流チャネルから前記開口区間を通って流れ、
熱交換チャネルは、前記プロセスマイクロチャネル、前記第二の流体流チャネル、または前記プロセスマイクロチャネルと前記第二の流体流チャネルとの両方に隣接して、前記プロセスマイクロチャネルと前記熱交換チャネルとの間、前記第二の流体流チャネルと熱交換チャネルとの間、あるいは前記プロセスマイクロチャネルと前記第二の流体流チャネ

ルとの両方と熱交換チャネルとの間で熱が交換され、熱交換液体が熱交換チャネル内にある、プロセス。

【請求項２】

前記第一の流体流と前記第二の流体流とは、前記プロセスマイクロチャネルの中の混合ゾーンの中で互いに接触する、請求項１に記載のプロセス。

【請求項３】

前記プロセスマイクロチャネルは、狭くなった断面を有する混合ゾーンを有する、請求項１または２に記載のプロセス。

【請求項４】

前記プロセスマイクロチャネルは、離間した壁と、前記離間した壁のそれぞれの中に開口区間を有し、前記第二の流体流は、開口区間のそれぞれを通って前記プロセスマイクロチャネルに流入する、請求項１から３のいずれか一項に記載のプロセス。

【請求項５】

前記プロセスマイクロチャネルは、第一のプロセスマイクロチャネルであり、多相混合物形成ユニットの中にあり、該多相混合物形成ユニットは、第二のプロセスマイクロチャネル、および前記第一のプロセスマイクロチャネルと前記第二のプロセスマイクロチャネルとの間に位置する第二の流体流チャネルを含み、各プロセスマイクロチャネルは、開口区間を有する壁を有し、前記第一の流体流は、前記第一のプロセスマイクロチャネルおよび前記第二のプロセスマイクロチャネルを通って流れ、前記第二の流体流は、前記第二の流体流チャネルから、前記開口区間を通って前記第一のプロセスマイクロチャネルの中に流れて前記第一の流体流と接触し、前記開口区間を通って前記第二のプロセスマイクロチャネルの中に流れて前記第一の流体流と接触する、請求項１から４のいずれか一項に記載のプロセス。

【請求項６】

多相混合物を作るためのプロセスであって、

第一の流体流をプロセスマイクロチャネルの中に流す工程であって、前記第一の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、複数の開口を含む開口区間を有する工程であって、前記開口区間は前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に沿った長さと前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に垂直な厚さ寸法を有し、

第二の流体流を第二の流体流チャネルの中に流す工程であって、前記第二の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、前記第二の流体流をプロセスマイクロチャネルに流入させることができるようにする複数の開口を含む開口区間を有する工程であって、前記開口区間は第二の流体流チャネル内を流れる前記第二の流体流の流路に沿った長さと前記第二の流体流チャネル内を流れる前記第二の流体流の流路に垂直な厚さ寸法を有し、

第三の流体流を第三の流体流チャネルの中に流す工程であって、前記第三の流体流は気体を含む気体流であり、第二の流体流チャネルは、前記第三の流体流を第二の流体流チャネルに流入させることができるようにする複数の開口を含む別の開口区間を有する工程であって、前記別の開口区間は前記第三の流体流チャネル内を流れる前記第三の流体流の流路に沿った長さと前記第三の流体流チャネル内を流れる前記第三の流体流の流路に垂直な厚さ寸法を有し、

前記第三の流体流を前記第三の流体流チャネルから前記厚さを有する前記別の開口区間を通して前記第二の流体流チャネルに流入させて、前記第二の流体流と接触させて別の多相混合物を形成させる工程、

前記別の多相混合物を前記厚さを有する前記開口区間を通して前記プロセスマイクロチャネルに流入させて、前記第一の流体流と接触させて前記多相混合物を形成させる工程、

熱交換チャネルは、前記プロセスマイクロチャネルおよび／または前記第二の流体流チャネルまたは前記第三の流体流チャネルのどちらかに隣接し、前記プロセスチャネルと前記熱交換チャネルとの間で熱が交換され、熱交換液体が熱交換チャネル内にある工程、

を含むプロセス。
【請求項７】
前記プロセスマイクロチャネルは、平行な離間したシートおよび／またはプレートから形成される、請求項１から６のいずれか一項に記載のプロセス。
【請求項８】
第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成される請求項７に記載のプロセス。
【請求項９】
前記熱交換チャネルは、平行な離間したシートおよび／またはプレートから形成される請求項８に記載のプロセス。
【請求項１０】
前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、複数の前記プロセスマイクロチャネルおよび第二の流体流チャネルを含み、各プロセスマイクロチャネルは、開口区間を有する壁および隣接する第二の流体流チャネルを有し、前記第二の流体流は、前記第二の流体流チャネルから前記開口区間を通って前記プロセスマイクロチャネルに流入して前記第一の流体流と接触し、前記プロセスマイクロチャネルおよび第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成され、前記プロセスマイクロチャネルおよび第二の流体流チャネルは、互いに隣接し、横に並べられた交互平面、または上下に積み重ねられた交互平面の中に配置される、請求項１から９のいずれか一項に記載のプロセス。
【請求項１１】
前記マイクロチャネルミキサは、平行な離間したシートおよび／またはプレートから形成される複数の熱交換チャネルをさらに備え、前記熱交換チャネルは、前記プロセスマイクロチャネル、前記第二の流体流チャネル、または前記プロセスマイクロチャネルと前記第二の流体流チャネルとの両方に隣接する、請求項１０に記載のプロセス。
【請求項１２】
前記プロセスマイクロチャネルおよび前記第二の流体流チャネルは、同心状に配置された円形の管を含む、請求項１から６のいずれか一項に記載のプロセス。
【請求項１３】
前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、複数の前記プロセスマイクロチャネルを含み、前記プロセスマイクロチャネルのそれぞれの中で別個の多相混合物が形成され、前記プロセスマイクロチャネルの少なくとも二つの中で形成された前記多相混合物は互いに異なる、請求項１から１２のいずれか一項に記載のプロセス。
【請求項１４】
前記開口区間は、シートおよび／またはプレートと、前記シートおよび／またはプレートの中にある複数の開口とを含む、請求項１から１３のいずれか一項に記載のプロセス。
【請求項１５】
前記シートおよび／またはプレートの少なくとも一部の上を覆っており、前記開口の一部に充填される、コーティングを有し、または、前記シートおよび／またはプレートは熱処理される、請求項１４に記載のプロセス。
【請求項１６】
前記開口区間は、多孔質材料から作られ、前記多孔質材料は、金属、非金属、酸化されている、またはアルミナ、ニッケルまたはそれらの組み合わせでコーティングされている、請求項１から１５のいずれか一項に記載のプロセス。
【請求項１７】
前記第一の流体流は、水または有機液体を含み、前記第二の流体流は、少なくとも一種類の気体を含み、または前記第二の流体流は、空気、水素、窒素、二酸化炭素またはそれらの二種類以上の混合物から選択される気体を含む、請求項１から１６のいずれか一項に記載のプロセス。

【請求項１８】
前記プロセスマイクロチャネルは、前記プロセスマイクロチャネルを通る前記第一の流体流の前記流れに垂直な、１０ミリメートル以下の内部寸法を有する、請求項１から１７のいずれか一項に記載のプロセス。
【請求項１９】
前記第二の流体流は、第二の流体流チャネルから前記開口区間を通って流れ、前記第二の流体流チャネルは、前記第二の流体流チャネルを通る前記第二の流体流の前記流れに垂直な、１００センチメートル以下の内部寸法を有する、請求項１から１８のいずれか一項に記載のプロセス。
【請求項２０】
前記熱交換チャネルは、前記熱交換チャネルを通る熱交換流体の前記流れに垂直な５０ミリメートル以下の内部寸法を有する、請求項１から１９のいずれか一項に記載のプロセス。
【請求項２１】
前記プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルは、鋼、モネル、インコネル、アルミニウム、チタン、ニッケル、銅、真鍮、これら金属の任意のものの合金、重合体、セラミック、ガラス、重合体とガラス繊維とを含むコンポジット、石英、ケイ素、またはそれらの二種類以上の組み合わせを含む材料で作られている、請求項１から２０のいずれか一項に記載のプロセス。
【請求項２２】
前記熱交換流体は、前記熱交換チャネル内で相変化を行う、請求項１から２１のいずれか一項に記載のプロセス。
【請求項２３】
前記熱交換チャネル中で吸熱プロセスまたは発熱プロセスが実行される、請求項１から２１のいずれか一項に記載のプロセス。
【請求項２４】
前記熱交換流体は、空気、水蒸気、液体水、一酸化炭素、二酸化炭素、気体窒素、液体窒素、少なくとも一種類の気体炭化水素、少なくとも一種類の液体炭化水素またはそれらの二つ以上の組み合わせ、前記第一の流体流、前記第二の流体流、または前記第一の流体流と前記第二の流体流との混合物を含む、請求項１から２３のいずれか一項に記載のプロセス。
【請求項２５】
前記多相混合物は、泡を含む、請求項１から２４のいずれか一項に記載のプロセス。
【請求項２６】
前記多相混合物は、乳化剤、界面活性剤、紫外線保護因子、ワックス、ちょう度因子、増粘剤、過脂肪剤、安定剤、カチオン性、アニオン性、双性イオン、両性または非イオン性重合体、シリコン化合物、脂肪、ワックス、レシチン、リン脂質、生体薬剤、酸化防止剤、脱臭剤、発汗抑制剤、フケ防止剤、膨潤剤、駆虫剤、自己なめし剤、チロシン阻害剤、可溶化剤、防腐剤、香油または色素、あるいはそれらの二種類以上の混合物、の一つ以上を含む、請求項１から２５のいずれか一項に記載のプロセス。
【請求項２７】
前記多相混合物の中に固体が分散される、請求項１から２６のいずれか一項に記載のプロセス。
【請求項２８】
前記第一の流体流は水素化反応を行うための反応媒質を含み、前記第二の流体流は水素を含む、請求項１から２７のいずれか一項に記載のプロセス。
【請求項２９】
前記第一の流体流は液体流を含み、前記第二の流体流は、空気、酸素、窒素、二酸化炭素、水素、アンモニア、塩素ガス、オゾンの一種類以上、一種類以上の気体炭化水素、またはそれらの二種類以上の組み合わせを含み、または前記第一の流体流は液体廃棄物流を

含み、前記第二の流体流は空気を含み、または前記第一の流体流は液体の有害廃棄物流を含み、前記第二の流体流は空気を含み、または前記第一の流体流は液体のサラダドレッシングまたはマスタードを含み、前記第二の流体流は窒素を含み、または前記第一の流体流は液体飲料またはビールを含み、前記第二の流体流は二酸化炭素を含み、または前記第一の流体流は液体の漂白パルプを含み、前記第二の流体流は塩素を含み、または前記第一の流体流は水中に分散した石炭を含み、前記第二の流体流は空気を含み、または前記第一の流体流は随伴水を含むモータ油を含み、前記第二の流体流は窒素を含み、または前記第一の流体流は培養反応用の、液体を含有する細胞を含み、前記第二の流体流は酸素または空気を含み、または前記第一の流体流は液体反応媒質を含み、前記第二の流体流は空気または酸素を含み、または前記第一の流体流は油と水との混合物を含み、前記第二の流体流は空気または天然ガスを含み、または前記第一の流体流は液体の漂白パルプを含み、前記第二の流体流は酸素を含み、または前記第一の流体流は食用油、ワインまたはジュースを含み、前記第二の流体流は窒素を含み、または前記第一の流体流は魚の養殖に用いられる水を含み、前記第二の流体流は酸素を含み、または前記第一の流体流は水を含み、前記第二の流体流はオゾンを含み、または前記第一の流体流は液体の廃棄物流またはプロセス流を含み、前記第二の流体流は二酸化炭素またはアンモニアを含み、または前記第一の流体流は揮発性有機化合物を含む液体の廃棄物流を含み、前記第二の流体流は空気を含む、請求項１から２７のいずれか一項に記載のプロセス。

【請求項３０】

前記プロセスは、毎分少なくとも１リットルの多相混合物を製造する、請求項１から２９のいずれか一項に記載のプロセス。

【請求項３１】

前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、少なくとも二つのプロセスマイクロチャネルを含む、請求項１から３０のいずれか一項に記載のプロセス。

【請求項３２】

前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは複数のプロセスマイクロチャネルと複数の第二の流体流チャネルを含み、前記プロセスマイクロチャネルは、少なくとも一つの第一の流体流マニホルドに接続されており、前記第一の流体流は、前記少なくとも一つの第一の流体流マニホルドを通って前記プロセスマイクロチャネルへ流れ、前記第二の流体流チャネルは、前記プロセスマイクロチャネルに隣接し、少なくとも一つの第二の流体流マニホルドは前記第二の流体流チャネルに接続し、前記第二の流体流は、前記少なくとも一つの第二の流体流マニホルドを通って前記第二の流体流チャネルへ流れる、請求項１から３１のいずれか一項に記載のプロセス。

【請求項３３】

前記マイクロチャネルミキサは、前記熱交換チャネルに接続された少なくとも一つの熱交換マニホルドをさらに含み、前記少なくとも一つの熱交換マニホルドを通って前記熱交換チャネルへと熱交換流体が流れる、請求項３２に記載のプロセス。

【請求項３４】

前記プロセスマイクロチャネルは、前記プロセスマイクロチャネル内の流れを変化させるために一つ以上の内壁の中および／または上に形成された表面構成要素を含む、請求項１から３３のいずれか一項に記載のプロセス。

【請求項３５】

前記表面構成要素は、前記プロセスマイクロチャネルを通る流体の流れの前記方向に対して斜めの角度に配向された前記マイクロチャネル内壁の一つ以上の中にあるくぼみ、および／または、前記マイクロチャネル内壁の一つ以上からの突起の形状であり、または前記表面構成要素は、少なくとも二つの表面構成要素領域の形状であって、前記第一の流体と第二の流体との混合は、第一の表面構成要素領域の中とそれに続く第二の表面構成要素領域の中の流れの中で実行され、前記第二の表面構成要素領域の中の前記流れのパターンは、前記第一の表面構成要素領域の中の前記流れのパターンとは異なり、または前記開口

区間は、前記プロセスマイクロチャネルの前記内壁の一つ以上の部分を形成する内部部分と、前記開口区間の前記内部部分の上を覆う表面構成要素シートとを含み、前記表面構成要素シートの中および／または上に表面構成要素があり、または前記多相混合物は、前記第一および／または第二の流体流の中に分散した固体粒子を含み、前記流動床の形であり、前記プロセスマイクロチャネルは、前記プロセスマイクロチャネル内の流れを変えるためにその内壁の一つ以上の中および／または上に形成された表面構成要素を含み、または前記表面構成要素は、互いに重ねられて積層され、および／または、三次元パターンにからみ合った二つ以上の層を含み、または前記表面構成要素は、円形、楕円形、正方形、長方形、市松模様、Ｖ字型、波型またはそれらを組み合わせた形であり、または前記表面構成要素は、副構成要素を含み、前記表面構成要素の主壁は、ノッチ形、波形、ギザギザ形、孔形、バリ形、市松模様、扇形またはそれらを組み合わせた形のさらに小さな表面構成要素をさらに含む、請求項３４に記載のプロセス。

【発明の詳細な説明】

【技術分野】

【０００１】

本発明は、マイクロチャネルプロセス技術を用いる多相混合プロセスに関する。

【背景技術】

【０００２】

液体の中の気泡の分散は、化学反応の有無にかかわらず、気‐液接触させて吸収またはストリッピングを促進するために、あるいは泡状製品生産のために有用なものとすることができる。これらのものの例は、廃液流のＢＯＤ（生物学的酸素要求量）要件を満たすための空気吹き込み、槽の中の液体を混合するための空気噴射、有害廃棄物処理用の細菌の成長を刺激するための空気吹き込み、サラダドレッシングまたはマスタードを増量するための窒素吹き込み、炭酸飲料およびビールのためのCO_2吹き込み、紙の製造においてパルプを漂白するための塩素吹き込み、石炭浮遊選鉱およびその他の固体の分離のための空気吹き込み、モータオイルから随伴水分を除去するための窒素吹き込み、培養反応において細胞発育を増強するための酸素または空気吹き込み、性能の改善のために空気、酸素またはその他の気体を反応器の中に吹き込むこと、多様な種類の化学的水素化反応のための水素吹き込み、油井からの湧水からのオイル除去のための空気または天然ガス吹き込み、紙の製造においてパルプを漂白するための酸素吹き込み、食用油、ワインおよびジュースから酸素を除去するための窒素吹き込み、魚の養殖における魚成長の刺激のための酸素吹き込み、医薬品プラントの超純水システムを滅菌するオゾン吹き込み、廃棄物またはプロセス流の中のｐＨを調節するためのCO_2またはNH_3吹き込み、効率的加熱、および蒸気ハンマリングを鎮めるための直接水蒸気噴射、廃液流からのＶＯＣ（揮発性有機化合物）の除去のための空気吹き込み、および類似の操作を含む。これらの操作の多くに伴う一問題は、気体の分散の効率がよくないことである。

【発明の開示】

【課題を解決するための手段】

【０００３】

本発明は、この問題に解決法を提供する。一実施態様では、本発明は、比較的大きな表面積を有する比較的小さな気泡の液体への分散を提供する。その結果、比較的大きな気／液接触面積が得られる。気泡が小さく、表面積が大きいので、液体の中に気体を効率的に溶解させることができる。これによって、気体消費量の低減が得られる。また、気体を液体の中に溶解するために必要な時間も短縮し、その結果、プロセス処理が迅速化し、生産性が高くなる。

【０００４】

本発明は、多相混合物を作るためのプロセスであって、プロセスマイクロチャネルの中に第一の流体流を流す工程であって、第一の流体流は、少なくとも一種類の液体および／または少なくとも一種類の気体を含み、プロセスマイクロチャネルは開口区間を有する工程、開口区間を通して第二の流体流をプロセスマイクロチャネルの中に流し、第一の流体

流と接触させて多相混合物を形成させる工程であって、第二の流体流は、少なくとも一種類の気体および／または少なくとも一種類のマイクロボディ形成材料を含み、第一の流体流は、多相混合物の中の連続相を形成し、第二の流体流は、連続相の中に分散した不連続相を形成する工程を含む。

【０００５】

一実施態様では、第二の流体は、第一の流体の中に溶解する。これは、プロセスマイクロチャネルの中で起こることもあり、多相混合物がプロセスマイクロチャネルから出た後で起こることもある。本発明のプロセスの一利点は、少なくとも一実施態様では、多相混合物の中の第二の流体が、マイクロチャネルプロセス技術を用いない従来の技法によって形成されたより大きな気泡と比較すると、第一の流体の中により効率的に溶解する、比較的小さな気泡を含むことができる点にある。

【０００６】

一実施態様では、多相混合物は、第一の流体流の中に分散した固体粒子をさらに含む。

【０００７】

一実施態様では、プロセスマイクロチャネルと発熱源および／または吸熱源との間で熱が交換される。一実施態様では、発熱源および／または吸熱源は、少なくとも一つの熱交換チャネルを含む。

【０００８】

一実施態様では、開口区間は、プロセスマイクロチャネルの軸方向長さの少なくとも一部に沿って延在する。一実施態様では、開口区間は、プロセスマイクロチャネルの軸方向長さの少なくとも約１０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約２０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約３５％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約５０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約６５％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約８０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約９５％に沿って延在する。

【０００９】

一実施態様では、第二の流体流は、第二の流体流チャネルから開口区間を通って流れる。

【００１０】

一実施態様では、プロセスマイクロチャネルと発熱源および／または吸熱源との間、第二の流体流チャネルと発熱源および／または吸熱源との間、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方と、発熱源および／または吸熱源との間で、熱が交換される。発熱源および／または吸熱源は、加熱、冷却、または冷却と加熱との両方に用いてもよい。発熱源は、熱交換チャネルおよび／または加熱素子を含んでもよい。吸熱源は、熱交換チャネルおよび／または冷却素子を含んでもよい。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネル、第二の流体流チャネル、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方に隣接させることができる。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネルおよび／または第二の流体流チャネルから離してもよいが、プロセスマイクロチャネルおよび／または第二の流体流チャネルへ、またはプロセスマイクロチャネルおよび／または第二の流体流チャネルから熱を移動させるために、プロセスマイクロチャネルおよび／または第二の流体流チャネルに十分近くするとよい。

【００１１】

一実施態様では、本プロセスは、多相ミキサの中で実行される。多相ミキサの中では、プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルの中への流体の流れを提供するために、一つ以上のヘッダまたはマニホルドが使用され、プロセスマイクロチャネルおよび熱交換チャネルから出る流体の流れを提供するために、一つ以上のフッタまたはマニホルドが使用される

【００１２】

一実施態様では、第一の流体流と第二の流体流とは、プロセスマイクロチャネルの中の混合区域の中で互いと接触する。一実施態様では、発熱源および／または吸熱源と、混合区域の中のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。一実施態様では、発熱源および／または吸熱源と、混合区域の上流のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。一実施態様では、発熱源および／または吸熱源と、混合区域の下流のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。

【００１３】

一実施態様では、プロセスマイクロチャネルは、混合区域の中で制限された断面を有する。

【００１４】

一実施態様では、プロセスマイクロチャネルは、離間した壁と、離間した壁のそれぞれの中の開口区間とを有し、第二の液体は、開口区間のそれぞれを通って、プロセスマイクロチャネルの中に流入する。一実施態様では、離間した壁のそれぞれの中の開口区間は、複数の開口を含み、一方の壁の開口区間の中の開口は、反対側の壁の開口区間の中の開口の真向かいに配置される。一実施態様では、離間した壁のそれぞれの中の開口区間は、複数の開口を含み、一方の壁の開口区間の中の開口の少なくともいくつかは、他方の壁の開口区間の中の開口の真向かいにならないようにずらして配置される。

【００１５】

一実施態様では、プロセスマイクロチャネルは、多相混合物形成ユニットの中にある。多相混合物形成ユニットは、第一のプロセスマイクロチャネル、第二のプロセスマイクロチャネル、および第一のプロセスマイクロチャネルと第二のプロセスマイクロチャネルとの間に位置する第二の流体チャネルを含み、各プロセスマイクロチャネルは、開口区間を含む壁を有し、第一の流体流は、第一のプロセスマイクロチャネルと第二のプロセスマイクロチャネルとを通って流れ、第二の流体流は、第二の流体流チャネルから、第一のプロセスマイクロチャネルの中の開口区間を通って流れて第一の流体流と接触し、第二のプロセスマイクロチャネルの中の開口区間を通って流れて第一の流体流と接触する。

【００１６】

一実施態様では、第三の流体流チャネルの中に第三の流体流が流れ、第三の流体流チャネルは、別の開口区間を有する別の壁を有し、本プロセスは、別の開口区間を通して第二の流体流を流し、第三の流体流と接触させて別の多相混合物を形成させる工程、および開口区間を通して別の多相混合物をプロセスマイクロチャネルの中に流し、第一の流体流と接触させる工程、をさらに含む。

【００１７】

一実施態様では、プロセスマイクロチャネルは、平行な離間したシートおよび／またはプレートから形成される。一実施態様では、第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成され、第二の流体流チャネルは、プロセスマイクロチャネルに隣接する。一実施態様では、熱交換チャネルは、平行な離間したシートおよび／またはプレートから形成され、熱交換チャネルは、プロセスマイクロチャネル、第二の流体流チャネル、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方に隣接する。

【００１８】

一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、複数のプロセスマイクロチャネルと第二の流体流チャネルとを含み、各プロセスマイクロチャネルは、開口区間を有する壁と隣接する第二の流体流チャネルとを有し、第二の流体流は、第二の流体流チャネルから開口区間を通ってプロセスマイクロチャネルの中に流れて第一の流体流と接触し、プロセスマイクロチャネルと第二の流体流チャネルとは、平行な離間したシートおよび／またはプレートから形成され、プロセスマイクロチャネルと第二の流体流チャネルとは、互いに隣接し、交互に横に並べられた面または交互に上下に重ねられた面の形で配置される。

【００１９】
一実施態様では、プロセスマイクロチャネルは、二つ以上の開口区間を含み、開口区間のそれぞれを通って、別々の第二の流体流が流れる。一実施態様では、開口区間のそれぞれを通って流れる別々の第二の流体流は、異なる組成を有する。一実施態様では、開口区間のそれぞれを通って流れる別々の第二の流体流は、異なる性質を有する。
【００２０】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、少なくとも二つのプロセスマイクロチャネル、一実施態様では少なくとも約１０のプロセスマイクロチャネル、一実施態様では少なくとも約１００のプロセスマイクロチャネル、一実施態様では少なくとも約１０００のプロセスマイクロチャネルを含む。
【００２１】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、少なくとも一つの第一の流体流マニホルドに接続された複数のプロセスマイクロチャネルを含み、第一の流体流は、少なくとも一つの第一の流体流マニホルドを通ってプロセスマイクロチャネルへ流れる。一実施態様では、プロセスマイクロチャネルに第二の流体流チャネルが隣接し、マイクロチャネルミキサは、第二の流体流チャネルに接続された少なくとも一つの第二の流体流マニホルドをさらに含み、第二の流体流は、少なくとも一つの第二の流体流マニホルドを通って第二の流体流チャネルへ流れる。一実施態様では、プロセスマイクロチャネルおよび／または液体チャネルに熱交換チャネルが隣接し、マイクロチャネルミキサは、熱交換チャネルに接続された少なくとも一つの熱交換マニホルドをさらに含み、少なくとも一つの熱交換マニホルドを通って熱交換チャネルへ熱交換流体が流れる。
【００２２】
一実施態様では、第二の流体流は、第二の流体流チャネルから開口区間を通ってプロセスマイクロチャネルの中に流れ、プロセスマイクロチャネルおよび液体チャネルは、同心状の環状管を含む。
【００２３】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、複数のプロセスマイクロチャネルを含み、プロセスマイクロチャネルのそれぞれの中で別々の多相混合物が形成され、プロセスマイクロチャネルの少なくとも二つの中で形成される多相混合物は、互いに異なっている。これらの多相混合物は、異なる組成および／または異なる性質を有してもよい。このマイクロチャネルミキサは、コンビナトリアル合成およびスクリーニングデバイスと呼ぶことができる。本発明のこの実施態様の一利点は、同じ装置を用いて同時に、複数の多相混合物製品の形成および評価を提供する点である。これは、新製品の候補として、複数の製剤をスクリーニングすることが望まれるとき、利点とすることができる。
【００２４】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、横に並べられるか、または上下に重ねられた、複数の多相混合物形成ユニットを含み、各多相混合物形成ユニットは、プロセスマイクロチャネルおよび隣接する第二の流体流チャネルを含み、プロセスマイクロチャネルおよび隣接する第二の流体流チャネルは、共通の壁と、共通の壁の中の開口区間とを有し、開口区間は、第二の流体流を第二の流体流チャネルから開口区間を通してプロセスマイクロチャネルの中に流すのに適し、各プロセスマイクロチャネルと第二の流体流チャネルとは、平行な離間したシート、プレート、またはそのようなシートおよびプレートの組み合わせから形成され、本プロセスは、プロセスマイクロチャネルの中に第一の流体流を流す工程、第二の流体流チャネルから開口区間を通してプロセスマイクロチャネルの中に第二の流体流を流す工程、および第一の流体流と第二の流体流とをプロセスマイクロチャネルの中で混合して多相混合物を形成させる工程を含む。

【００２５】
一実施態様では、本発明のプロセスは、プロセスマイクロチャネルを通る第一の流体流の流れの圧力降下を比較的低くして、動作させることができる。一実施態様では、本発明のプロセスは、開口区間を通るプロセスマイクロチャネルへの第二の流体流の流れの圧力降下を比較的低くして、動作させることができる。
【００２６】
一実施態様では、プロセスマイクロチャネル内の混合は、プロセスマイクロチャネルの一つ以上の内壁の上に形成された表面構成要素の使用によって改善することができる。一実施態様では、第二の流体は、プロセスマイクロチャネル内で第一の流体と接触し、次に、プロセスマイクロチャネルの一つ、二つまたは三つ以上の内壁の上に表面構成要素が形成されたプロセスマイクロチャネル内の領域を通って流れてもよい。表面構成要素は、プロセスマイクロチャネルを通る流体の流れの方向に対して斜めの角度で配向した、マイクロチャネル内壁の一つ以上の中にあるくぼみ、および／または、マイクロチャネル内壁からの突起物の形状であるとよい。角度のある構成要素は、流れの方向と同じに、または流れの方向と逆に配置してもよい。表面構成要素は、流れの方向に対して、ある角度（例えば、約１°から約８９°、一実施態様では約３０°から約７５°）で、配置するとよい。表面構成要素と接触する流体の流れによって、流体流の一部がくぼみまたは表面構成要素の中へ流れることを強いられるが、一方、流体流の一部は表面構成要素の上をそのまま流れる。表面構成要素内の流れは、表面構成要素と同じ形になり、バルクの流れに対して角度ができる。流体は、表面構成要素から出るとき、バルク流体がｚ方向に流れるｘ、ｙ、ｚ座標系で、ｘおよびｙ方向に運動量を及ぼすことができる。この効果によって、流体流を撹拌または回転させることができる。このパターンは、付与された速度勾配が流体せん断を発生させ、第二の流体を小さな良く分散した気泡または微粒子に細分化するので、二相の流れを混合するために特に有用なものとすることができる。
【００２７】
一実施態様では、第一の表面構成要素領域とそれに続く、別の流れのパターンを作り出す少なくとも一つの第二の構成要素領域とを用いて、第一の流体と第二の流体との混合が実現できるように、プロセスマイクロチャネル内の表面構成要素領域を直列に配置してもよい。第二の流れのパターンは、第一の流体と第二の流体とを分けるか、または引き離すために用いてもよい。この工程は、気体または液体回収を支援するために用いてもよい。本発明のこの実施態様は、液体の中に気体が導入された後、その結果得られた混合物が不均一触媒または均一触媒を含むか、あるいは触媒を含まない第一の表面構成要素領域を通って流れる、気液反応の場合に特に有用なものとすることができる。混合物は、次に、オプションとして、流れパターンが遠心力を発生させ、液体を環状流れパターンでプロセスマイクロチャネルの内壁の方へ押しやる一方、気体は流体コアの中に残る第二の表面構成要素領域を通って流れてもよい。この後者のプロフィルによって、未反応気体を反応体混合物から分けるか、または引き離すのを支援してもよい。流体の中に強い中心渦を作り出すことができる表面構成要素の一パターンは、プロセスマイクロチャネルの上部と底部との角度のある一対のスロットのことがある。中心渦流れパターンを作り出すことができる。一実施態様では、泡の多い混合物によって、液体をプロセスマイクロチャネルの壁の方へ流し、気体をプロセスマイクロチャネルの中心へ押しやるとよい。
【００２８】
一実施態様では、開口区間は、プロセスマイクロチャネルの内壁の一つ以上の一部を形成する内部部分を含んでもよい。開口区間のこの内部部分の上に表面構成要素シートがあってもよい。表面構成要素シートの中および／または上に、表面構成要素を形成してもよい。第二の流体は、開口区間と表面構成要素シートとを通って流れてもよい。開口区間を通って入って来る流体の流束は、表面構成要素シートの表面構成要素の中にある間は、表面構成要素シートの表面から離すことができる。表面構成要素シートは、流れの長さ全体と比較すると、比較的小さな幅またはスパンを有する角度のある構成要素を含んでもよい。表面構成要素シートは、開口区間に機械的支持を提供してもよい。さらに、表面構成要

素によって作り出される流れの渦または角度のある流れは、開口区間を通って流れる第二の流体にせん断をさらに付与し、ひいてはバルク流路の中の第二の流体の粒子または泡のサイズを減らす上で好ましいものとすることができる。

【００２９】

一実施態様では、多相混合物は、液体－固体の流れ、または気体－液体－固体の流れを含んでもよい。第二の流体流は、気体または液体どちらかの中の固体の分散を含んでもよい。第一の流体流は、気体、液体、あるいは気体または液体の中に分散した固体を含んでもよい。プロセスマイクロチャネルの中の表面構成要素区間を通る多相混合物の流れは、付与された流れの方向と異なる運動量が混合物を良く混合された、または分散された状態に保つように作用することができるので、有利なものとすることができる。この利用は、液体反応体の中の固体触媒の分散に有用なものとすることができる。

【００３０】

一実施態様では、多相混合物は、第一および／または第二の流体流の中に分散した固体粒子を含んでもよく、流動床の形であり、プロセスマイクロチャネルは、プロセスマイクロチャネル内の流れを変更するためにその内壁の一つ以上の中および／または上に形成された表面構成要素を含む。これは、固体粒子含有流体流の中に気体流を混合することを含んでもよい。固体は、キャリア流体の中に吹き込んでもよく、またはキャリア流体によって取り込んでもよい。表面構成要素は、多相混合物の混合を促進することがある。

【００３１】

一実施態様では、化学反応および／または沈殿の結果として、多相混合物の中に固体が形成されてもよい。

【００３２】

一実施態様では、多相混合物は泡の形である。一実施態様では、多相混合物は、オプションとして、一種類以上の界面活性剤を含んでもよい。気泡によっては、界面活性剤の存在は必要ではないが、気泡を形成させるために、これらを含んでもよい。

【００３３】

添付の図面では、同様な部品および構成要素は、同様な参照符号を有する。

【発明を実施するための最良の形態】

【００３４】

用語「マイクロチャネル」は、最大約１０ミリメートル（ｍｍ）、一実施態様では最大約５ｍｍ、一実施態様では最大約２ｍｍ、一実施態様では最大約１ｍｍの高さまたは幅のうちの少なくとも一方の内部寸法を有するチャネルを指す。マイクロチャネルを通る流体の流れは、マイクロチャネルの高さおよび幅に垂直なマイクロチャネルの長さ方向に進むことができる。本発明のプロセスでプロセスマイクロチャネル、オプションとして、第二の流体流チャネル、第三の流体流チャネルおよび／または熱交換チャネルとして用いることができるマイクロチャネルの例が図１に示される。図１に例が示されるマイクロチャネル１０は、高さ（ｈ）、幅（ｗ）および軸方向長さ（ｌ）を有する。矢印１２および１４によって示される方向のマイクロチャネルの長さに沿って、マイクロチャネル１０を通って流体が流れる。マイクロチャネルの高さ（ｈ）または幅（ｗ）は、約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．０５から約１．５ｍｍ、一実施態様では約０．０５から約１ｍｍ、一実施態様では約０．０５から約０．７５ｍｍ、一実施態様では約０．０５から約０．５ｍｍの範囲にあるとよい。高さまたは幅のうち、他方の寸法は、任意の寸法、例えば最大約３メートル、一実施態様では約０．０１から約３メートル、一実施態様では約０．１から約３メートルであるとよい。マイクロチャネルの軸方向長さ（ｌ）は、任意の寸法、例えば最大約１０メートル、一実施態様では約０．１から約１０メートル、一実施態様では約０．２から約６メートル、一実施態様では約０．２から約３メートルであるとよい。図１に例が示されるマイクロチャネル１０は、長方形の断面を有するが、マイクロチャネルは、任意の形状、例えば正方形、円形、半円形、台形等の断面を有してもよいと理解すべきである。マイクロチャネルの断面の形状および／またはサイズは、その長さにわた

って変化してよい。例えば、高さまたは幅は、マイクロチャネルの長さにわたって、比較的大きな寸法から比較的小さな寸法へ、またはその逆に、テーパを有してもよい。

【００３５】

用語「隣接する」は、別のチャネルに対する一つのチャネルの相対的な位置を指すとき、直接隣接し、その結果、これらの二つのチャネルを一枚の壁が分断することを意味する。この壁は、厚さが変化してもよい。しかし、「隣接する」チャネル同士は、チャネル間の伝熱に干渉する介在チャネルで分断されることはない。

【００３６】

用語「表面構成要素」は、マイクロチャネル内の流れを変更する、マイクロチャネル壁の中のくぼみおよび／またはマイクロチャネル壁からの突起を指す。表面構成要素は、円形、楕円形、正方形、長方形、市松模様、Ｖ字形、波形および類似の形状であってもよい。表面構成要素は、副構成要素を含んでもよい。この場合、表面構成要素の主壁は、より小さな表面構成要素をさらに含み、これらの表面構成要素は、ノッチ形、波形、ギザギザ形、孔形、バリ形、チェック形、扇形および類似の形であってもよい。表面構成要素は、深さ、幅を有し、非円形表面構成要素なら長さを有する。図２２～２６に例が示される。表面構成要素は、本発明のプロセスで用いられるプロセスマイクロチャネルの内部側壁の一つ以上の上または中に形成することができる。表面構成要素は、本発明のプロセスで用いられる第二の流体流チャネルおよび／または熱交換チャネルの内部側壁の一つ以上の上または中に形成することができる。表面構成要素は、受動表面構成要素または受動混合構成要素と呼ぶことができる。

【００３７】

用語「上流」および「下流」は、マイクロチャネルを含む本発明のプロセスで用いられるチャネルの中の位置を指し、チャネルを通る流体の流れの方向に対するものである。例えば、チャネルを通って流れてその位置に向かって来る流体の一部分がまだ到着していないチャネル内の位置は、流体のその一部分の下流にある。チャネルを通って流れてその位置から遠ざかる流体の一部分が既に通り過ぎたチャネル内の位置は、流体のその一部分の上流にある。本発明のプロセスで用いられるプロセスチャネルは、水平、垂直、あるいはある角度に配向させてもよいので、用語「上流」および「下流」は、必ずしも垂直位置を指すものではない。

【００３８】

用語「マイクロボディ」は、最大約２００ミクロン、一実施態様では約０．０１から約２００ミクロン、一実施態様では約０．０１から約１００ミクロン、一実施態様では約０．０１から約５０ミクロン、一実施態様では約０．０１から約２５ミクロン、一実施態様では約０．０１から約１０ミクロン、一実施態様では約０．０１から約５ミクロン、一実施態様では約０．０１から約２ミクロン、一実施態様では約０．０１から約１ミクロン、一実施態様では約０．０１から約０．５ミクロン、一実施態様では約０．０１から約０．２ミクロン、一実施態様では約０．０１から約０．１ミクロン、一実施態様では約０．０１から約０．０８ミクロン、一実施態様では約０．０１から約０．０５ミクロン、一実施態様では約０．０１から約０．０３ミクロンの範囲の平均寸法（例えば直径、高さ、幅、長さ）を有する三次元ボディを指す。これらのマイクロボディは、円および／または楕円の形状の断面を有するボディを含む。マイクロボディは、球体、楕円球体、卵形体および類似の形であってもよい。マイクロボディは、針状の形を有してもよい。マイクロボディは、中空であってもよく、あるいは中空でなくてもよい。マイクロボディは、マイクロスフェアであってもよい。マイクロボディは、主寸法（例えば直径、長さ）と副寸法（例えば直径、高さ、幅）とを有してもよく、副寸法に対する主寸法の比は、約１０：１から約１：１、一実施態様では約５：１から約１：１、一実施態様では約２：１から約１：１の範囲にある。

【００３９】

用語「流体」は、気体、液体、分散固体を含む気体または液体、液滴を含む気体、気泡を含む液体、液滴および分散固体を含む気体、あるいは気泡および分散固体を含む液体、

および類似物を指す。

【００４０】

用語「発熱源」は、熱を放出し、別の物体またはデバイスを加熱するために用いることができる物体またはデバイスを指す。発熱源は、熱交換流体を内部に有し、別の物体またはデバイスへ熱を伝える熱交換チャネルの形であってもよく、別の物体またはデバイスは、例えば、熱交換チャネルに隣接するか、または熱交換チャネルから伝えられる熱を受け取るのに十分に近いチャネルである。熱交換流体は、熱交換チャネルの中に収容されてもよく、および／または、熱交換チャネルを通って流れてもよい。発熱源は、加熱素子、例えば、電熱素子または抵抗加熱器の形であってもよい。用語「吸熱源」は、熱を吸収し、別の物体またはデバイスを冷却するために用いることができる物体またはデバイスを指す。吸熱源は、熱交換流体を内部に有し、別の物体またはデバイスから伝えられる熱を受け取る熱交換チャネルの形であってもよい。別の物体またはデバイスは、例えば、熱交換チャネルに隣接するか、または熱交換チャネルへ熱を伝えるのに十分に近いチャネルである。熱交換流体は、熱交換チャネルの中に収容されてもよく、および／または、熱交換チャネルを通って流れてもよい。吸熱源は、冷却素子、例えば、非流体冷却素子の形であってもよい。

【００４１】

用語「発熱源および／または吸熱源」は、熱を放出するか、または熱を吸収することができる物体またはデバイスを指す。発熱源および／または吸熱源は、熱交換流体を内部に有し、熱交換チャネルに隣接するかまたは近くにある別の物体またはデバイスが加熱されるとき、それらの別の物体またはデバイスに熱を伝えるか、あるいは、熱交換チャネルに隣接するかまたは近くにある別の物体またはデバイスが冷却されるとき、それらの別の物体またはデバイスから伝えられる熱を受け取る、熱交換チャネルの形であってもよい。発熱源および／または吸熱源として機能する熱交換チャネルは、あるときは加熱チャネル、他のときは冷却チャネルとして機能してもよい。熱交換チャネルの一部分（単数または複数）が加熱チャネルとして機能し、一方、熱交換チャネルの別の一部分（単数または複数）が冷却チャネルとして機能してもよい。

【００４２】

用語「熱交換チャネル」は、熱交換流体を内部に有し、熱を放出し、および／または熱を吸収することができるチャネルを指す。

【００４３】

用語「熱交換流体」は、熱を発生し、および／または熱を吸収することができる流体を指す。

【００４４】

図２を参照すると、本プロセスは、マイクロチャネルミキサ１００を用いて実行することができ、マイクロチャネルミキサ１００は、マイクロチャネルミキサコア１０２、プロセス流体ヘッダ１０４、生成物フッタ１０６および熱交換マニホルド１０８を含む。マイクロチャネルミキサコア１０２は、複数のプロセスマイクロチャネル、隣接する第二の流体流チャネルおよび熱交換チャネルを含む。第二の流体流チャネルおよび／または熱交換チャネルは、マイクロチャネルであってもよい。プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルは、上下に重ねられるか、または横に並べられて、層状に配置してもよい。プロセスヘッダ１０４は、第一の流体流がプロセスマイクロチャネルに流入し、第二の流体流が第二の流体流チャネルに流入し、これらのチャネルの流れの分布を一様にまたは実質的に一様にするための通路を提供する。生成物フッタ１０６は、多相混合物生成物がプロセスマイクロチャネルから迅速に流れ、比較的高い流速を有するための通路を提供する。第一の流体流は、矢印１１０で示されるように、ヘッダ１０４を通ってマイクロチャネルミキサ１００に流入する。第二の流体流は、矢印１１２で示されるように、ヘッダ１０４を通ってマイクロチャネルミキサ１００の中に流入する。第一の流体流と第二の流体流とは、マイクロチャネルミキサコア１０２の中に流入し、混合されて多相混合物を形成する。多相混合物は、マイクロチャネル混合コア１０２から生成物フッ

タ１０６を通り、矢印１１４で示されるように、生成物フッタ１０６から流出する。一実施態様では、多相混合物は、任意の回数、例えば、１回、２回、３回、４回等、マイクロチャネルミキサコア１０２を通って戻り、リサイクルしてもよい。矢印１１６で示されるように、熱交換マニホルド１０８の中に熱交換流体が流入し、熱交換マニホルド１０８からマイクロチャネルミキサコア１０２の中の熱交換チャネルを通ってから熱交換マニホルド１０８に戻り、矢印１１８で示されるように、熱交換マニホルド１０８から流出する。マイクロチャネルミキサ１００は、貯槽、ポンプ、バルブ、流量制御デバイスおよび類似デバイスとともに使用してもよい。これらは、図面に示していないが、当業者には自明である。

【００４５】

マイクロチャネルミキサコアは、複数の多相混合物形成ユニットを含んでもよい。図３～９および１２に、多相混合物形成ユニットの有用な実施態様の例が示される。図３を参照すると、本発明のプロセスは、対向する側壁２１２および２１４と、側壁２１２の中の開口区間２４０とを有するプロセスマイクロチャネル２１０を含む多相混合物形成ユニット２００を用いて実行することができる。開口区間２４０は、多孔質区間または多孔質基板と呼んでもよい。開口区間２４０は、開口区間全体に広がる開口のアレイ２４４を有するシートまたはプレート２４２を含んでもよい。側壁２１２に隣接して第二の流体流２７０があり、開口区間２４０の中の開口２４４を通ってプロセスマイクロチャネル２１０に開放される。プロセスマイクロチャネル２１０は、非開口領域または非多孔質領域２１１および２１７と、混合区域２１３とを有する。非開口領域２１１は、プロセスマイクロチャネルへの入口から混合区域３１３への入口へ延在する。非開口領域２１１は、混合区域２１３の上流である。混合区域２１３は、開口区間２４０に隣接する。非開口領域２１７は、混合区域２１３の終りからプロセスマイクロチャネル２１０の出口へ延在する。非開口領域２１７は、混合区域２１３の下流である。側壁２１４に隣接して、熱交換チャネル２９０がある。動作時、第一の流体流は、矢印２１６で示されるように、プロセスマイクロチャネル２１０に流入し、非開口領域２１１を通って混合区域２１３に流入する。矢印２７２で示されるように、第二の流体流が第二の流体流チャネル２７０に流入し、次に、矢印２７４で示されるように、開口区間２４０を通って混合区域２１３に流入する。混合区域２１３の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の流体流の中の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、混合区域２１３から非開口領域２１７を通り、矢印２１８で示されるように、プロセスマイクロチャネル２１０から流出する。加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネルおよび液体チャネルのある区間では無視できるか、または存在しなくてもよく、他の区間では中程度または比較的大きくてもよい。あるいは、加熱または冷却は、熱交換チャネル以外を用いて実現してもよい。例えば、加熱は、電熱素子または抵抗加熱器を用いて実現してもよい。電熱素子または抵抗加熱器は、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の一つ以上の壁を形成するために用いてもよい。電熱素子または抵抗加熱器は、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の一つ以上の壁の中にあってもよい。冷却は、非流体冷却素子を用いて実現してもよい。プロセスマイクロチャネル２１０の長さに沿って、複数の加熱または冷却区域が使用されてもよい。同様に、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の長さに沿って、一つ以上の熱交換チャネルの中でさまざまな温度の熱交換流体を使用してもよい。

【００４６】

図４に例が示される多相混合物形成ユニット２００Ａは、プロセスマイクロチャネル２

１０の側壁２１０が開口区間２４０に対向して配置されたテーパを有する区間２２０を含む点を除けば、図３に例が示される多相混合物形成ユニット２００と同一である。テーパを有する区間２２０は、混合区域２１３の中のプロセスマイクロチャネル２１０の幅または高さを小さくし、従って、混合区域２１３の中のプロセスマイクロチャネル２１０に狭くなった断面を提供する。この幅または高さは、約０．００１から約５ｍｍ、一実施態様では約０．０１から約２ｍｍの範囲にあるとよい。テーパを有する区間２２０が存在すると、混合区域２１３を通って流れる流体の速度の増加がもたらされる。混合区域２１３を通って流れる液体の速度が増加すると、開口２４４を通って混合区域２１３に流入する第二の流体に作用するせん断力が増加する。これは、開口２４４を通る第二の流体流の流れを容易にする。プロセスマイクロチャネル２１０の狭くなった断面を通って流れる流体が混合区域２１３を通る速度は、１秒あたり約０．００５から約１００メートル（ｍ／ｓ）、一実施態様では約０．０１から約５０ｍ／ｓの範囲にあるとよい。

【００４７】

図５に例が示される多相混合物形成ユニット２００Ｂは、多相混合物形成ユニット２００Ｂが第二の流体流チャネル２７０ａおよび開口区間２４０ａも含む点を除けば、図３に例を示した多相混合物形成ユニット２００と類似している。第二の流体流チャネル２７０ａは、プロセスマイクロチャネル２１０と熱交換チャネル２９０との間に位置する。側壁２１４の中に開口区間２４０ａが形成される。開口区間２４０ａを通って第二の流体流チャネル２７０ａがプロセスマイクロチャネル２１０に開放される。開口区間２４０ａは、全体に広がる開口のアレイ２４４ａを有するシートまたはプレート２４２ａを含んでもよい。プロセスマイクロチャネル２１０は、非開口領域または非多孔質領域２１１および２１７と、混合区域２１３とを有する。非開口領域２１１は、プロセスマイクロチャネルへの入口から混合区域２１３への入口へ延在し、混合区域２１３の上流である。混合区域２１３は、開口区間２４０と２４０ａとの間に位置する。非開口領域２１７は、混合区域２１３の終わりからプロセスマイクロチャネル２１０の出口へ延在する。非開口領域２１７は、混合区域２１３の下流である。動作時、矢印２１６で示されるように、プロセスマイクロチャネル２１０に第一の液体流が流入し、非開口領域２１１を通って混合区域２１３に流入する。矢印２７２および２７２ａでそれぞれ示されるように、第二の流体流チャネル２７０および２７０ａの中に第二の流体流が流入する。第二の流体流は、矢印２７４および２７４ａでそれぞれ示されるように、開口区間２４０および２４０ａを通って混合区域２１３に流入する。混合区域２１３の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の液体内の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、非開口領域２１７を通り、矢印２１８で示されるように、プロセスマイクロチャネル２１０から流出する。加熱または冷却は、選択肢としてもよい。加熱または冷却が望まれるとき、方向矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、プロセスマイクロチャネルおよび第二の流体流チャネルの長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネルおよび液体チャネルの中のある区間では無視できるかまたは存在しなくてもよく、他の区間では中程度または比較的大きくてもよい。

【００４８】

図６に例が示される多相混合物形成ユニット２００Ｃは、図５に例が示される開口２４４と２４４ａとは互いに真向かいに配置されていたが、一方、図６に例が示される開口２４４と２４４ａとはそのような直接配置からずらされている点を除けば、図５に例が示される多相混合物形成ユニット２００Ｂと同一である。図５では、開口２４４と２４４ａとを通って流れる第二の流体流の流れは、互いと直接衝突し、それによって、第一の流体流の中への第二の流体流の拡散を促進する。一方、図６では、開口２４４と２４４ａとを通って流れる第二の流体流の流れは、互いにずらされ、それによって、混合区域２１３内の渦巻き効果を提供することによって拡散を促進する。

【００４９】
図７に例が示される多相混合物形成ユニット２００Ｄは、プロセスマイクロチャネル２１０および２１０ａ、開口区間２４０および２４０ａ、第二の流体流チャネル２７０および熱交換チャネル２９０を含む。側壁２１２の中に開口区間２４０が形成され、側壁２１２ａの中に開口区間２４０ａが形成される。開口区間２４０および２４０ａは、多孔質区画または多孔質基板と呼んでもよい。開口区間２４０および２４０ａを通って、第二の流体流チャネル２７０がプロセスマイクロチャネル２１０および２１０ａにそれぞれ開放される。開口区間２４０は、全体に広がる開口のアレイ２４４を有するシートまたはプレート２４２を含んでもよい。同様に、開口区間２４０ａは、全体に広がる開口のアレイ２４４ａを有するシートまたはプレート２４２ａを含んでもよい。プロセスマイクロチャネル２１０および２１０ａは、非開口領域または非多孔領域２１１および２１７、ならびに２１１ａおよび２１７ａ、混合区域２１３および２１３ａをそれぞれ有する。非開口領域２１１および２１１ａは、プロセスマイクロチャネル２１０および２１０ａへの入口から、混合区域２１３および２１３ａへの入口へそれぞれ延在する。非開口領域２１１および２１１ａは、混合区域２１３および２１３ａのそれぞれ上流である。混合区域２１３および２１３ａは、開口区間２４０および２４０ａにそれぞれ隣接する。非開口領域２１７および２１７ａは、混合区域２１３および２１３ａの終わりから、プロセスマイクロチャネル２１０および２１０ａの出口へそれぞれ延在する。非開口領域２１７および２１７ａは、混合区域２１３および２１３ａのそれぞれ下流である。プロセスマイクロチャネル２１０に隣接して、熱交換チャネル２９０がある。動作時、矢印２１６および２１６ａで示されるように、プロセスマイクロチャネル２１０および２１０ａの中に、それぞれ第一の流体流が流れ、非開口領域２１１および２１１ａを通って混合区域２１３および２１３ａに流入する。矢印２７２で示されるように、第二の流体流チャネル２７０に第二の流体流が流入し、次に、矢印２７４および２７４ａで示されるように、開口区間２４０および２４０ａを通って混合区域２１３および２１３ａにそれぞれ流入する。混合区域２１３および２１３ａの中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の流体流内の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、非開口区画２１７および２１７ａを通り、矢印２１８および２１８ａで示されるように、プロセスマイクロチャネル２１０および２１０ａからそれぞれ流出する。加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、チャネル２１０、２１０ａおよび２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、チャネルの長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネル２１０および２１０ａ、ならびに第二の流体流チャネル２７０のある区画では無視できるかまたは存在しなくてもよく、他の区画では中程度または比較的大きくてもよい。

【００５０】
一実施態様では、単一のマイクロチャネルミキサ内で、多重の多相混合調合物および／またはプロセス処理条件の組を用いて、別個の多相混合物を発生させることができる。例えば、単一のマイクロチャネルミキサが、二つ以上のプロセスマイクロチャネル、関連する第二の流体流チャネル、および熱交換チャネルを使用して、単一のマイクロチャネルミキサ内で、２、３、４、５、６、７、８、９、１０、数１０、数１００、数１０００、数万、数１０万等の別個の多相混合物を作ることができる。この種類のミキサは、コンビナトリアル合成デバイスと呼んでもよい。多相混合物形成ユニット３００の例が示される図８に、これが示される。多相混合物形成ユニット３００は、４つのプロセスマイクロチャネルを使用し、その結果、最大４つの別個の多相混合物を発生することができる。多相混合物形成ユニット３００は、任意の所望の回数、例えば２回、３回、４回、５回、６回、７回、８回、９回、１０回、数１０回、数１００回、数１０００回、数万回等繰り返し、上記で示した多重の別個の多相混合物の可能性を提供することができる。多相混合物形成ユニット３００は、プロセスマイクロチャネル３１０、３２０、３３０および３４０、第

二の流体流チャネル３５０および３６０、ならびに熱交換チャネル３７０および３８０を含む。側壁３１２の中に開口区間３１１が形成される。側壁３２２の中に開口区間３２１が形成される。側壁３３２の中に開口区間３３１が形成される。側壁３４２の中に開口区間３４１が形成される。開口３１３、３２３、３３３および３４３が開口区間３１１、３２１、３３１および３４１の中に位置し、それぞれ全体に広がる。プロセスマイクロチャネル３１０、３２０、３３０および３４０は、混合区域３１５、３２５、３３５および３４５の上流にそれぞれ位置する非開口区画３１４、３２４、３３４および３４４を含む。混合区域３１５、３２５、３３５および３４５が、開口区間３１１、３２１、３３１および３４１にそれぞれ隣接して位置する。プロセスマイクロチャネル３１０、３２０、３３０および３４０は、混合区域３１５、３２５、３３５および３４５のそれぞれ下流に位置する非開口区画３１６、３２６、３３６および３４６も含む。動作時、矢印３１７、３２７、３３７および３４７でそれぞれ示されるように、プロセスマイクロチャネル３１０、３２０、３３０および３４０の中に第一の流体流が流入する。プロセスマイクロチャネル３１０、３２０、３３０および３４０に入る第一の流体流は、互いに同じ組成を有してもよく、あるいは互いに異なる組成を有してもよい。第一の流体流は、非開口区画３１４、３２４、３３４および３４４を通って、混合区域３１５、３２５、３３５および３４５にそれぞれ流入する。第二の流体流は、矢印３５１および３６１で示されるように、第二の流体流チャネル３５０および３６０に流入する。第二の流体流チャネル３５０に入る第二の流体流は、第二の流体流チャネル３６０に入る第二の流体流と同じであってもよく、あるいは異なっていてもよい。第二の流体流チャネル３５０に入る第二の流体流と、液体チャネル３６０に入る第二の液体との間の差は、組成、プロセス処理条件、物理的性質（例えば粘度、密度、表面張力等）および／または操作パラメータにもとづくものでもよい。矢印３５１で示されるように、第二の流体流チャネル３５０に入る第二の流体流は、矢印３５２および３５３で示されるように、開口区間３１１および３２１を通って流れ、混合区域３１５および３２５にそれぞれ流入する。混合区域３１５および３２５の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。同様に、第二の流体流は、矢印３６１示されるように、第二の流体流チャネル３６０に流れ、次に、矢印３６２および３６３で示されるように、開口区間３３１および３４１を通って混合区域３３５および３４５それぞれ流入する。混合区域３１５、３２５、３３５および３４５の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。混合区域３１５、３２５、３３５および３４５の中で形成される多相混合物は、同じであってもよく、あるいは異なっていてもよい。異なる場合、多相混合物は、組成および／または物理的性質、あるいは操作パラメータ（例えば分散相および／または連続相の組成、粒子サイズ、粒子サイズ分布、粘度、密度、表面張力、温度、圧力、流量等）が互いに異なっていてもよい。多相混合物は、混合区域３１５、３２５、３３５および３４５から非開口区画３１６、３２６、３３６および３４６を通り、矢印３１８、３２８、３３８および３４８でそれぞれ示されるように、プロセスマイクロチャネル３１０、３２０、３３０および３４０から流出する。熱交換チャネル３７０および３８０を用いる加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印３７１および３７２、ならびに３８１および３８２で示されるように、熱交換チャネル３７０および３８０を通って熱交換流体が流れ、チャネル３１０、３２０、３３０、３４０、３６０および３６０の中の流体を加熱または冷却する。加熱または冷却の度合いは、チャネルのそれぞれの長さにわたって変化してもよい。プロセスチャネルおよび／または液体チャネルのある区間では、加熱または冷却は無視できるかまたは存在しなくてもよく、他の区間では中程度または比較的大きくもよい。本発明のこの実施態様の一利点は、同時に同じ装置を用いて、複数の多相混合物製品の形成および評価を提供できる点である。これは、新製品の候補として複数の製剤をスクリーニングすることが望まれるとき、利点とすることができる。

【００５１】

一実施態様では、本発明のプロセスは、二重多相混合物をつくるのに適する。これらの二重多相混合物は、図９に例が示される多相混合物形成ユニット４００を用いて作ること

ができる。図９では、多相混合物形成ユニット４００は、中心線４０２と４０４との間に配置される。多相混合物形成ユニット４００は、プロセスマイクロチャネル４１０と、液体チャネル４２０、４３０、４４０および４５０とを含む。流体流チャネル４２０および４３０が、プロセスマイクロチャネル４１０に隣接する。流体流チャネル４４０が、流体流チャネル４２０に隣接し、流体流チャネル４５０が流体流チャネル４３０に隣接する。粗い開口区間４１５を含む共通壁４１２が、プロセスマイクロチャネル４１０と流体チャネル４２０とを分ける。粗い開口区間４２５を含む共通壁４２２が、プロセスマイクロチャネル４１０と流体チャネル４３０とを分ける。開口区間４１５および４２５は、開口４１６および４２６をそれぞれ含む。流体流チャネル４４０と流体流チャネル４２０との間に、開口４３６を含む微開口区間４３５が位置し、流体流チャネル４４０と流体流チャネル４２０とを分ける。流体流チャネル４５０と流体流チャネル４３０との間に、開口４４６を含む微開口区間４４５が位置し、流体流チャネル４５０と流体流チャネル４３０とを分ける。粗開口区間４１５および４２５の開口４１６および４２６は、微開口区間４３５および４４５の開口４３６および４４６より大きい。プロセスマイクロチャネル４１０は、非開口領域または非多孔領域４１１および混合区域４１３を有する。非開口領域４１１は、プロセスへの入口から混合区域４１３への入口へ延在する。混合区域４１３は、開口区間４１５および４２５に隣接する。選択肢として、中心線４０２および／または４０４で示される位置に熱交換チャネルを挿入し、所望の加熱または冷却を流体に提供してもよい。

【００５２】

中心線４０２の下に、同じく図９に例が示される隣接する多相混合物形成ユニット４００ａの一部が位置する。多相混合物形成ユニット４００ａは、プロセスマイクロチャネル４１０ａ、粗開口区間４１５ａおよび４２５ａ、流体流チャネル４３０ａおよび微開口区間４４５ａを含む。これらは、上記で考察したプロセスマイクロチャネル４１０、粗開口区間４１５および４２５、流体流チャネル４３０および微開口区間４４５と同じである。図９の中心線４０４の上に、別の隣接する多相混合物形成ユニット４００ｂの一部も位置する。多相混合物形成４００ｂは、微開口区間４３５ｂおよび流体流チャネル４２０ｂを含む。これらは、上記で考察した微開口区間４３５および流体流チャネル４２０と同じである。図９に多相混合物形成ユニット４００ａと４００ｂとの一部を含むことによって、本発明のプロセスを希求してマイクロチャネルミキサの中で使用されるときの多相混合物形成ユニット４００の反復する性質の例が示される。

【００５３】

動作時、図９を参照すると、矢印４１４で示されるように、第一の流体流がプロセスマイクロチャネル４１０に入り、非開口領域４１１を通って混合区域４１３に流入する。矢印４２３および４３３で示されるように、第二の流体流が流体流チャネル４２０および４３０にそれぞれ入る。矢印４４２および４５２で示されるように、第三の流体流が液体チャネル４４０および４５０にそれぞれ入る。第三の流体流は、流体流チャネル４４０から開口区間４３５を通って流体流チャネル４２０に流入し、第二の流体流と混合されて別の多相混合物を形成する。第三の流体流は、流体流チャネル４５０から開口区間４４５を通って流体流チャネル４３０にも流入し、第二の流体流と混合されて別の多相混合物を形成する。流体流チャネル４２０および４３０の中で形成される別の多相混合物の中で、第三の流体流は不連続相を形成し、第二の流体流は連続相を形成する。流体流チャネル４２０および４３０の中で形成された別の多相混合物は、開口区間４１５および４２５をそれぞれ通って混合区域４１３に流入し、第一の流体流と混合される。混合区域４１３の中で、別の多相混合物は、第一の流体流の中に不連続相として分散し、第一の流体流は連続相の形になる。混合区域４１３の中で形成される多相混合物は、二重多相混合物と呼んでもよい。二重多相混合物の中で、第三の流体流の少なくとも一部は、第二の流体流の泡またはマイクロボディ（例えばマイクロスフェア）の中にカプセル化することができる。カプセル化された泡またはマイクロボディは、連続相の形であってもよい第一の流体流の中の不連続相として分散させることができる。二重多相混合物は、矢印４１８で示されるように

、プロセスマイクロチャネル４１０から出る。多相混合物４９０として図１０に概略が示される形であってもよい二重多相混合物は、一実施態様では、第一の流体流４９６（例えば気体または液体）の中に分散した第二の流体流４９４（例えば液体またはマイクロボディ）の中にカプセル化された第三の流体流４９２（すなわち気体）を含む。

【００５４】

一実施態様では、本発明のプロセスは空気吹き込みプロセスの中で用いることができる。図１１および１２に、これの例が示される。この実施態様では、本プロセスは、マイクロチャネルミキサ５０２を含む空気吹き込みタンク５００を用いて実行される。動作時、空気吹き込みされる流体は、タンク５００内に収容され、矢印５０４で示されるように、第一の流体流としてマイクロチャネルミキサ５０２に入る。空気吹き込みすることができる流体の例は、細胞培養液である。矢印５０６で示されるように、マイクロチャネルミキサ５０２の中に、第二の流体流が入る。第二の流体流は、空気または酸素を含んでもよい。マイクロチャネルミキサの中で、第一の流体流（例えば細胞培養液）と第二の流体流（例えば空気または酸素）と混合され、その結果、多相混合物（例えば空気吹き込みされた細胞培養液）が形成される。マイクロチャネルミキサ５０２は、複数の多相混合物形成ユニットを含んでもよい。多相混合物形成ユニット５１０は、プロセスマイクロチャネル５２０、第二の流体流チャネル５３０および５４０、微細セラミック膜の形であってもよい開口区間５５０および５６０、マクロ多孔質担体の形であってもよい開口区間５７０および５８０、ならびに熱交換チャネル５９０を含む。動作時、第一の流体流は、矢印５２２で示されるように、プロセスマイクロチャネル５２０に入る。第二の流体流は、矢印５３２および５４２でそれぞれ示されるように、第二の流体流チャネル５３０および５４０に入る。第二の流体流は、第二の流体流チャネル５３２から開口区間５７０を通った後、開口区間５５０を通ってプロセスマイクロチャネル５２０に流入する。同様に、矢印５４２で示されるように、別の第二の流体流が、第二の流体流チャネル５４０に入り、開口区間５８０を通った後、開口区間５６０を通り、プロセスマイクロチャネル５２０に流入する。第一の流体流と第二の流体流とは、プロセスマイクロチャネル５２０の中で混合され、その結果、多相混合物が形成される。多相混合物は、矢印５２４で示されるように、プロセスマイクロチャネル５２０から出る。多相混合物の中で、第一の流体流は連続相を形成してもよく、第二の流体流は不連続相を形成してもよい。一実施態様では、多相混合物は、細胞培養液全体に分散した高められたレベルの酸素または空気を有する細胞培養液を含むことができる。流体は、矢印５０７で示されるように、熱交換流体をマイクロチャネルミキサ５０２の中に流し、熱交換チャネル５９０を通した後、マイクロチャネルミキサ５０２から流出させることによって、加熱または冷却することができる。

【００５５】

図３～９および１２のそれぞれでは、一つの多相混合物形成ユニットしか完全に例が示されていないが、本発明のプロセスを実行するためにマイクロチャネルミキサの中で用いてもよい多相混合物形成ユニットの数に、事実上、上限はない。例えば、１、２、３、４、５、６、８、１０、２０、５０、１００、数１００、１０００、数１０００、一万、数万、１０万、数１０万、数１００万等の上記で説明した多相混合物形成ユニットを用いてもよい。一実施態様では、各多相混合物形成ユニットは、マニホルド接続してもよい。マニホルド接続は、各ユニットにマクロ配管、パイプ配管またはダクト配管を接続することによって実現してもよい。あるいは、各ユニットの間に比較的等しい圧力降下回路を創り出すことによって、多相混合物形成ユニットを含むマイクロチャネルミキサ内で、多相混合物形成ユニットの多数を内部マニホルド化してもよい。一方、幾分かの流れ不均衡があっても、製品の品質に影響を及ぼさないことがあるので、圧力降下は、各ユニットの間で等しくなくてもよい。一実施態様では、本発明のプロセスを用いる多相混合物を形成させるに際して、最大約５０％の流れ不均衡は許容できる。プロセスマイクロチャネル、関連する第二および第三の流体流チャネル、および熱交換チャネルは、横に並べるか、または上下に重ねて配置するとよい。例えば、多相混合物形成ユニット２００および２００Ａでは、プロセスマイクロチャネル２１０は、一平面内に平行に配置するとよく、第二の流体

流チャネル２７０は、プロセスマイクロチャネル２１０の一方の側の隣接平面内に平行に配置するとよく、熱交換チャネル２９０は、プロセスマイクロチャネル２１０の反対側の別の平面内に平行に配置するとよい。例えば、多相混合物形成ユニット２００Ｂおよび２００Ｃでは、プロセスマイクロチャネル２１０は、一平面内に平行に配置するとよく、第二の流体流チャネル２７０および２７０ａは、プロセスマイクロチャネル２１０のそれぞれの側の隣接平面内に平行に配置するとよく、熱交換チャネル２９０は、第二の流体流チャネル２７０ａに隣接する平面内に平行に配置するとよい。多相混合物形成ユニット２００Ｄでは、第二の流体流チャネル２７０は、一平面内に平行に配置するとよく、プロセスマイクロチャネル２１０および２１０ａは、液体チャネル２７０のそれぞれの側の隣接する平面内に平行に配置するとよく、熱交換チャネル２９０は、プロセスマイクロチャネル２１０に隣接する平面内に平行に配置するとよい。これらの多相混合物形成ユニットは、図３～９および１２には示していないが、当業者なら提供することができる、プロセス液体および熱交換流体の入出力を制御するために、適切なヘッダ、フッタ、マニホルド、バルブ、導路、配管、制御機構等を有してもよい。例えば、多相混合物形成ユニットを含むマイクロチャネルミキサへの入口および出口で、導路または配管を接続するために傾斜したヘッダおよびフッタを用いて、プロセスマイクロチャネルのサイズに伴う不必要な圧力降下を回避してもよい。

【００５６】

一実施態様では、複数の多相混合物形成ユニット（２００、２００Ａ、２００Ｂ、２００Ｃ、２００Ｄ、３００、４００、５１０）を上下に積み重ねて、オンデマンドの大きな生産能力用のスケールアップしたユニットのコアを形成してもよい。スケールアップしたユニットは、多相混合物製品のためだけでなく、多相混合物を形成させるために用いられる液体のためのマニホルドとしても、傾斜したヘッダおよびフッタを有してもよい。プロセスチャネル、分散相チャネルまたは熱交換チャネルの入口にオリフィスプレートまたはその他の開口区間を加えることによって、より一様な流れの分布を容易にしてもよい。フレーム区間を用いて、多相混合物形成ユニットを保持し、封止してもよい。

【００５７】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）のそれぞれは、任意の構成、例えば正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。プロセスマイクロチャネルは、管状であってもよい。プロセスマイクロチャネルは、横に並べられるか、または上下に重ねられた平行な離間したシートおよび／またはプレートから形成してもよい。用語「シート」は、最大約５ｍｍの壁の厚さを指す。用語「プレート」は、約５ｍｍ以上の壁の厚さを指す。シートは、ロールの形でユーザに供給されてもよく、一方、プレートは、平らな材料の片の形でユーザに供給されてもよい。プロセスマイクロチャネルのそれぞれは、プロセスマイクロチャネルを通る流体の流れに垂直な、最大約５０ｍｍ、一実施態様では最大約１０ｍｍ、一実施態様では最大約２ｍｍの範囲の内部寸法（例えば、高さ、幅または直径）を有するとよい。この寸法は、約０．０５から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．０５から約１．５ｍｍ、一実施態様では約０．０５から約１ｍｍ、一実施態様では約０．０５から約０．５ｍｍの範囲にあるとよい。プロセスマイクロチャネルを通る液体の流れに垂直な別の内部寸法（例えば、高さまたは幅）は、任意の値であってもよく、例えば、約０．０１ｃｍから約１００ｃｍ、一実施態様では約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。

【００５８】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）は、プロセスマイクロチャネルの中の第一の液体の流れの均一な分布を提供するために、混合区域（２１３、２１３ａ、３１５、３２５、３３５、３４５、４１３）の上流の入口の中の非開口領域または非多孔質領域（２１１、２１１

ａ、３１４、３２４、３３４、３４４、４１１）を有してもよい。これは、複数のプロセスマイクロチャネルが横に並べられ、および／または上下に重ねられて配置され、複数のプロセスマイクロチャネルの中への第一の液体流が一様でないとき、有用になることがある。これらの非開口領域を設けると、混合区域に到達する前の第一の流体流の流れを安定化することがある。非開口領域または非多孔質領域を使用すると、プロセスマイクロチャネルが円形の断面（すなわち管状幾何構造）を有するとき、利点になることがある。一実施態様では、非開口領域または非多孔質領域の中のプロセスマイクロチャネルの最小内部寸法に対する、プロセスマイクロチャネルへの入口から混合区域への入口までの非開口領域の長さの比は、約０．０００１から約１００００、一実施態様では約０．００１から約１０００の範囲にあるとよい。

【００５９】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）の内部壁の一つ以上は、プロセスマイクロチャネルの中の流れを変更するための表面構成要素を有してもよい。図２２～２６に、これらの表面構成要素の例が示される。表面構成要素は、三次元パターンで互いの上に重ねられるか、または絡み合った二つ以上の層を有してもよい。各別個の層の中のパターンは、同じであってもよく、あるいは異なっていてもよい。各層の中で、または一つの層の中だけで、流れが回転するか、または平行移動してもよい。バルクの流れのチャネルに隣接していなくてもよい副層を用いて、追加の表面積を作り出してもよい。例えば、これらを用いて触媒を析出させてもよい。流れは、表面構成要素の第一のレベルの中で回転し、第二の副層以降の中に分子拡散して反応を促進してもよい。金属キャスティングまたはその他のプロセスによって三次元構成要素を作ってもよい。これらの方法では、互いの上に積層されているかのように変化するパターンも個別の平面に分解しなくてよい。バルクの流れのチャネルに隣接して、三次元的に変化する表面構成要素を置くことができる。これらの構成要素は、さまざまな深さ、形状および位置を有し、さまざまな深さ、形状および位置のパターンを有する副構成要素を伴う。表面構造物は、触媒析出のために追加の表面積を必要とする化学反応、または蒸留などの化学的分離の場合に利点となることがある。

【００６０】

図２３は、三次元表面構成要素構造物の平面概略図である。図２４には、三次元表面構成要素構造物の背面図の例が示され、バルクの流れのマイクロチャネルの隣接する界面にくぼんだＶ字形があり、Ｖ字形の下には、バルクの流れの通路に隣接する構成要素に接続されるが、多彩な形状、深さおよび位置の構造物から作られた一連の三次元構造がある。開いた表面構成要素の直下にはなく、バルクの流れのマイクロチャネルに隣接するが、一つ以上の曲がりくねった二次元または三次元の通路によって接続される、副層通路を作り出すとさらに有利になることがある。この手法は、狭い滞留時間分布ではなく、広い滞留時間分布を有することが望ましい反応器の中に調整された滞留時間分布を作り出すために利点となることがある。

【００６１】

図２５は、くぼんだＶ字形がバルク流れのマイクロチャネルに接し、Ｖ字形の後ろには変化する深さおよび位置にあるさまざまな形状の追加の構成要素がある、三次元表面構成要素の前面図である。

【００６２】

表面構成要素は、約２ｍｍより小さい、一実施態様では約１ｍｍより小さい、一実施態様では約０．０１ｍｍから約０．５ｍｍの範囲にある深さを有するとよい。表面構成要素の横幅は、マイクロチャネル幅にほぼ達する（魚骨設計で示されるように）のに十分であるとよいが、一実施態様（充填構成要素など）ではマイクロチャネル幅の約６０％以下、一実施態様では約４０％以下、一実施態様では約０．１％から約６０％、一実施態様では約０．１％から約５０％の幅であるとよい。

【００６３】

表面構成要素の横幅は、約０．０５ｍｍから約１００ｃｍの範囲、一実施態様では約０

．５ｍｍから約５ｃｍの範囲、一実施態様では約１から約２ｃｍの範囲にあるとよい。

【００６４】

表面構成要素の長さおよび幅は、マイクロチャネルの長さおよび幅と同様に定めるとよい。深さは、表面構成要素がマイクロチャネル表面の中に沈む距離であってもよく、この場合は、マイクロチャネル高さまたはマイクロチャネルギャップと同じ方向である。これは、シート表面の上または中に形成された表面構成要素を有し、積層され、ボンディングされたマイクロチャネルデバイスを積層する方向に対応してもよい。表面構成要素のこれらの寸法は、表面構成要素の最大寸法を指す。例えば、角を丸めた溝の深さは、最大の深さ、すなわち、溝の底での深さを指すことがある。

【００６５】

マイクロチャネルの中に、一つ以上のマイクロチャネル壁の中にさまざまな深さでくぼむ構成要素を含む、複数の表面構成要素または表面構成要素の領域を含んでもよい。くぼみの間の間隔は、約０．０１から約１０ｍｍの範囲、一実施態様では約０．１から約１ｍｍの範囲にあるとよい。表面構成要素は、マイクロチャネルの長さ全体に存在してもよく、またはマイクロチャネルの部分または領域に存在してもよい。表面構成要素を有する部分または領域は、専用に調整された区域の中で所望の反応または単位操作を促進するように断続的であってもよい。例えば、マイクロチャネルの１インチの区間は密集した表面構成要素のアレイを有し、続く４インチは構成要素のない平坦なチャネルとし、続く２インチは疎な表面構成要素の区間としてもよい。疎に離間した表面構成要素とは、表面構成要素の長さの５倍より大きなピッチまたは構成要素間距離を有する表面構成要素を指す。

【００６６】

一実施態様では、表面構成要素は、実質的にマイクロチャネルの軸方向長さ全体にわたって延在してもよい。一実施態様では、マイクロチャネルは、その軸方向長さの約５０％以下にわたって、一実施態様ではその軸方向長さの約２０％以下にわたって表面構成要素を有するとよい。一実施態様では、表面構成要素は、マイクロチャネルの軸方向長さの約１０％から約１００％にわたって延在するとよい。

【００６７】

図２６は、表面構成要素のために用いることができる複数のさまざまなパターンを示す。これらのパターンは、本発明を限定するものではなく、複数の可能性の例を示すことだけとする。任意の表面構成要素の場合と同じく、パターンは、マイクロチャネルのさまざまな軸方向の区間または横の区間の中で用いてもよい。

【００６８】

第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）および第三の流体流チャネル（４４０、４５０）は、マイクロチャネルと特徴づけるには大きすぎる寸法を有することがあるが、マイクロチャネルであるとよい。これらのチャネルのそれぞれは、任意の構成、例えば、正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。これらのチャネルは、上記で説明したように、表面構成要素を含んでもよい。第二および第三の流体流チャネルは管状であってもよい。第二および第三の流体流チャネルは、横に並べられるか、または上下に重ねられて配置された平行な離間したシートおよび／またはプレートから形成してもよい。各第二および第三の流体流チャネルは、最大約１００ｃｍの範囲、一実施態様では約０．０５ｍｍから約１００ｃｍの範囲、一実施態様では約０．０５ｍｍから約５０ｃｍ、一実施態様では約０．０５ｍｍから約１０ｃｍ、一実施態様では約０．０５ｍｍから約５ｃｍ、一実施態様では約０．０５ｍｍから約１０ｍｍ、一実施態様では約０．０５ｍｍから約５ｍｍ、一実施態様では約０．０５ｍｍから約２ｍｍ、一実施態様では約０．０５ｍｍから約１ｍｍの、第二および第三の流体流チャネルを通る流体流に垂直な内部寸法（例えば高さ、幅または直径）を有するとよい。第二および第三の流体流チャネルを通る流体流に垂直な別の内部寸法（例えば高さまたは幅）は、約０．０１ｃｍから約１００ｃｍ、一実施態様では約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。第二および第三の流体流チャネルの長さは、

任意の値、例えば、約０．１ｃｍから約５００ｃｍ、一実施態様では約０．１ｃｍから約２５０ｃｍ、一実施態様では約１ｃｍから約１００ｃｍ、一実施態様では約１ｃｍから約５０ｃｍ、一実施態様では約２ｃｍから約２５ｃｍの範囲にあるとよい。各プロセスマイクロチャネルと次の隣接する第二の流体流チャネルまたは隣接する第二および第三の流体流チャネルとの間の距離は、約０．０５ｍｍから約５０ｍｍ、一実施態様では約０．１から約１０ｍｍ、一実施態様では約０．２ｍｍから約２ｍｍの範囲にあるとよい。

【００６９】

発熱源および／または吸熱源は、冷却、加熱、あるいは冷却と加熱との両方のために用いてもよい。発熱源および／または吸熱源は、一つ以上の熱交換チャネルを含んでもよい。発熱源は、一つ以上の電熱素子または抵抗加熱器を含んでもよい。吸熱源は、一つ以上の非流体冷却素子を含んでもよい。これらは、プロセスマイクロチャネルおよび／または第二または第三の流体流チャネルに隣接してもよい。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルに接触も隣接もせず、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルのどちらかまたは両方から離れているが、発熱源および／または吸熱源とプロセスマイクロチャネルおよび／または第二および第三の流体流チャネルとの間で熱を移動させるために、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルに十分に近くすることができる。電熱素子、抵抗加熱器および／または非流体冷却素子を用いてプロセスマイクロチャネル（２１０、３１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）および／または第三の流体流チャネル（４４０、４５０）の一つ以上の壁を形成してもよい。電熱素子、抵抗加熱器および／または非流体冷却素子は、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの一つ以上の壁の中に構築してもよい。電熱素子および／または抵抗加熱器は、プロセスマイクロチャネルおよび／または液体チャネルの壁の中に埋め込まれた薄いシート、ロッド、ワイヤ、ディスクまたはその他の形状の構造物であってもよい。電熱素子および／または抵抗加熱器は、プロセスマイクロチャネル壁および／または液体チャネル壁に接着されたフォイルまたはワイヤの形状であってもよい。加熱および／または冷却は、ペルティエ型熱電冷却および／または加熱素子を用いて実現してもよい。プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの長さに沿って、複数の加熱および／または冷却区域を使用してもよい。同様に、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの長さに沿って、一つ以上の熱交換チャネルの中のさまざまな温度の伝熱流体を使用してもよい。発熱源および／または吸熱源は、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネル内の精密な温度調節を提供するために用いてもよい。

【００７０】

熱交換チャネル（２９０、３７０、３８０、５９０）は、マイクロチャネルであってもよいが、典型的マイクロチャネルとは言えないような大きな寸法を有してもよい。これらのチャネルのそれぞれは、任意の構成、例えば、正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。熱交換チャネルは、管状であってもよい。熱交換チャネルは、横に並べられるか、または上下に重ねられて配置された平行な離間したシートおよび／またはプレートから、隣接するプロセスマイクロチャネルまたは第二および第三の流体流チャネルと一緒に形成してもよい。これらのチャネルは、上記で説明された表面構成要素を含んでもよい。熱交換チャネルのそれぞれは、最大約５０ｍｍ、一実施態様では最大約１０ｍｍ、一実施態様では最大約２ｍｍの範囲の熱交換チャネルを通る熱交換流体流に垂直な内部寸法、例えば高さ、幅または直径を有するとよい。この寸法は、約０．０５から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．５から約１ｍｍの範囲にあるとよい。熱交換チャンルを通る熱交換流体流に垂直な別の内部寸法、例えば高さまたは幅は、任意の値、例えば約０．０１ｃｍから約１００ｃｍ、一実施態様で

は約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。熱交換チャネルの長さは、例えば約０．１ｃｍから約５００ｃｍ、一実施態様では約０．１ｃｍから約２５０ｃｍ、一実施態様では約１ｃｍから約１００ｃｍ、一実施態様では約１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲の任意の値であるとよい。各プロセスマイクロチャネルあるいは第二または第三の流体流チャネルと次の隣接する熱交換チャネルとの間の距離は、約０．０５ｍｍから約５０ｍｍ、一実施態様では約０．１から約１０ｍｍ、一実施態様では約０．２ｍｍから約２ｍｍの範囲にあるとよい。

【００７１】

熱交換チャネル（２９０、３７０、３８０、５９０）は、チャネルを通って隣接するプロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体の流れと平行な、並流の方向に熱交換流体が流れるようにしてもよい。あるいは、熱交換流体は、熱交換チャネルを通って、プロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体流に対して向流となる方向に流れてもよい。あるいは、熱交換チャネルは、プロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体流に対して交差流となる方向の熱交換流体流を提供するように、プロセスマイクロチャネルまたは第二および第三の流体流チャネルに対して配向してもよい。熱交換チャネルは、交差流と並流または向流との組み合わせを提供するために、蛇行する構成を有してもよい。

【００７２】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および／または熱交換チャネル（２９０、３７０、３８０、５９０）は、正方形または長方形の断面を有し、平行な離間したシートまたはプレートから形成される。これらのチャネルは、横に並べられた垂直配向の交互面、または上下に積層された水平配向の交互面に配列してもよい。平行プレート構成と呼んでもよいこれらの構成には、複数の利点がある。例えば、円形の管と比較すると、平行プレート構成は、同じ連続相物質流束での高さ、幅または直径に対して、同じせん断力を実現しながら、受ける圧力降下が小さい。例えば、長方形チャネルのアスペクト比が約１０に近づくと、すなわち平行シートまたはプレート構成に近づくと、その圧力降下は、同じ条件下の円形チャネルの中の圧力降下のわずか約５０％にすることができる。平行板構成を有するプロセスマイクロチャネル、第二の流体流チャネル、第三の流体流チャネルおよび熱伝達チャネルは、スケールアップのために、小型デバイスの中に容易に配置することができる。円形の管と比較すると、平行プレート構成を用いることによって、多相混合物形成プロセスのより高い単位体積あたり処理能力を実現することもできる。

【００７３】

平行プレート構成を用いる利点は、これらの構成が円形の管と比較してより大きな流体／壁材料比を有し、従ってより小型であり、より大きな製造能力または出力の可能性を有する点である。

【００７４】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および／または熱交換チャネル（２９０、３７０、３８０、５９０）は、同心状に配置された円形の管の形であるとよい。プロセスマイクロチャネルおよび第二の流体流チャネルは、互いに隣接し、一方のチャネルは環状の空間にあり、他方のチャネルは中心の空間または隣接する環状の空間にあるとよい。一実施態様では、本発明のプロセスで有用なマイクロチャネルミキサは、複数の交互に重ねられた同心円の管のプロセスマイクロチャネル、第二の流体流チャネル、および選択肢として第三の流体流チャネルを含み、マイクロチャネルミキサは円筒形の形状であるとよい。

【００７５】
開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）は、開口区間を通る示された流体の流れを可能にする十分なサイズであるとよい。開口は、細孔と呼んでもよい。開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、約０．０１から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．１から約２ｍｍの範囲の厚さを有するとよい。開口は、最大約５０ミクロンの範囲、一実施態様では約０．００１から約５０ミクロンの範囲、一実施態様では約０．０５から約５０ミクロン、一実施態様では約０．１から約５０ミクロンの平均直径を有するとよい。一実施態様では、開口は、約０．５から約１０ナノメートル（ｎｍ）、一実施態様では約１から約１０ｎｍ、一実施態様では約５から約１０ｎｍの範囲の平均直径を有するとよい。開口区間の中の開口の数は、平方センチメートルあたり約１０から約５×１０^{8}開口、一つの実施態様では平方センチメートルあたり約１から約１×１０^{6}開口の範囲にあるとよい。開口は、互いに孤立していてもよく、孤立していなくてもよい。開口の一部またはすべては、開口区間内の他の開口と流体連通していてもよい。プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）を通って流れる流体の流れの経路に沿った開口区間の長さに対する、開口区間の厚さの比は、約０．００１から約１００、一実施態様では約０．０１から約５０、一実施態様では約０．０３から約２５、一実施態様では約０．０５から約１０、一実施態様では約０．０８から約５、一実施態様では約０．１から約１の範囲にあるとよい。開口区間は、本発明のプロセスの動作を可能にするのに十分な強度および寸法安定性を提供する任意の材料で構築するとよい。これらの材料は、鋼（例えばステンレス鋼、炭素鋼および類似物）、モネル、インコネル、アルミニウム、チタン、ニッケル、白金、ロジウム、銅、クロム、真鍮、上記金属の任意のものの合金、重合体（例えば熱硬化性樹脂）、セラミック、ガラス、一つ以上の重合体（例えば熱硬化樹脂）およびガラス繊維を含むコンポジット、石英、ケイ素、カーボンナノチューブまたはカーボンモレキュラーシーブを含む微多孔質炭素、ゼオライトまたはそれらの二つ以上の組み合わせを含む。開口は、レーザ穿孔、マイクロエレクトロマシニングシステム（ＭＥＭＳ）、リソグラフィー電着および成型（ＬＩＧＡ）、電気スパークリングまたは電気化学エッチングなどの既知の技法を用いて作製してもよい。開口は、押し出しなどの構造を有するプラスチックを作るために用いられる技法、または配列カーボンナノチューブ（ＣＮＴ）膜などの膜を作るために用いられる技法を用いて、作製してもよい。開口は、金属粉末または粒子を焼結または圧縮して曲がりくねって相互連絡した毛管チャネルを形成させるなどの技法、および膜作製の技法を用いて作製してもよい。開口は、これらの方法の任意のものによって提供されるサイズから、開口を部分的に埋める開口内部側壁へのコーティングの塗布によって大きさを小さくしてもよい。選択なコーティングによって、多孔質ボディの外に薄層を形成させ、連続する流れの経路に隣接して最小の細孔サイズを提供してもよい。最小平均細孔開口は、多相混合物用の所望の液滴サイズによって、約１ナノメートルから約数百ミクロンの範囲にあるとよい。開口は、熱処理によって、ならびに、開口内部側壁上に酸化物スケールまたはコーティングを形成させる方法によって、サイズを小さくしてもよい。これらの技法は、開口を部分的に閉塞して流れに当てられる開口のサイズを減らすために用いてもよい。図１３および１４は、熱処理の前後の、同じ倍率で、同じ位置のステンレス鋼多孔基板のＳＥＭ表面構造の比較を示す。図１３は熱処理前の表面を示し、図１４は熱処理後の表面を示す。熱処理後の多孔質材料の表面は、著しく小さなギャップおよび開口部サイズを有する。対応して、開口の間の平均距離は、増加する。

【００７６】
開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、約０．０１から約２００ミクロンの範囲の平均細孔サイズの相互連結チャネルまたは細孔を有する金属または非金属多孔質材料から作ってもよい。これらの細孔は、開口（２４４、２４４ａ、３１３、３２３、３

３３、３４３、４１６、４２６、４３６、４４６）として機能してもよい。多孔質材料は、平均細孔間距離が平均細孔径と同様になるように、粉末または微粒子から作ってもよい。非常に小さな細孔サイズが用いられると、細孔間距離も非常に小さくなることがあり、液滴は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、４１０、５２０）または第二の流体流チャネル（４２０、４３０）の側の表面で合体して望ましくない大きな液滴を形成することがある。多孔質材料は、約３００℃から約１０００℃の範囲の高温で、約１時間から約２０日間の長さの酸化によって、またはゾルコーティングによるアルミナまたは化学蒸着法を用いるニッケルなどの別の材料の薄層を表面の上および細孔の内部にコーティングして、小さな細孔をふさぎ、大きな細孔の細孔サイズを小さくし、その結果細孔間距離を増加させることによって、調整してもよい。そのようにして、液滴の合体を減らすか、またはなくし、より小さな液滴の生成を可能にしてもよい。図１５に、調整された基板または開口区間のＳＥＭ画像が示される。

【００７７】

開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）は、混合区域（２１３、２１３ａ、３１５、３２５、３３５、３４５、４１３）全体にわたって規則的に離間してもよい。開口は、小さな開口ほど、または大きな開口ほど、混合区域の前後のどちらかの近くで用いられるように、優先して離間してもよい。開口は、一緒に、混合区域の始めで互いに近く、混合区域の終わり近くで遠く離れて液滴融合を抑制する助けとしてもよい。約１ミクロンより小さな泡またはミクロスフェアサイズを有する多相混合物を提供するのに十分に小さなマイクロスケール開口または細孔（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）を有する開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）として用いられる基板の製作は、問題となることがある。これの理由の一つは、圧縮および／または焼結によって粉末／粒子から作られた金属多孔質基板などの未処理の通常の多孔質材料では、比較的大きな表面粗さが生じるという事実にある。一般に、これらの金属多孔質基板では、所定の名目細孔径が特定の値より低いとき、表面領域に必要な細孔サイズがない。多孔質材料のバルクは指定された名目細孔サイズを有するが、多くの場合、表面領域ははるかに大きなサイズの融合細孔および空洞を特徴とする。この問題は、これらの基板を調整して所望の細孔サイズおよび細孔間距離を表面領域の中に提供することによって、克服することができる。これは、多孔質基板から表面層を除去し、より小さな開口を有する滑らかな新しい表面を露出させるか、または加えることによって実施するとよい。これらの調整された基板を用いて形成される多相混合物の中の泡またはマイクロスフェアサイズは、基板にかかる圧力降下を増加させずに小さくすることができる。多孔質表面を直接研磨または機械加工すると、表面構造のスミアリングおよび細孔の閉塞の原因となることがあるので、多孔質構造を液体充填材で満たした後、固形化および機械研磨／磨き仕上げしてもよい。次に、充填材を除去して材料の多孔質構造を再び得る。充填材は、亜鉛またはスズなどの低い融点を有する金属またはエポキシなどの重合体の前駆体であってもよい。液体充填および除去工程は、真空の使用によって支援してもよい。研磨／磨き仕上げは、研削盤および研削粉を用いて実行してもよい。金属充填剤除去は、融解および真空吸引によって、または酸エッチングによって実現してもよい。エポキシまたはその他の重合体は、溶媒溶解によって、または空気中での燃焼除去によって除去してもよい。

【００７８】

図１６～１９を参照すると、一実施態様では、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、比較的小さな開口６０２を含む比較的薄いシート６００と、開口６００と同軸配置されるかまたは接続された比較的大きな開口６１２のアレイを含む比較的厚いシートまたはプレート６１０とで構築するとよい。比較的薄いシート６００は、比較的厚いシート６１０の上にあってボンディングされ、比較的薄いシート６００は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０）または第二

の流体流チャネル（４２０、４３０）の内部に対向し、比較的厚いシート６１０は、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）または第三の流体流チャネル（４４０、４５０）の内部に対向する。比較的薄いシート６００は、任意の適当な手順（例えば拡散結合）を用いて比較的厚いシート６１０にボンディングされ、機械的強度が大きくなったコンポジット構造６２０を提供することができる。比較的薄いシート６００は、約０．００１から約０．５ｍｍ、一実施態様では約０．０５から約０．２ｍｍの範囲の厚さを有するとよい。比較的小さな開口６０２は、任意の形状、例えば円形、三角形または長方形を有するとよい。比較的小さな開口６０２は、約０．０５から約５０ミクロン、一実施態様では約０．０５から約２０ミクロンの範囲の平均直径を有するとよい。比較的厚いシートまたはプレート６１０は、約０．１から約５ｍｍ、一実施態様では約０．１から約２ｍｍの範囲の厚さを有するとよい。比較的大きな開口６１２は、任意の形状、例えば円形、三角形または長方形を有するとよい。比較的大きな開口６１２は、約０．１から約４０００ミクロン、一実施態様では約１から約２０００ミクロン、一実施態様では約１０から約１０００ミクロンの範囲の平均直径を有するとよい。シート６００の中の開口６０２の数およびシートまたはプレート６１０の中の開口６１２の数は、それぞれ平方センチメートルあたり約２から約１００００開口、一実施態様では平方センチメートルあたり約２から約１０００開口の範囲にあるとよい。シート６００およびシートまたはプレート６１０は、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）を構築するために有用であるとして上記で説明した材料の任意のもので構築するとよい。開口６０２および６１２は、開口区間を通って流れる液体が最初に開口６１２を通り、次に開口６０２を通って流れるように同軸配置されるか、または接続されるとよい。液体が比較的小さな開口６０２を通って流れるための比較的短い通路は、開口の中の通路が開口６０２と６１２とを合わせた長さに等しい長さを有していたら起こると考えられる圧力降下と比べると比較的低い圧力降下で、液体が開口６０２を通って流れることを可能にする。

【００７９】

図１９に例が示される実施態様では、コンポジット構造物６２０ａは、開口６１２を覆う比較的薄いシート６００の凸部分６０４が提供される点を除けば、図１８に例が示されるものと同じ設計を有する。凸部分６０４は、隣接するチャネルの中の局所せん断力の増加をもたらす。図１９の方向矢印６３０は、開口６０２に隣接するチャネルの中の流体の流れを示す。せん断力がより大きいため、開口６０２を通って流れる流体の泡またはミクロスフェアサイズが小さくなる。

【００８０】

図２０に例が示される実施態様では、シートまたはプレート６４０の表面と、開口６４６の内部側壁６４４との上に表面コーティング６４２が析出される。このコーティングは、開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）の直径を小さくする、より容易な方法を提供する。コーティング６４２を形成させるために用いられるコーティング材料は、アルミナ、ニッケル、金または重合材料（例えばテフロン（登録商標））を含んでもよい。コーティング６４２は、化学蒸着、金属スパッタリング、金属メッキ、焼結、ゾルコーティング、重合体コーティングおよび類似法を含む既知の技法を用いて、シートまたはプレート６４０に塗布してもよい。開口の直径は、コーティング６４２の厚さを調節することによって制御してもよい。

【００８１】

一実施態様では、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、非対称多孔質材料、例えば、複数の焼結粒子の層を有する多孔質材料で形成してもよい。層の数は、２、３または４以上であってもよい。これらの多層基板の利点は、耐久性および接着強さの増加をもたらす点である。例は、一方の側に比較的大きな細孔、他方の側に比較的小さな細孔を有する焼結セラミックスを含む。比較的小さな細孔は、約２から約１０ｎｍの範囲の

直径を有するとよい。比較的小さな細孔は、多層基板の比較的薄い層に位置するとよい。比較的薄い層は、約１から約１０ミクロンの範囲の厚さを有するとよい。比較的小さな細孔を有する側は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）または第二の流体流チャネル（４２０、４３０）の内部に面して配置し、比較的高いせん断力を利用して比較的小さな多相混合物の泡またはミクロスフェアが形成されると除去するとよい。

【００８２】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および熱交換チャネル（２９０、３７０、３８０、５９０）は、関連するヘッダ、フッタ、マニホルド等とともに、本発明のプロセスの動作を可能にするのに十分な強度、寸法安定性、耐食性および伝熱特性を提供する任意の材料で作ってもよい。これらの材料は、鋼（例えばステンレス鋼、炭素鋼および類似物）、モネル、インコネル、アルミニウム、チタン、ニッケル、白金、ロジウム、銅、クロム、真鍮、前述の金属の任意のものの合金、重合体（例えば熱硬化性樹脂）、セラミックス、ガラス、一つ以上の重合体（例えば熱硬化性樹脂）とガラス繊維を含むコンポジット、石英、ケイ素、またはそれらの二つ以上の組み合わせを含む。

【００８３】

第一の流体流は、気体または液体を含んでもよい。第二の流体流は、気体またはマイクロボディ形成材料を含んでもよい。第三の流体流は、気体を含んでもよい。

【００８４】

気体は、任意の気体を含んでもよい。一実施態様では、気体は、空気、酸素、窒素、二酸化炭素、水蒸気、アンモニア、オゾン、塩素ガス、水素および類似物の一種類以上を含んでもよい。気体は、一つ以上の気体炭化水素、例えば、１から約５個の炭素原子を含む炭化水素を含んでもよい。これらは、飽和および不飽和炭化水素を含む。炭化水素は、メタン、エタン、エチレン、プロパン、イソプロパン、プロピレン、ブタン類、ブチレン類、ペンタン類、シクロペンタン、ペンチレン類、シクロペンチレンおよび類似物を含む。

【００８５】

液体は、任意の液体を含んでもよい。液体は、水、有機液体またはそれらの組み合わせを含んでもよい。液体は、一つ以上の液体炭化水素を含んでもよい。これらは、１個から約２４個の炭素原子、一実施態様では約５個から約２４個の炭素原子、一実施態様では約６個から約１８個の炭素原子、一実施態様では約６個から約１２個の炭素原子を含む炭化水素化合物を含む。用語「炭化水素」は、炭化水素または主に炭化水素の性格を有する化合物を示す。これらの炭化水素化合物は、以下のものを含む。

（１）純炭化水素化合物、すなわち、脂肪族化合物（例えばアルカンまたはアルキレン）、脂環式化合物（例えばシクロアルカン、シクロアルキレン）、芳香族化合物、脂肪族および脂環式置換芳香族化合物、芳香族置換脂肪族化合物および芳香族置換脂環式化合物および類似物。例は、ヘキサン、１－ヘキセン、ドデカン、シクロヘキセン、シクロヘキサン、エチルシクロヘキサン、ベンゼン、トルエン、キシレン類、エチルベンゼン、スチレン等を含む。

（２）置換炭化水素化合物、すなわち、化合物の主に炭化水素の性格を変えない非炭化水素置換基を含む炭化水素化合物。非炭化水素置換基の例は、ヒドロキシ、アシル、ニトロ、ハロ等を含む。

（３）ヘテロ置換炭化水素化合物、すなわち性格としては主に炭化水素であるが、通常は炭素原子で構成される分子鎖または環の中に炭素以外の原子を含む炭化水素化合物。例えば、ヘテロ原子は、窒素、酸素および硫黄を含む。

【００８６】

液体は、天然オイル、合成オイルまたはそれらの混合物を含んでもよい。天然オイルは、動物オイルおよび植物オイル（例えばヒマシ油、ラード油）、ならびに液体石油系オイ

ル分およびパラフィン系、ナフテン系または混合パラフィン系－ナフテン系型の溶媒処理または酸処理鉱物オイルなどの鉱物オイルを含む。天然オイルは、石炭または頁岩から誘導されるオイルを含む。オイルは、トリグリセリドの仲間からのケン化可能なオイル、例えばダイズ油、ゴマ種子油、綿実油、サフラワー油および類似物であってよい。オイルは、シリコーンオイル（例えばシクロメチコーン、シリコンメチコーン類等）であってもよい。オイルは、ワセリン、スクアラン、スクアレンまたは一つ以上のジアルキルシクロヘキサン類、またはそれらの二つ以上の混合物などの脂肪族またはナフテン系炭化水素であってもよい。合成オイルは、重合および高分子間反応したオレフィン（例えばポリブチレン類、ポリプロピレン類、プロピレンイソブチレン共重合体等）、ポリ（１－ヘキセン類）、ポリ（１－オクテン類）、ポリ（１－デセン類）等およびそれの混合物などの炭化水素オイル、アルキルベンゼン類（例えばドデシルベンゼン類、テトラデシルベンゼン類、ジノニルベンゼン類、ジ－（２－エチルヘキシル）ベンゼン類等）、ポリフェニル類（例えばビフェニル類、テルフェニル類、アルキル化ポリフェニル類等）、アルキル化ジフェニルエーテル類およびアルキル化ジフェニルスルフィド類およびそれらの誘導体、類縁体および同族体ならびに類似物を含む。末端ヒドロキシル基がエステル化、エーテル化等によって修飾されたアルキレンオキシド重合体類およびそれらの共重合体および誘導体は、用いることができる合成オイルである。合成オイルは、ポリ－アルファ－オレフィンまたはフィッシャー－トロプシュ合成炭化水素を含んでもよい。

【００８７】

液体は、通常は液体の炭化水素燃料、例えば、ＡＳＴＭ規格Ｄ４３９で定められる自動車ガソリンなどの留出燃料、またはＡＳＴＭ規格Ｄ３９６で定められるディーゼル燃料または重油を含んでもよい。

【００８８】

液体は、脂肪族アルコール、脂肪酸エステルまたはそれらの混合物を含んでもよい。脂肪族アルコールは、ゲルベ（Ｇｕｅｒｂｅｔ）アルコールであってもよい。脂肪族アルコールは、約６個から約２２個の炭素原子、一実施態様では約６個から約１８個の炭素原子、一実施態様では約８個から約１２個の炭素原子を含むとよい。脂肪酸エステルは、約６個から約２２個の炭素原子の直鎖脂肪酸と約６個から約２２個の炭素原子の直鎖または分岐脂肪族アルコールとのエステル、約６個から約１３個の炭素原子の分岐カルボン酸と約６個から約２２個の炭素原子の直鎖または分岐脂肪族アルコールとのエステル、またはそれらの混合物であってもよい。例は、ミリスチン酸ミリスチル、パルミチン酸ミリスチル、ステアリン酸ミリスチル、イソステアリン酸ミリスチル、オレイン酸ミリスチル、ベヘン酸ミリスチル、エルシン酸ミリスチル、ミリスチン酸セチル、パルミチン酸セチル、ステアリン酸セチル、イソステアリン酸セチル、オレイン酸セチル、ベヘン酸セチル、エルシン酸セチル、ミリスチン酸ステアリル、パルミチン酸ステアリル、ステアリン酸ステアリル、イソステアリン酸ステアリル、オレイン酸ステアリル、ベヘン酸ステアリル、エルシン酸ステアリル、ミリスチン酸イソステアリル、パルミチン酸イソステアリル、ステアリン酸イソステアリル、イソステアリン酸イソステアリル、オレイン酸イソステアリル、ベヘン酸イソステアリル、オレイン酸イソステアリル、ミリスチン酸オレイル、パルミチン酸オレイル、ステアリン酸オレイル、イソステアリン酸オレイル、オレイン酸オレイル、ベヘン酸オレイル、エルシン酸オレイル、ミリスチン酸ベヘニル、パルミチン酸ベヘニル、ステアリン酸ベヘニル、イソステアリン酸ベヘニル、オレイン酸ベヘニル、ベヘン酸ベヘニル、エルシン酸ベヘニル、ミリスチン酸エルシル、パルミチン酸エルシル、ステアリン酸エルシル、イソステアリン酸エルシル、オレイン酸エルシル、ベヘン酸エルシルおよびエルシン酸エルシルを含む。脂肪酸エステルは、約１８個から約３８個の炭素原子のアルキルヒドロキシカルボン酸と、約６個から約２２個の炭素原子の直鎖または分枝脂肪族アルコールとのエステル（例えばりんご酸ジオクチル）、約６個から約２２個の炭素原子の直鎖または分枝脂肪酸と、多価アルコール（例えばプロピレングリコール、二量体ジオールまたは三量体トリオール）および／またはゲルベアルコールとのエステル、約６個から約１８個の炭素原子の一種類以上の脂肪酸から作られるトリグリセリド、約６個から

約１８個の炭素原子の一種類以上の脂肪酸から作られるモノ、ジおよび／またはトリグリセリドの混合物、約６個から約２２個の炭素原子の一種類以上の脂肪族アルコールおよび／またはゲルベアルコールと一種類以上の芳香族カルボン酸とのエステル（例えば安息香酸）、２個から約１２個の炭素原子の一種類以上のジカルボン酸と１個から約２２個の炭素原子を含む一種類以上の直鎖または分岐アルコール、２個から約１０個の炭素原子および２個から約６個のヒドロキシル基を含む一種類以上のポリオール、またはそのようなアルコールとポリオールとの混合物とのエステル、２個から約１２個の炭素原子の一種類以上のジカルボン酸（例えばフタル酸）と１個から２２個の炭素原子の一種類以上のアルコール（例えばブチルアルコール、ヘキシルアルコール）とのエステル、安息香酸と約６個から約２２個の炭素原子の直鎖および／または分岐アルコールとのエステル、またはそれらの二種類以上の混合物を含んでもよい。

【００８９】

液体は、約６個から約２２個の炭素原子の一種類以上の分岐第一アルコール、約６個から約２２個の炭素原子の一種類以上の直鎖および／または分岐脂肪族アルコール炭酸エステル、約６個から約２２個の炭素原子の一種類以上の脂肪族アルコールから作られる一種類以上のゲルベ炭酸エステル、各アルキル基が１個から約１２個の炭素原子を含む一種類以上のジアルキル（例えばジエチルヘキシル）ナフタレート、アルキル基あたり約６個から約２２個の炭素原子を含む一種類以上の直鎖または分岐、対称または非対称ジアルキルエーテル、約６個から約２２個の炭素原子のエポキシ化された脂肪酸エステルと、２個から１０個の炭素原子および２個から６個のヒドロキシル基を含むポリオールとの一種類以上の開環生成物、またはそれらの二種類以上の混合物を含んでもよい。

【００９０】

水は、任意の簡便な供給源から採取してもよい。水は、浸透法または蒸留法を用いて脱イオンまたは精製してもよい。

【００９１】

マイクロボディ形成材料は、任意のマイクロボディ形成材料を含んでもよい。マイクロボディ形成材料は、液体または固体メルトの形であってもよい。マイクロボディ形成材料は、ガラス、例えば、ガラスマイクロボディ（例えばマイクロスフェア）形成材料、重合体、例えば、重合体マイクロボディ（例えば重合体マイクロスフェア）形成材料を含んでもよい。重合体マイクロボディ形成材料は、一種類以上のアクリル樹脂、シリコン樹脂、ウレタン樹脂、酢酸ビニル樹脂、テフロン（登録商標）樹脂、ポリアミド樹脂、塩化ビニル樹脂、スチレン系樹脂、フェノール樹脂、エポキシ樹脂、スチレン－ブタジエン－スチレンブロック共重合体樹脂、スチレン－エチレン－ブチレン－スチレンブロック共重合体樹脂、スチレン－イソプレン－スチレンブロック共重合体樹脂、ｎ－ブチルゴム、クロロプレンゴム、天然ゴムまたはそれらの二種類以上の組み合わせを含んでもよい。一実施態様では、重合体マイクロボディ形成材料は、１個から約１４個の炭素原子のアルコールの（メタ）アクリル酸エステルを含んでもよい。一実施態様では、重合体マイクロボディ形成材料は、少なくとも一種類の（メタ）アクリル酸アルキルを含んでもよい。

【００９２】

本発明の一つ以上の実施態様では、乳化剤および／または界面活性剤は必要ないが、本発明のプロセスによって調製される多相混合物を形成する際に一つ以上の乳化剤および／または界面活性剤を用いてもよい。乳化剤および／または界面活性剤は、液体と予め混合してもよい。乳化剤および／または界面活性剤は、グリフィン（Ｇｒｉｆｆｉｎ）のシステムで０から約１８、一実施態様では約０．０１から約１８の範囲の親水性親油性バランス（ＨＬＢ）を有するイオン性または非イオン性化合物を含んでもよい。イオン化合物は、カチオン性または両性化合物のことがある。例は、「マッカチオンズ界面活性剤および洗剤（ＭｃＣｕｔｃｈｅｏｎｓ Ｓｕｒｆａｃｔａｎｔｓ ａｎｄ Ｄｅｔｅｒｇｅｎｔｓ）」、１９９８年版、北米版および国際版に開示されているものを含む。北米版の１～２３５頁および国際版の１～１９９頁は、そのような乳化剤の開示に関する部分が参照によって本明細書に組み込まれる。用いることができる乳化剤および／または界面活性剤は

、アルキレンオキシド繰り返し単位、カルボキシル化アルコールエトキシレート類、エトキシ化アルコール類、エトキシ化アルキルフェノール類、エトキシ化アミン類およびアミド類、エトキシ化脂肪酸、エトキシ化脂肪酸エステルおよびオイル、脂肪酸エステル、脂肪酸アミド、グリセロールエステル、グリコールエステル、ソルビタンエステル、イミダゾリン誘導体、レシチンおよび誘導体、リグニンおよび誘導体、モノグリセリドおよび誘導体、オレフィンスルホン酸エステル、リン酸エステルおよび誘導体、プロポキシル化およびエトキシル化脂肪酸またはアルコール類またはアルキルフェノール類、ソルビタン誘導体、ショ糖エステルおよび誘導体、硫酸エステルまたはアルコール類またはエトキシル化アルコール類または脂肪酸エステル類、ドデシルベンゼン類およびトリデシルベンゼン類または縮合ナフタレンまたは石油のスルホン酸エステル、スルホコハク酸エステルおよび誘導体、トリデシルベンゼンおよびドデシルベンゼンスルホン酸を含む。乳化剤および／または界面活性剤は、一種類以上のポリアルキレングリコール類、グリセロールまたはソルビタンと、約１２個から約２２個の炭素原子を含む脂肪酸との一種類以上の部分エステル、またはそれらの混合物を含んでもよい。乳化剤および／または界面活性剤は、レシチンなどの薬学上許容される材料を含んでもよい。本発明のプロセスによって作られる多相混合物の中のこれらの乳化剤および／または界面活性剤の濃度は、多相混合物の最大約２０重量％、一実施態様では約０．０１から約５重量％の範囲、一実施態様では約０．０１から約２重量％の範囲にあるとよい。一実施態様では、この濃度は、最大約２重量％、一実施態様では最大約１重量％、一実施態様では最大約０．５重量％であるとよい。

【００９３】

一実施態様では、第一の流体流は液体流を含み、第二の流体流は空気を含む。

【００９４】

一実施態様では、第一の流体流は液体廃棄流を含み、第二の流体流は空気を含む。

【００９５】

一実施態様では、第一の流体流は有害液体廃棄流を含み、第二の流体流は空気を含む。

【００９６】

一実施態様では、第一の流体流はサラダドレッシングまたはマスタードを含み、第二の流体流は窒素を含む。

【００９７】

一実施態様では、第一の流体流は液体飲料またはビールを含み、第二の流体流は二酸化炭素を含む。

【００９８】

一実施態様では、第一の流体流は紙の製造に用いられる漂白パルプを含み、第二の流体流は塩素を含む。

【００９９】

一実施態様では、第一の流体流は水の中の石炭の分散を含み、第二の流体流は空気を含む。

【０１００】

一実施態様では、第一の流体流は随伴水を含むモーター油を含み、第二の流体流は窒素を含む。

【０１０１】

一実施態様では、第一の流体流は培養反応用の細胞を含み、第二の流体流は酸素または空気を含む。

【０１０２】

一実施態様では、第一の流体流は液体反応媒質を含み、第二の流体流は空気または酸素を含む。

【０１０３】

一実施態様では、第一の流体流は水素化反応を実行するための反応媒質を含み、第二の流体流は水素を含む。

【０１０４】

一実施態様では、第一の流体流はオイルと水との混合物を含み、第二の流体流は空気または天然ガスを含む。

【０１０５】

一実施態様では、第一の流体流は紙の製造に用いられる漂白パルプを含み、第二の流体流は酸素を含む。

【０１０６】

一実施態様では、第一の流体流は食用油、ワインまたはジュースを含み、第二の流体流は窒素を含む。

【０１０７】

一実施態様では、第一の流体流は魚の養殖に用いられる水を含み、第二の流体流は酸素を含む。

【０１０８】

一実施態様では、第一の流体流は水を含み、第二の流体流はオゾンを含む。

【０１０９】

一実施態様では、第一の流体流は廃液流またはプロセス流を含み、第二の流体流は二酸化炭素またはアンモニアを含む。

【０１１０】

一実施態様では、第一の流体流は空気を含み、第二の流体流は水蒸気を含む。

【０１１１】

一実施態様では、第一の流体流は揮発性有機化合物を含む廃液流またはプロセス流を含み、第二の流体流は空気を含む。

【０１１２】

一実施態様では、第一の流体流は気体または液体を含み、第二の流体流はマイクロボディ形成材料を含む。

【０１１３】

一実施態様では、第一の流体流は水系組成物を含み、第二の流体流は水素および／または酸素を含む。これは、過酸化水素生成のための直接組み合わせのために用いてもよい。

【０１１４】

一実施態様では、第一の流体流は２‐アルキルアントラキノンを含み、第二の流は水素を含む。これは、過酸化水素の生成に用いてもよい。

【０１１５】

第一の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、約０．１から約８０重量％、一実施態様では約１から約５０重量％、一実施態様では約１から約２０重量％の範囲の濃度で存在するとよい。第二の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、約１から約９５重量％、一実施態様では約１０から約５０重量％、一実施態様では約１０から約２５重量％の範囲の濃度で存在するとよい。第三の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、最大約０．０１％から約５０重量％、一実施態様では約１から約１５重量％、一実施態様では約０．１から約１重量％の範囲の濃度で存在するとよい。

【０１１６】

一実施態様では、第二の流体は第一の流体の中に溶解してもよい。これは、プロセスマイクロチャネルの中で起こってもよく、あるいは多相混合物がプロセスマイクロチャネルから出た後で起こってもよい。一実施態様では、第二の流体は、第一の流体と混合された後、最大約１０時間後の期間内に、一実施態様では最大約１時間の期間内に第一の流体の中に溶解するとよい。

【０１１７】

本発明の多相混合物は、一種類以上の固体粒子を含んでもよい。これらは、第一、第二および／または第三の液体と予め混合してもよい。固体粒子は、有機物、無機物またはそれらの組み合わせであってもよい。固体粒子は、触媒（例えば、CeO_2／$BaAl_{12}O_{19}$、Pt／Al_2O_3等などの燃焼触媒、重合触媒および類似物）、顔料（例えば、

TiO_2、カーボンブラック、酸化鉄等）、充填材（例えば、雲母、シリカ、滑石、硫酸バリウム、ポリエチレン類、ポリテトラフルオロエチレン、ナイロン粉、メタクリル酸メチル粉末）等を含んでもよい。固体粒子は、ナノサイズの粒子を含んでもよい。固体粒子は、約０．００１から約１０ミクロン、一実施態様では約０．０１から約１ミクロンの範囲の平均粒子直径を有するとよい。多相混合物の中の固体粒子の濃度は、多相混合物の重量を基準として最大約７０重量％、一実施態様では約０．１から約３０重量％の範囲にあるとよい。

【０１１８】

一実施態様では、本発明のプロセスによって作られる多相混合物は、連続相の中に分散した不連続相を含む。不連続相は、最大約２００ミクロン、一実施態様では約０．０１から約２００ミクロン、一実施態様では約０．０１から約１００ミクロン、一実施態様では約０．０１から約５０ミクロン、一実施態様では約０．０１から約２５ミクロン、一実施態様では約０．０１から約１０ミクロン、一実施態様では約０．０１から約５ミクロン、一実施態様では約０．０１から約２ミクロン、一実施態様では約０．０１から約１ミクロン、一実施態様では約０．０１から約０．５ミクロン、一実施態様では約０．０１から約０．２ミクロン、一実施態様では約０．０１から約０．１ミクロン、一実施態様では約０．０１から約０．０８ミクロン、一実施態様では約０．０１から約０．０５ミクロン、一実施態様では約０．０１から約０．０３ミクロンの範囲の体積基準平均寸法（例えば直径、高さ、幅、長さ）を有する泡またはマイクロボディを含むとよい。本発明のプロセスの一利点は、少なくとも一実施態様で、泡またはマイクロボディが比較的狭い平均直径（または高さ、幅または長さ）の分布を有することを特徴とする点である。

【０１１９】

「相対スパン」は、多くの場合「スパン」と呼ばれる。相対スパンは、体積分布から計算される無次元パラメータである。体積メジアン泡またはマイクロボディサイズ（ＶＭＤ）の場合と同じく、Ｄ［ｖ，０．１］およびＤ［ｖ，０．９］は、分散した泡またはマイクロボディの体積のそれぞれ１０％および９０％がそれより小さな直径の泡またはマイクロボディの中にある点を表す直径（または高さ、幅または長さ）である。スパンは、Ｄ［ｖ，０．９］からＤ［ｖ，０．１］を引いた後、ＶＭＤ（Ｄ［ｖ，０．５］）で除した商と定義してもよい。一実施態様では、本発明のプロセスによって作られる多相混合物の中の泡またはマイクロボディのスパンは、約１．３から約５、一実施態様では約１．８から約２．５の範囲にあるとよい。一実施態様では、本発明のプロセスは、単一のプロセスマイクロチャネルの中で実行され、スパンは約１．３から約２．５の範囲にあるとよい。一実施態様では、本発明のプロセスは複数のプロセスマイクロチャネルを使用するスケールアップされた多相混合プロセスの中で実行され、スパンは約１．３から約５の範囲にあるとよい。

【０１２０】

一実施態様では、本発明のプロセスによって作られる多相混合物の中の泡またはマイクロボディの体積基準の平均直径（または高さ、幅または長さ）は、約０．１から約１００ミクロンの範囲にあるとよく、スパンは、約１から約２５の範囲にあるとよい。一実施態様では、体積基準の平均直径（または高さ、幅または長さ）は、約１から約１０ミクロンの範囲にあるとよく、スパンは、約１．８から約２．５の範囲にあるとよい。

【０１２１】

一実施態様では、気泡が形成され、気泡は最大約２５ミクロンの範囲の体積基準の平均直径と、約１．９から約２．５の範囲のスパンとを有する。

【０１２２】

一実施態様では、マイクロボディが形成され、マイクロボディは最大約５ミクロンの範囲の体積基準の平均直径（または高さ、幅または長さ）と、約１．８から約２．５の範囲のスパンとを有する。

【０１２３】

本発明のプロセスによって形成されるマイクロボディは、多数の用途を有する。これら

は、密度を減らすキャストファイリング用のガラスミクロスフェア、流動床反応装置の中の選択化学種固定化用のガラスミクロスフェア、および類似物を含む。その他の例は、免疫試験および処理のために用いられるミクロスフェア重合体、ゲルまたはコロイド懸濁系発生を含む。マイクロボディ（例えばマイクロスフェア）は、第二のプロセスで処理して凝集体、触媒流動床または充填床、ドラッグデリバリシステム（例えば蛋白質酵素反応）、および最新の分離および流動床用途（例えば、磁気振動によって有利に分離または励起することができる被覆磁気担体）を含むいくつかの用途のためのカプセル化された固体を形成してもよい。

【０１２４】

少なくとも一つの実施態様では、本発明のプロセスの一利点は、プロセスが実験室用であろうと、パイロットプラント規模用であろうと、または実生産規模用であろうと、プロセスマイクロチャネル、第二の流体流チャネル、オプションとして、第三の流体流チャネル、および／または熱交換チャネルの間のギャップ距離が同じであってよいことである。その結果、マイクロチャネルミキサが実験室またはパイロットプラント規模で、または実生産規模のプラントユニットとして構築されても、本発明のプロセスで用いられるマイクロチャネルミキサによって製造される多相混合物の粒子サイズ分布は、実質的に同じにすることができる。

【０１２５】

液体制御素子（離散形）に対する速度ｕの方向のせん断力は、式　$F_X = mu * du / dy$によって計算することができる。ここで、ｍｕは粘度、ｄｕ／ｄｙは開口区間に垂直な液体の流れの速度勾配である。しかし、液体の位置（制御素子によって表される）の場合と同じく、速度は、一般に、三つの成分を有し、せん断力も三つの成分を有する。表面近くおよび表面上のチャネルの流れの場合、一次元の仮定を置くことができ、F_Xによって素子表面での液体の正味のせん断力を近似できる。ＦｌｕｅｎｔまたはＦＥＭＬＡＢなどの市販のソフトウェアパッケージを含む計算機流体力学を用いて、必要な輸送方程式を解き、その結果、表面せん断力を計算することができる。チャネル長さ方向の流れの方向に平行な表面せん断力を計算することができる。平行なチャネルの間のせん断力も、計算することができ、流れ分布効果を取り込んでそれぞれの平行なチャネル中への物質流束を詳細なチャネルおよびマニホルドの幾何形状の関数として決定する。例えば、「流体力学の基礎（Ｆｕｎｄａｍｅｎｔａｌｓ　ｏｆ　Ｆｌｕｉｄ　Ｍｅｃｈａｎｉｃｓ）」、第３版、ビー・アール・マンソン（Ｂ．Ｒ．Ｍｕｎｓｏｎ）、ディー・エフ・ヤング（Ｄ．Ｆ．Ｙｏｕｎｇ）およびティー・エイチ・オキイシ（Ｔ．Ｈ．Ｏｋｉｉｓｈｉ）、ジョン・ワイリー・アンド・サンズ社（Ｊｏｈｎ　Ｗｉｌｅｙ　＆　Ｓｏｎｓ，Ｉｎｃ）、ヴァインハイム（Ｗｅｉｎｈｅｉｍ）、１９９８年、にさらに詳しい計算方法がある。

【０１２６】

一実施態様では、単一のプロセスマイクロチャネルを使用するプロセスのせん断力偏差因子（ＳＦＤＦ）は、複数のプロセスマイクロチャネルを含むスケールアップされたプロセスのＳＦＤＦの約５０％の範囲内にすることができる。ＳＦＤＦは、式

$SFDF = (F_{max} - F_{min}) / (2F_{mean})$

を用いて計算することができる。ここで、F_{max}は、特定の液体に対するプロセスマイクロチャネルの中の最大せん断力、F_{min}は同じ液体に対するプロセスマイクロチャネルの中の最小せん断力、F_{mean}はプロセスマイクロチャネル内の開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）の表面における同じ液体に対する算術平均せん断力である。本発明のプロセスによって動作する単一のプロセスマイクロチャネル内では、ＳＦＤＦは約２より小さく、一実施態様では約１より小さく、一実施態様では約０．５より小さく、一実施態様では約０．２より小さいとよい。

【０１２７】

一実施態様では、本発明のプロセスは、複数のプロセスマイクロチャネルを使用しながら、比較的一様なせん断力を提供することができる。複数のプロセスマイクロチャネルの

間のせん断力一様性を測定するためには、各チャネルの平均せん断力を計算し、比較する。F_{max}は平均チャネルせん断力の最大値であり、F_{min}は平均せん断力の最小値である。F_{mean}は、すべてのチャネルの平均せん断力の平均値である。ＳＦＤＦは、これらの値から計算することができる。複数のプロセスマイクロチャネルの間で、本発明のプロセスの少なくとも一つの実施態様では、ＳＦＤＦは約２より小さく、一実施態様では約１より小さく、一実施態様では約０．５より小さく、一実施態様では約０．２より小さくすることができる。

【０１２８】

熱交換流体は、任意の流体を含んでもよい。これらは、空気、蒸気、液体の水、気体窒素、液体窒素、不活性気体を含むその他の気体、一酸化炭素、二酸化炭素、融解塩、鉱油などのオイル、気体炭化水素、液化炭化水素およびダウ・ユニオンカーバイド（Ｄｏｗ－Ｕｎｉｏｎ　Ｃａｒｂｉｄｅ）から入手できるダウサームＡ（Ｄｏｗｔｈｅｒｍ　Ａ）およびサーミノール（Ｔｈｅｒｍｉｎｏｌ）などの熱交換流体を含む。

【０１２９】

熱交換流体は、多相混合物を作るのに用いられる第一、第二および／または第三の流体を含んでもよい。これによって、プロセス予備加熱または予備冷却を提供し、プロセスの総合的な熱効率を高くすることができる。

【０１３０】

一実施態様では、熱交換チャネルは、吸熱または発熱プロセスが実行されるプロセスチャネルを含む。これらの熱交換プロセスチャネルは、マイクロチャネルであってもよい。熱交換チャネル中で実行することができる吸熱プロセスの例は、水蒸気改質および脱水素反応を含む。一実施態様では、吸熱源の増強を提供する同時吸熱反応の組み込みによって、通常、対流冷却熱流束よりほぼ一桁大きな熱流束が可能になる。熱交換チャネルの中で実行することができる発熱プロセスの例は、水性ガスシフト反応、メタノール合成反応およびアンモニア合成反応を含む。

【０１３１】

一実施態様では、熱交換流体は熱交換チャネルの中で相変化を行う。この相変化によって、対流加熱または冷却によって供給される熱の他に、プロセスマイクロチャネルまたは液体チャネルからの追加の加熱または除熱が提供される。蒸発する液体熱交換流体の場合、プロセスマイクロチャネルから移動するこの追加の熱は、その熱交換流体が必要とする蒸発潜熱から生じさせることが可能である。そのような相変化の例は、核沸騰するオイルまたは水である。一実施態様では、相変化流体の沸騰の蒸気質量分率品質は、最大約１００％、一実施態様では最大約７５％、一実施態様では最大約５０％にすることができる。

【０１３２】

相変化または化学反応による伝熱促進の使用は、多相混合物発生がプロセスチャネルの中の化学反応と協同して起ると、さらに有利なものにすることができる。一実施態様では、例えば、多相混合物は、重合反応用の反応性モノマーまたはその他の追加の熱交換を必要とするものであってもよい。

【０１３３】

マイクロチャネルミキサの中の対流加熱または冷却の熱流束は、マイクロチャネルミキサの中のプロセスマイクロチャネルの表面積の平方センチメートルあたり約０．０１から約１２５ワット（Ｗ／ｃｍ^2）、一実施態様では約０．１から約５０Ｗ／ｃｍ^2、一実施態様では約１から約２５ｃｍ^2、一実施態様では約１から約１０Ｗ／ｃｍ^{2}の範囲にあるとよい。加熱または冷却用の相の熱流束は、約１から約２５０Ｗ／ｃｍ^{2}の範囲、一実施態様では約１から約１００Ｗ／ｃｍ^2、一実施態様では約１から約５０Ｗ／ｃｍ^2、一実施態様では約１から約２５Ｗ／ｃｍ^2、一実施態様では約１から約１０Ｗ／ｃｍ^{2}であるとよい。

【０１３４】

熱交換チャネルを用いて、本発明のプロセスを用いる多相混合物の作製時に無菌状態を提供することができる。バッチミキサと異なって、本発明のプロセスは環境に対して閉じ

たものにすることができ、環境から切り離すために不活性気体で覆う必要がない。熱交換チャネルは、プロセスマイクロチャネルまたは液体チャネルに隣接するので、比較的短い熱輸送および拡散距離を提供して、マイクロチャネルミキサの中の液体を迅速に加熱および冷却して温度勾配を小さくすることができる。その結果、本発明のプロセスを用いると、長時間の加熱に適さないか、または大きな温度勾配の下では劣化する可能性のある多相混合物を調製することができる。一実施態様では、プロセスマイクロチャネルの中の同じ軸位置のプロセスマイクロチャネル壁とプロセスマイクロチャネルの内のバルクの流れとの間の温度勾配を、約５℃より小さく、一実施態様では約２℃より小さく、一実施態様では約１℃より小さくすることができる。

【０１３５】

制御された加熱および／または冷却を有するプロセスマイクロチャネルおよび／または第二または第三の流体流チャネルに密着する熱交換チャネルは、複数のプロセスマイクロチャネルの間に一様な温度プロフィルを提供することができる。これによって、混合タンクなどの従来の処理設備を用いて得ることができるよりも速い速度での一様な加熱および冷却が可能になる。多重チャネルマイクロチャネルミキサの中で、プロセス流れの長さに沿って少なくともいくつかの軸位置で、プロセスマイクロチャネルの間の温度差を約５℃より小さく、一実施態様では約２℃より小さく、一実施態様では約１℃より小さくすることができる。

【０１３６】

プロセスマイクロチャネルおよび／または第二または第三の流体流液体チャネルのどちらかに隣接する熱交換チャネルは、そのようなチャネルの長さに沿った温度区域を使用することができる。一実施態様では、プロセスマイクロチャネルへの入口に近い第一の区域の中の温度は、プロセスマイクロチャネルの終わりに近い第二の区域の中の第二の温度より高い温度に維持される。プロセスマイクロチャネルの中に冷却またはクエンチ区域を組み込んで多相混合物を急速に冷却し、安定化させてもよい。原料およびまたは多相混合物生成物を加熱および／または冷却するプロセスマイクロチャネルの中の混合区域の前および／または後ろの両方の区間の可能性を含めて、プロセスマイクロチャネルの長さに沿って最適な熱プロフィルを可能にする熱プロフィルの多数の組み合わせが可能である。

【０１３７】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）を通る流体の流速は、約０．０１から約５０１ｐｍ、一実施態様では約０．０１から約１０１ｐｍの範囲にあるとよい。プロセスマイクロチャネルを通って流れる流体の速度は、約０．１から約１００ｍ／ｓ、一実施態様では約０．１から約１０ｍ／ｓの範囲にあるとよい。プロセスマイクロチャネルを通って流れる流体のレイノルズ数は、約２５から約１０，０００、一実施態様では約２５０から約５０００の範囲にあるとよい。プロセスマイクロチャネルに入る流体の温度は、約１０℃から約５５０℃、一実施態様では約２５℃から約４００℃の範囲にあるとよい。プロセスマイクロチャネル内の絶対圧力は、約１から約２０気圧、一実施態様では約１から約５気圧の範囲にあるとよい。

【０１３８】

第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）を通る第二の流体流および第三の流体流チャネル（４４０、４５０）を通る第三の流体流の流速は、約０．０１から約１０ｍｌ／ｓ、一実施態様では約０．１から約２ｍｌ／ｓの範囲にあるとよい。第二の流体流および第三の流体流の速度は、約０．１から約１００ｍ／ｓ、一実施態様では約０．１ｍ／ｓから約１０ｍ／ｓの範囲にあるとよい。第二の流体流および第三の流体流のレイノルズ数は、約５０から約５０００、一実施態様では約５０から約５００の範囲にあるとよい。第二の流体流チャネルに入る第二の流体流および第三の流体流チャネルに入る第三の流体流の温度は、約－１０℃から約６５０℃、一実施態様では約２５℃から約４５０℃の範囲にあるとよい。第二の流体流チャネルおよび第三の流体流チャネル内の絶対圧力は、約１から約２５気圧、一実施態様では約１から約５気圧の範囲にあるとよい。開口（２４４、２４４ａ、３１３、３２３、３３３、３４

３、４１６、４２６、４３６、４４６）を通って流れる流体の圧力降下は、約０．００５から約０．５気圧、一実施態様では約０．０５から約０．１気圧の範囲にあるとよい。

【０１３９】

本発明のプロセスによる気泡またはマイクロボディの形成の概略が図２１に示される。図２１を参照すると、気泡またはマイクロボディ６５０は、マイクロチャネル６５４の中の開口６５２から出現し、第一の流体流６５６の中に分散する。気泡またはマイクロボディは、開口６５２内の気体またはマイクロボディ形成材料基部６５８に付着している間、例えば、開口のサイズの約１０倍以上にサイズが成長してもよい。最終的には、気体またはマイクロボディ形成材料基部６５８の基部のせん断力によって泡またはマイクロボディは開口から分離され、泡またはマイクロボディは第一の流体流６５６の中に分散する。一実施態様では、比較的高い開口区間の圧力降下、または対応して、第二の流体流チャネルを通る高い第二の流体流の流速は、第一の流体流の中の第二の流体流の分散を実現するのに必要ないこともある。圧力降下が低いこと、または流速が低いことによって、開口区間を通って流れる第二の流体流のより慣性が低くなり、泡またはマイクロボディが開口から分離する前の泡またはマイクロボディ成長を減らすことがあるので、より小さな泡またはマイクロボディを生じさせることがある。

【０１４０】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）から出る多相混合物は、約１０℃から約６００℃、一実施態様では約２５℃から約４５０℃の範囲の温度にあるとよい。

【０１４１】

熱交換チャネル（２９０、３７０、３８０、５９０）に入る熱交換流体は、約－４０℃から約３００℃、一実施態様では約２５℃から約１００℃の範囲の温度であるとよい。伝熱チャネルから出る熱交換流体は、約－３０℃から約５５０℃、一実施態様では約３０℃から約２００℃の範囲の温度を有するとよい。熱交換流体の圧力降下は、熱交換チャネルを通って流れるとき、約０．００５から約５気圧、一実施態様では約０．０５から約１気圧の範囲にあるとよい。熱交換チャネルを通って流れる熱交換流体流のレイノルズ数は、最大約１０，０００、一実施態様では最大約５０００、一実施態様では約１００から約５０００の範囲、一実施態様では約５００から約２０００の範囲にあるとよい。

【０１４２】

流体流は、マイクロチャネルミキサの中でまたはマイクロチャネルミキサに入る前にマイクロチャネルヒータまたはヒートパイプを含む任意の種類の伝熱デバイスを用いて予熱してもよい。一実施態様では、第一の流体流は、混合区域の上流のプロセスマイクロチャネルの非開口領域の中で予熱してもよい。マイクロチャネルミキサの中で作り出される多相混合物は、マイクロチャネルミキサの中で、またはマイクロチャネルミキサから出た後で、マイクロチャネル熱交換器を含む任意の種類の熱交換デバイスを用いて冷却してもよい。一実施態様では、多相混合物を安定化するために、または安定なままにしておくために、多相混合物をクエンチしてもよい。一実施態様では、多相混合物は、混合区域の下流のプロセスマイクロチャネルの非開口領域の中でクエンチしてもよい。一実施態様では、多相混合物は、室温に冷却してもよく、または約０．０１から約１００秒、一実施態様では約０．０１から約１０秒の範囲の時間内にクエンチしてもよい。

【０１４３】

本発明のプロセスを用いて、毎分少なくとも約０．０１リットル、一実施態様では毎分少なくとも約１リットルの速度で多相混合物を作ることができる。一実施態様では、本プロセスを用いて毎秒少なくとも約１０リットルの速度で多相混合物を作ることができる。

【０１４４】

一実施態様では、プロセスマイクロチャネルの中で、光学的または熱光学的特性を調節してもよい。これらの光学的または熱光学的特性を測定および／または調節するための技法の例は、平均液滴サイズおよびスパンを含む多相混合物品質管理および分析のためのインラインＬＳＤ（レーザ散乱回折）検出、製品粘度および固体含量を評価するための粘度

計、気泡またはマイクロスフェアサイズ測定のための写真を用いる光学測定、多相混合物の性質を調節することによる干渉計法を含むホログラフィー画像化および類似の方法を含む。

【実施例１】

【０１４５】

長方形の断面と、０．０４０×１．２５×３インチ（１．０２×３１．７５×７６．２ｍｍ）の内部寸法を有するアクリルのプロセスマイクロチャネルを含む多相混合装置が構築される。プロセスマイクロチャネルは、その側壁の一つの中に開口区間を有する。開口区間は、０．１ミクロンの名目開口または細孔サイズと、０．０１０×１×１．５インチ（０．２５４×２５．４×３８．１ｍｍ）の寸法とを有する。開口区間は、ステンレス鋼３１６Ｌで構築され、コネチカット州ファーミントン（Ｆａｒｍｉｎｇｔｏｎ，ＣＴ）のモット社（Ｍｏｔｔ　Ｃｏｒｐｏｒａｔｉｏｎ）によってカタログ番号１１１０－１２－１２－０１８－０１－Ａで供給される。開口区間は、開口区間を通ってプロセスマイクロチャネルの中に入る気体の流れを可能にするために、気体分配プレナムおよび配管に接続される。プロセスマイクロチャネルは、プロセスマイクロチャネルを通る液体の流れを可能にするために、配管に接続される。気体は、開口区間を通ってプロセスマイクロチャネルに流入し、プロセスマイクロチャネルを通って流れる液体と接触する。気体が開口区間の開口を通って流れるにつれ、プロセスマイクロチャネルの中で泡が形成される。プロセスは、空気を気体として、脱イオン水を液体として用いて実行される。空気の流速は毎分２から２０標準立方センチメートル（ＳＣＣＭ）との間で変化し、水の流速は毎分１０から８０ミリリットル（ｍｌ／分）との間で変化する。５から１５ミクロンの範囲にある直径を有する泡が形成される。

【実施例２】

【０１４６】

２ＳＣＣＭの気体流速と６０ｍｌ／分の液体流速とを用いて、実施例１に記載されたプロセスが実行される。

【実施例３】

【０１４７】

水素を気体として、１－ヘキセンを液体として用いて、実施例１に記載されたプロセスが実行される。

【実施例４】

【０１４８】

高速度の気体（１ＳＬＰＭより大きな流速）と液体（毎分０．１リットルより大きな流速）とが、プロセスマイクロチャネルの入口近くで混合されてから、表面構成要素領域を通って流れる。表面構成要素領域は、壁の片側の上に０．０１インチの深さと４５度の角度を有する構成要素を有する。表面構成要素内のバルク流路は、０．００６５インチである。平均直径が２５ミクロンより小さな一様な泡を有する発泡体が作り出される。流れの長さは１．５インチであり、チャネルの幅またはスパンは０．５インチである。プロセスマイクロチャネルは、室温および周囲圧力近くである。表面構成要素領域の上および全体に非常に小さな泡が観測される。

【実施例５】

【０１４９】

チャネルの中の層流から、チャネルの中の強い混合流れへの変化を誘起するマイクロチャネルの二つの側面への表面構成要素の追加を、Ｆｌｕｅｎｔ^{TM}を用いる計算機流体力学（ＣＦＤ）シミュレーションによって検討する。シミュレーションのために、流体の性質は一定と仮定し、密度５．０６７ｋｇ／ｍ^{3}、粘度３．６２ｅ$^{-5}$ｋｇ／ｍ・秒とした。境界条件として１２．１３ｍ／秒の一様な入口速度と、すべての壁で滑り流がないとした。３１５，１７４セルのグリッドサイズが用いられる。

【０１５０】

仮定された幾何構造は、４．０６ｍｍの幅、０．３１８ｍｍの高さおよび６３．５ｍｍ

の長さを有する連続チャネルの長方形の断面である。入口の０から３．５ｍｍ下流の区間と、出口の０から５．０ｍｍ上流の区間とは、混合用表面構成要素を含まない（簡単な長方形マイクロチャネル）。混合用表面構成要素（または溝）は、二つの対向する壁の中に切り込まれ、各構成要素は断面がほぼ長方形である。マイクロチャネルの中間区間（入口の３．５ｍｍから５８．５ｍｍ下流）は、混合用表面構成要素を含む。表面構成要素は、図２７および２８に示されるように、平均バルク層流の方向から６３°の角度でチャネル壁の一つに対角線状にまたがる。各表面構成要素は、深さ約０．２５ｍｍ、幅０．４８ｍｍ、長さ９ｍｍである。表面構成要素は、互いに平行に配置され、構成要素の間の間隔は０．４８ｍｍである。反対側の壁の上の表面構成要素は、第一の壁の上の表面構成要素と同じであり、チャネル中心線の周りに１８０°回転している（チャネル幾何構造は、入口面の中心点から出口面の中心点に延在する流れの軸の周りに対称である）。

【０１５１】

図２７は、ＣＦＤによってシミュレーションされた表面構成要素の幾何構造の平面図を示す。上部壁と下部壁との両方の混合用構成要素が重ね合わされている。図２８は、ＣＦＤによってシミュレーションされた、混合用構成要素を有するマイクロチャネルの等角投影図であり、チャネルに入る流れの方向を示す。図２９は、入口面の水平中心線（矢印の間に引かれている）に沿って開始される一般的な流れの経路線を示し、入口面から流れの軸を下に見ている。古典的な層流では、経路線は、入口面と出口面との間の直線を流れる（図２９に示される図では、古典的な層流の経路線は、矢印の間の中心線から逸脱しないと考えられる）。図３０で、入口面の水平中央線に沿って開始される流れの同じ経路線の側面図が示される（矢印は、流れの方向を示す）。図３０で、中心線からの流れ経路線の広がりと、表面構成要素の中の渦巻き運動とが、層流と比較すると改善された混合と、減少した熱および物質輸送抵抗を示す。図３１は、入口面の垂直中央線（矢印の間に引かれている）に沿って開始される流れの経路線を示し、入口面から流れの軸を下に見ている。図３１で、流れの渦巻き運動が、古典的な層流と比較すると改善された混合と、減少した熱および質量輸送抵抗を示唆する。

【０１５２】

ＣＦＤシミュレーションの結果によると、マイクロチャネルの中の層流と異なり、混合用表面構成要素は、連続チャネルの中の流れの経路線をねじれさせ、渦巻かせ、層流の場合に予想されるより速く壁に向かって押し広げる。計算された圧力降下は、５．２ｋＰａである。

【０１５３】

表面構成要素を含むマイクロチャネルに気体または第二の流体流を加えると、流れのパターンが作り出され、それによって、多相混合物は層流に近づき、泡は小さくなり、良く分散すると予測される。小さな泡とは、マイクロチャネルギャップの２５％より小さいと定義してもよい。

【０１５４】

特定の実施態様と関連させて本発明を説明してきたが、本明細書を読めば、これらの実施態様のさまざまな変更形は当業者にとって自明であると理解される。従って、本明細書に開示される本発明は、添付の請求項の範囲に属するものとしてそのような変更形を包含するものと理解される。

【図面の簡単な説明】

【０１５５】

【図１】本発明のプロセスで有用なものとすることができるマイクロチャネルの概略図である。

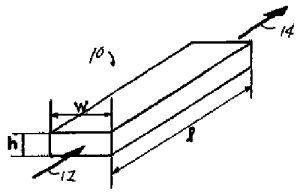
【図２】多相混合物を形成させるためにマイクロチャネルミキサが用いられる、特定の形の本発明のプロセスの例が示されるフローシートである。

【図３】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。第一の流体流がプロセスマイクロチャネルを通って流れ、隣接する第二の流体流チャネルからプロセスマイクロチャネルの中の開口区間を通ってプロセスマイクロチ

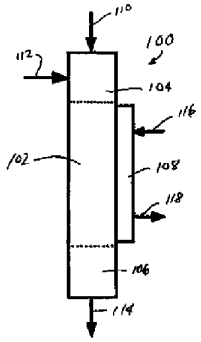
ャネルの中に流入する第二の流体流と混合される。
【図４】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図５】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図６】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図７】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図８】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図９】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図１０】二重多相混合物の概略図である。
【図１１】本発明のプロセスに従って用いることができるマイクロチャネル空気吹き込みユニットの概略図である。
【図１２】図１１に例を示した空気吹き込みユニットの中で用いることができるマイクロチャネル多相混合物形成ユニットの概略図である。
【図１３】多孔質ステンレス鋼基板の熱処理される前のＳＥＭ画像である。
【図１４】図８に示した基板の熱処理された後のＳＥＭ画像である。
【図１５】本発明のプロセスで有用な専用の多孔質基板のＳＥＭ画像である。
【図１６】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な開口シートの平面図である。
【図１７】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な開口シートまたはプレートの平面図である。
【図１８】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な、比較的厚い開口シートまたはプレートの上にある比較的薄い開口シートの例示である。
【図１９】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な、比較的厚い開口シートまたはプレートの上にある比較的薄い開口シートの例が示される。
【図２０】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間の中で用いることができる開口の代替実施態様の例が示される。開口は、部分的に開口を満たし、開口の側壁の上にあるコーティングを有する。
【図２１】本発明のプロセスの動作の間の気泡またはマイクロボディの形成を示す概略図である。
【図２２】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２３】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２４】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２５】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２６】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２７】実施例５で説明される計算機流体力学（ＣＦＤ）によってシミュレーションされた表面構成要素の幾何構造の平面図である。上部および下部壁の上の表面構成要素が見える。
【図２８】実施例５で説明されるＣＦＤによってシミュレーションされた表面構成要素を

有するマイクロチャネルの等角投影図である。
【図２９】入口面の水平中心線（矢印の間に引かれる）に沿って開始されるマイクロチャネルの中の流れの経路線の例が示される。実施例５で説明されるように、入口面から流れの軸を下に見ている。
【図３０】入口面の水平中心線に沿って開始されるマイクロチャネルの中の流れの経路線（矢印は流れの方向を示す）を示す。実施例５で説明されるように、側面から見ている。
【図３１】入口面の垂直中心線（矢印の間に引かれる）に沿って開始されるマイクロチャネルの中の流れの経路線を示す。実施例５で説明されるように、入口面から流れの軸を下に見ている。

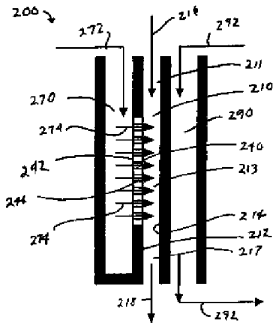
【図１】



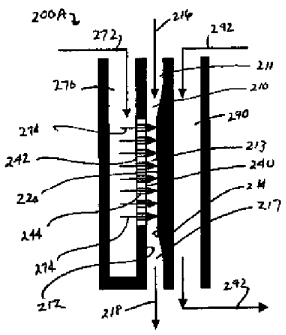
【図２】



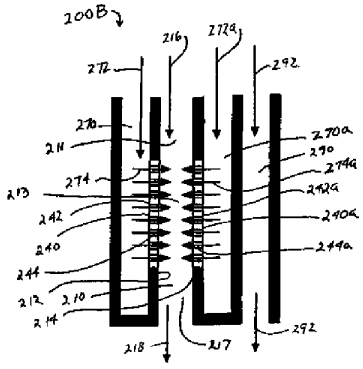
【図３】



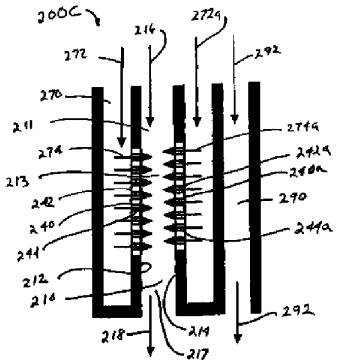
【図４】



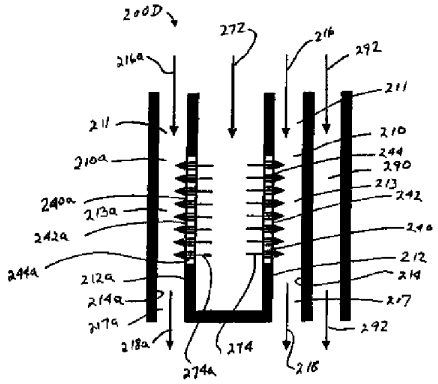
【図５】



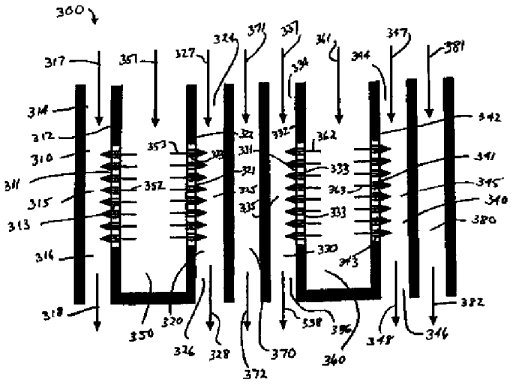
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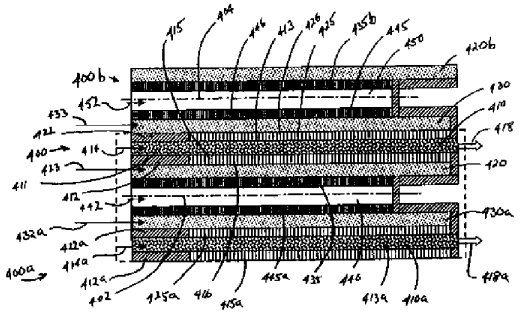
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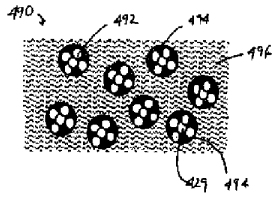
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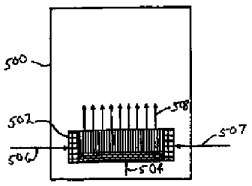
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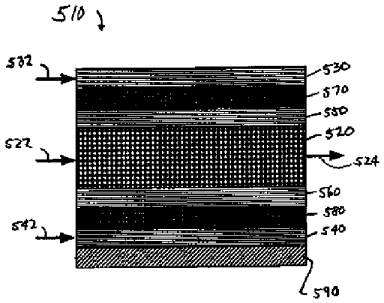
【図１０】



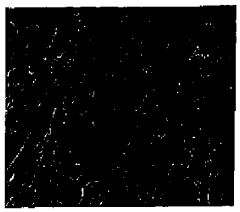
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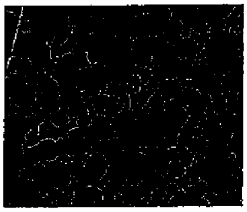
【図１２】



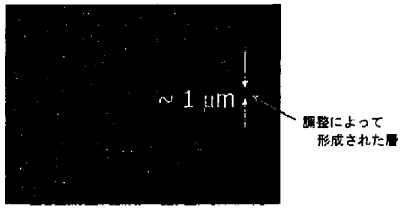
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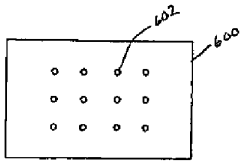
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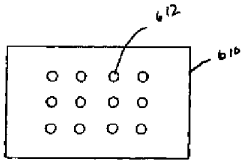
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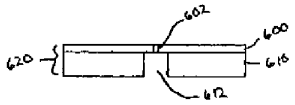
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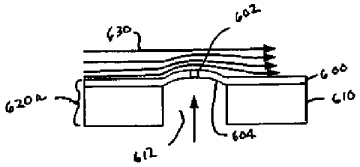
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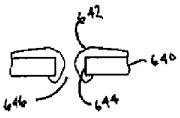
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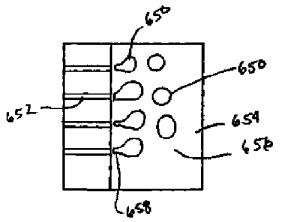
【図１９】



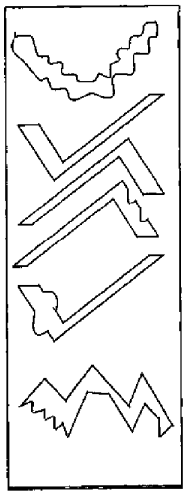
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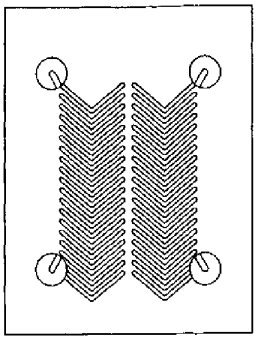
【図２１】



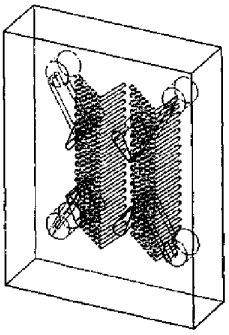
【図２２】



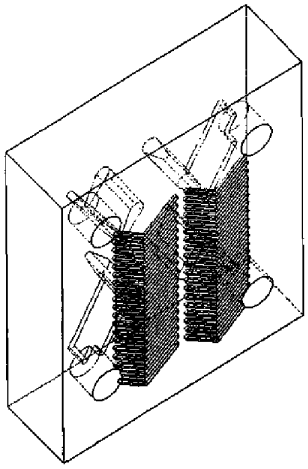
【図２３】



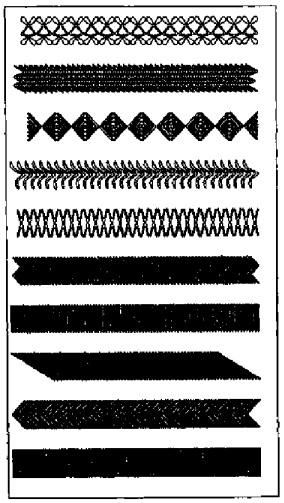
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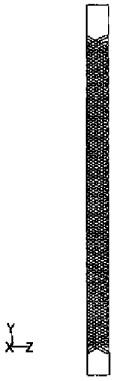
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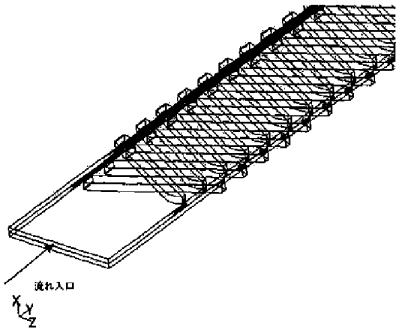
【図２６】



【図２７】



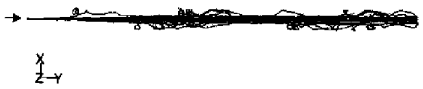
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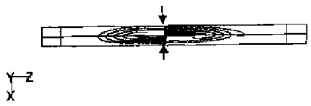
【図２９】



【図３０】



【図３１】



フロントページの続き

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B01F 15/06 Z

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合議体
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審判官 渡邊 豊英
審判官 熊倉 強

(56)参考文献 特開2003-210957 (JP, A)
特開2003-1076 (JP, A)
特表2000-509330 (JP, A)

特開平１０－１４６５２３（ＪＰ，Ａ）

(58)調査した分野(Int.Cl.，ＤＢ名)
B01F3/04

United States District Court,
E.D. Texas, Marshall Division.

RETRACTABLE TECHNOLOGIES, INC., and Thomas J. Shaw,
Plaintiffs.
v.
BECTON DICKINSON & CO,
Defendant.

Civil Action No. 2:07-CV-250 (DF)

Jan. 20, 2009.

Bradley Carroll Weber, Paul Featherstone Schuster, Locke Liddell & Sapp, George E. Bowles, Mark Richard Backofen, Michael V. Powell, Monty Lee Ross, Roy William Hardin, Locke Lorde Bissell & Liddell LLP, Dallas, TX, Deborah J. Race, Otis W. Carroll, Jr., Ireland Carroll & Kelley, Tyler, TX, G. William Lavender, Lavender Law, Texarkana, AR, for Plaintiffs.

Robert A. Atkins, Jacqueline Pilar Rubin, Paul Weiss Rifkind Wharton & Garrison, Alexandra B. McTague, Wilmer Cutler Pickering Hale & Dorr, New York, NY, Alistair Byrne Dawson, David J. Beck, Beck Redden & Secrest, Houston, TX, Heath A. Brooks, Mark L. Rienzi, Stephanie K. Wood, William G. McElwain, Los Angeles, CA, Lisa J. Pirozzolo, William F. Lee, Wilmer Cutler Pickering Hale & Dorr, Boston, MA, William David Carter, Sr., Mercy Carter Tidwell, L.L.P., Texarkana, TX, for Defendant.

Stephen David Wilson, Locke Lord Bissell & Liddell LLP, Dallas, TX.

CLAIM CONSTRUCTION ORDER

Construing Terms in U.S. Patent Nos. 5,632,733**,** 6,090,077**, and** 7,351,224

DAVID FOLSOM**, District Judge.**

Before the Court are RTI's Opening Brief on Claim Construction (Dkt. No. 111), BD's Opening Claim Construction Brief (Dkt. No. 112), RTI's Reply Brief on Claim Construction (Dkt. No. 113) and BD's Notice of Supplemental Authority (Dkt. No. 116). Also before the Court are the Local Patent Rule (LPR) 4-3 Joint Claim Construction and Prehearing Statement (Dkt. No. 110) and the LPR 4-5 Joint Claim Construction Chart (Dkt. No. 114). A claim-construction hearing, in accordance with Markman v. Westview Instruments, 52 F.3d 967 (Fed.Cir.1995) (en banc), *aff'd,* 517 U.S. 370 (1996), was held in Texarkana on December 4, 2008. *See* Dkt. No. 118 (hearing transcript). After hearing the arguments of counsel and reviewing the relevant pleadings, presentation materials, other papers, and case law, the Court finds the disputed terms of the patents-in-suit should be construed as set forth herein.

TABLE OF CONTENTS

I.	BACKGROUND	-1-
II.	LEGAL PRINCIPLES	-1-
III.	PATENTS-IN-SUIT	-2-
IV.	U.S. PATENT NO. 5,632,733	-3-

A. Overview -3-
B. Claim Construction -5-
1. "body" -5-
2. "barrel" -6-
3. "nose"/"nose portion" -9-
4. "transition zone" -10-
5. "inwardly facing surface" -11-
6. "retraction mechanism sealingly disposed in the nose" -12-
7. "retainer member" -12-
8. "bridging portion" -16-
9. "releaseably installed by sliding engagement of said retaine r member and said inwardly facing surface" -18-
10. "sliding engagement producing a holding force" -20-
11. "outwardly facing surface" -20-
V. U.S. PATENT NO. 6,090,077 -21-
A. Overview -21-
B. Claim Construction -22-
1. "body"/"barrel" -22-
2. "vent" -22-
3. "the barrel having a front end portion containing a retraction mechanism configured for operation by a plunger" -22-
4. "a front end configured to operate the retraction mechanism" -23-
VI. U.S. PATENT NO. 7,351,224 -23-
A. Overview -23-
B. Claim Construction -24-
1. "body"/"barrel"/"bridging portion"/"retainer member" -24-
2. "continuous retainer member surrounding the inner head" -25-
3. "end cap" -25-
4. "wherein the continuous retainer member is releasable from the inner head" -27-

VII. CONCLUSION -28-

I. BACKGROUND

In the present lawsuit, Retractable Technologies, Inc. and Thomas Shaw (collectively "RTI") contend certain safety syringes made by Becton, Dickinson and Co. ("BD") infringe claims of U.S. Patent Nos. 5,578,011 ("the '011 Patent), 5,632,733 ("the '733 Patent"), 6,090,077 ("the '077 Patent"), and 7,351,224 ("the '224 Patent"). Both the '011 and '733 Patents are entitled "Tamperproof retractable syringe," while the '077 Patent is entitled "Syringe plunger assembly and barrel," and the '224 Patent is entitled "Retractable syringe assembly designed for one use." All three later patents are continuations-in-part of the '011 Patent. '733 at [63]; '077 at [63]; '224 at [63]. FN1

FN1. The parties have agreed on the construction of one term in the ' 011 Patent. The parties agree that "frictionally held retraction mechanism" will be construed as "a retraction mechanism held by friction." The Court has no reason to disagree and therefore adopts the parties' construction. Because no terms from the '011 Patent are in dispute this Claim Construction Order will not address the '011 Patent further.

II. LEGAL PRINCIPLES

A determination of patent infringement involves two steps: first, the patent claims are construed, and, second, the claims are compared to the allegedly infringing device. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1455 (Fed.Cir.1998) (en banc). The legal principles of claim construction were reexamined by the Federal Circuit in Phillips v. AWH Corp., 415 F.3d 1303 (Fed.Cir .2005) (en banc). The Federal Circuit in *Phillips* expressly reaffirmed the principles of claim construction as set forth in Markman v. Westview Instruments, Inc., 52 F.3d 967 (Fed.Cir.1995) (en banc), *aff'd,* 517 U.S. 370 (1996), Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576 (Fed.Cir.1996), and Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111 (Fed.Cir.2004). Claim construction is a legal question for the courts. Markman, 52 F.3d at 979.

The Court, in accordance with the doctrines of claim construction that it has outlined in the past, will construe the claims of the RTI Patents below. *See Pioneer v. Samsung,* No. 2:07-CV-170, Dkt. No. 94, at 2-8 (E.D. Tex. filed Mar. 10, 2008) (claim-construction order).

III. PATENTS-IN-SUIT

The patents-in-suit are directed to particular features of a retractable syringe. The '773 Patent issued on May 27, 1997 from an application filed on September 29, 1995. The '773 Patent is a continuation-in-part of U.S. Patent App. No. 438,954, which was eventually issued as the '011 Patent. '733 at [63]. The '773 Patent abstract reads:

A tamperproof retractable non-reusable syringe has a one piece hollow outer body with a barrel for a slidable plunger, a transition zone and a smaller diameter nose portion. An elongated needle holder and spring combination is installable from the rear of the outer body, guided into the nose portion and held by cooperating inwardly and outwardly facing surfaces oriented in the direction of retraction at the most constricted part of the transition zone where the nose begins. The plunger has an opening with a dislodgable stopper for receiving parts of the retraction mechanism. The stopper and the head of the needle holder are of significantly reduced diameter from the injection fluid chamber to resist blowing out prematurely. In one embodiment the head of the needle holder is surrounded by a separable retainer member which is slidingly removed by contact with the tip of the plunger after the stopper is mostly or fully removed to avoid cumulation of force required for retraction after the injection. In a second embodiment the head of the

needle holder is clamped and held by constricting forces imposed by stress on the outer body induced by interference fit. Release occurs by slight expansion on the barrel by contact of the plunger tip with a small internal ramp in the outer barrel. Both embodiments have a plunger cap configured to enter an opening in the outer body to provide an additional tamperproof feature.

'773 Patent at [57].

The '077 Patent issued July 18, 2000 from an application filed on April 25, 1997. The '077 Patent is a continuation-in-part of both the '773 and '011 Patents. '077 at [63]. The abstract from the '077 Patent mirrors that of the '773 Patent, but contains one additional sentence: "The retraction cavity is provided with venting structure to assure that all uninjected fluid is retained within the syringe body." Id. at [57].

The '224 Patent issued April 1, 2008 from an application filed July 17, 2000. The '224 Patent is a continuation-in-part of the '007, '773, and ' 011 Patents. '224 at [63]. The '773 Patent abstract reads:

A syringe assembly having a retractable needle, the syringe assembly being rendered unusable after a single injection and having a hollow syringe body, a retraction mechanism with a spring disposed in the front portion of the syringe and an inner head, a continuous retainer member surrounding the inner head, and a bridging portion disposed between the continuous retainer member and the inner head, wherein the bridging portion couples the continuous retainer member and the inner head to form a fluid seal between a fluid passageway and the barrel prior to retraction, and a plunger reciprocally disposed inside the barrel and forming a variable chamber between the plunger and the needle holder prior to and during retraction, wherein the continuous retainer member is releasable from the inner head of the needle holder when the plunger is further depressed inside the barrel following injection.

Id. at [57].

IV. U.S. PATENT NO. 5,632,733

A. Overview

RTI has asserted claims 1, 24, and 36 of the '733 Patent against BD in this lawsuit. Dkt. No. 114. For reference, asserted claims 1 and 24 are reproduced below (terms to be construed emphasized):

1. A tamperproof retractable syringe for injecting fluid wherein the syringe has a one piece **body** and a retraction mechanism assembleable from the rear which resists high blowout pressure during an injection but can be retracted with low plunger force after injection comprising:

a one piece hollow outer **body** having a longitudinally extending wall, comprising an elongated **barrel** and **nose,** with a **transition zone** connecting the **barrel** and **nose,** the **nose** having a reduced cross sectional area relative to the **barrel** and an **inwardly facing surface** in the wall at the most constricted part of the **transition zone** where the nose begins;

a plunger assembly disposed partially within the elongated **barrel,** the plunger having a head in slidable sealed contact with the interior of the outer **body,** a forward portion and a retraction cavity therein for receiving parts of a retraction mechanism;

a **retraction mechanism sealingly disposed in the nose,** the retraction mechanism having a retractable part comprising a needle holder having an elongated **body** having a needle holding tip portion in front and a head in back, a passageway defining a fluid path into a variable fluid chamber in the **barrel** below the plunger, and a spring applying retraction force to the retractable part, said retractable part being configured to be able to retract into the retraction cavity of the plunger when retraction is initiated;

the retraction mechanism further including a nonretractable part comprising a **retainer member** surrounding the head of the needle holder, the retainer member and said head of the needle holder being removably coupled by a **bridging portion** between them;

the needle holder and spring being installable into the **nose** from the rear of the **barrel** and **releaseably installed by sliding engagement of said retainer member and said inwardly facing surface** while compressing said spring, said **sliding engagement producing a holding force** in opposition to the retraction force applied to the needle holder by said spring; and

the plunger being depressible to a first position which comprises the end of an injection cycle whereby fluid previously drawn into the variable chamber is expelled through said fluid path, and a retraction position beyond said first position wherein retraction is initiated by the forward portion of the plunger head moving through the **transition zone** in the **nose** to release the needle holder by uncoupling the **retainer member** and needle holder at said **bridging portion** thereby reducing the holding force to an amount less than the retraction force on the needle holder to cause retraction of the retractable part into the retraction cavity of the plunger.

24. A method of assembling a tamperproof retractable syringe which is well suited for automated assembly;

providing a one piece hollow syringe **body** having a longitudinally extending wall with an open back end, comprising an elongated **barrel** and **nose portion** of reduced cross sectional area relative to the **barrel,** and an **inwardly facing surface** in the wall at the most constricted part of a **transition zone** between the **barrel** and **nose** where the **nose** begins;

providing a plunger assembly having a front portion and a back portion, the front portion including a head configured for sliding sealed contact with the interior of the elongated **barrel,** said head having a retraction cavity and a leading end configured to contact and remove a **retainer member** from a needle holder to be mounted in the **nose;**

providing a needle holder having an elongated **body** portion in front and a head in back with a fluid path therethrough, the head of the needle holder having a **retainer member** which can be separated from the head of the

needle holder by contact with the leading end of the plunger, the **retainer member** having an **outwardly facing surface** configured to slidingly and frictionally engage said **inwardly facing surface** in the **nose** and hold the needle holder against a retraction force provided by the spring when the spring is compressed within the **nose;**

loading the spring followed by the needle holder into the back opening in the **barrel** part of the syringe **body** and positioning at least the forward portion of the spring and a portion of the elongated body of the needle holder within the **nose;**

moving the head end of the needle holder and the **retainer member** into the most constricted part of the transition zone where the **nose** begins; and

installing the needle holder and **retainer member** in the **nose** by sliding engagement of the **outwardly facing surface** of the **retainer member** with the **inwardly facing surface** in the wall while compressing the spring within the **nose.**

'733, 14:65-15:49, 16:64-17:37 (emphasis added).

B. Claim Construction

1. "body"

a. Parties' Positions

The parties propose the following constructions for "body," which is present in each of the asserted claims as well as the two other patents-in-suit. Dkt. No. 114. The primary dispute between the parties is whether the syringe body must be limited to a one-piece structure.

RTI	BD
A hollow outer structure that houses the syringe's components	A one-piece hollow outer structure that houses the syringe's components

RTI contends this term should not contain a one-piece limitation because many of the claims in the '733 Patent already contain such a limitation. Dkt. No. 111 at 22. To add this limitation to the definition of body itself would render the additional claim language meaningless. *Id.* RTI also contends the patentee expressly used a one-piece limitation in the '733 Patent while no such limitation is generally present in the '077 or '224 Patents. Id. at 23. In fact, the patentee in the '224 patent used the limitation to differentiate between certain claims. *Compare* '224, 22:38-40 (claim 43), *with* 24:23-25 (claim 57-"The syringe assembly of claim 43 wherein the body comprises a one-piece barrel.").

Judge Davis previously construed this term in connection with the '011 and ' 077 Patents. *See RTI v. New Medical Techs.*, Civil Action No. 4:02-CV-34, Dkt. No. 110 at 6-9 (E.D.Tex. March 8, 2008). Judge Davis, like RTI, found significant the fact that the patentee in this family of patents included the phrase "one piece" in some claims, but not in others. *Id.* at 7. As such, Judge Davis found it improper to limit the term to a preferred embodiment containing only a one-piece body. *Id.* at 8-9.

b. Court's Construction

At the outset, this Court notes that certain terms, such as barrel, pervade all of the patents-in-suit. Because all of these patents are related-the latter patents being continuations-in-part of earlier patents and patent applications-this Court finds that terms should be construed consistently throughout absent some evidence to the contrary. In addition, the specifications and claims of each patent within this family may provide guidance when construing such pervasive terms.

Regardless of whether collateral estoppels applies to the construction of this term, the Court finds no reason to deviate from Judge Davis' previous construction. *See Id.* at 6-9. Accordingly, this Court finds that "body" means "a hollow outer structure that houses the syringe's components."

2. "barrel"

a. Parties' Positions

The parties propose the following constructions for "barrel," which is present in each of the asserted claims as well as the other two patents-in-suit. Dkt. No. 114. The primary dispute between the parties is whether the syringe barrel must be cylindrical in shape.

RTI	BD
The elongated part of the syringe body including a portion within which the plunger moves during	The elongated cylindrical portion of the syringe body through which the plunger moves during

injection injection

RTI contends the claimed barrel could take a number of conceivable shapes and should not be limited to a cylindrical form. Dkt. No. 111 at 26-27. RTI further argues that the '224 specification specifically contemplates a non-cylindrical barrel. *Id.* (citing '224, 10:47-50). Moreover, the principle of claim differentiation supports RTI's broad construction as certain claims specifically contain a cylindrical limitation while others do not. *Id.* at 27 (citing '224, 20:22-23 (claim 25)). Finally, RTI contends that it is improper to limit the claimed barrel to the portion of the syringe through which the plunger moves. *Id.* Instead, some claims within the '224 and ' 077 Patent suggest that the term may encompass other structures through which the plunger does not move; specifically, the term may also define the front end portion of the syringe, including the nose portion and retraction mechanism. Id. at 27-28 (citing *inter alia* '224, 22:37-40 (claim 43) & '077, 22:13-15).

In response, BD relies on numerous dictionaries, which suggest that a barrel is limited to a cylindrical shape. Dkt. No. 112 at 30-31. BD also maintains that every figure in this family of patents shows a cylindrical barrel and expressly labels the non-cylindrical parts of the syringe as a 'nose' or 'transition zone'. *Id.* Thus, BD argues that the patent figures make clear that the term is limited to a cylindrical shape and does not include narrow parts in the front end of the syringe. *Id.* In addition, BD contends that the terms barrel, nose, and transition zone should each be given distinct meanings because they are given different names and labels throughout the patent-to do otherwise would render the different labels superfluous. *Id.*

b. Court's Construction

The Federal Circuit has made it clear that when the specification discloses only a single preferred embodiment, limitations from that embodiment generally should not be imported into the claim language. Phillips v. AWH Corp., 415 F.3d at 1323 (rejecting the contention that "if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment"). Limitations from the specification may be imported into the claims where it is clear that the patentee intended for the "claims and embodiments in the specification to be strictly coextensive." *Id.* (citing SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1341 (Fed.Cir.2001)). Such intention is evidenced by the manner in which the patentee uses a term within the specification and the claims. *Id.* (citing Snow v. Lake Shore & M.S. Ry. Co., 121 U.S. 617, 630 (1887) (it was clear from the specification that there was "nothing in the context to indicate that the patentee contemplated any alternative" embodiment to the one presented)).

RTI is correct that all figures in the patents-in-suit generally depict syringes having a cylindrical barrel. The specification of the '224 Patent, however, makes it clear that the patentee contemplated alternative shapes. Specifically, the patent states that the "head of the needle holder is preferably circular but could conceivably be another shape with the retainer member correspondingly configured to conform to it." '224, 10:47-50. As the ' 224 Patent generally depicts a syringe having a barrel and needle holder having similar shape, such a statement evidences the patentee's belief that both the needle holder and related barrel could have a non-circular shape. Thus, the patentee may have contemplated a non-cylindrical barrel.

Moreover, claim 25 of the '224 Patent specifically recites a "substantially cylindrical barrel," which strongly suggests that the term is not inherently cylindrical. Furthermore, the absence of this "substantially cylindrical" limitation in other claims suggests that it should not be read into claims in which it is not present. *See* Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1326 (Fed.Cir.2003) ("when a patent claim does not contain a certain limitation and another claim does, that limitation cannot be read into the former claim"). The Court therefore finds that the term barrel should not be limited to a cylindrical shape.

Finally, although this Court believes that the terms barrel, nose, and transition zone are generally distinct

components within the patents-in-suit, the patents also suggest that the barrel may encompass some portion of the syringe through which the plunger does not move. Specifically, claim 25 of the '077 Patent recites a "barrel having a front end portion containing a retraction mechanism." If this front end portion of the claimed barrel contains the retraction mechanism, then it cannot logically also be a portion through which the plunger moves. Although the plunger will assuredly move through some portion of the barrel, this Court finds that it would be improper to limit the barrel to that portion.

Accordingly, this Court finds that "barrel means "the elongated part of the syringe body including a portion through which the plunger moves during injection."

3. "nose"/"nose portion"

The parties have agreed on a meaning for the term "nose," which appears in each asserted claim. The proposed construction is "the portion of the syringe at the injection end that has a reduced diameter relative to the barrel." Dkt. No. 110 at 1. The parties have further agreed that these claims require the "nose" to be distinct from the barrel and transition zone.

The parties have also agreed on a meaning for the term "nose portion," which appears in claims 24 and 36. The proposed construction is "section of the syringe body that has a reduced diameter relative to the barrel portion of the body." *Id.*

The Court has no reason to disagree and therefore adopts the parties' constructions.

4. "transition zone"

a. Parties' Positions

The parties propose the following constructions for "transition zone," which is present in each asserted claim. Dkt. No. 114.

RTI	BD
Portion of the syringe located between the barrel and the nose	Portion of the syringe with varied inner diameter located between the barrel and the nose

RTI contends this term should not be limited to the preferred embodiment, which identifies a transition zone with a sloping inner wall. Dkt. No. 111 at 21. While RTI concedes that the transition zone has a "constricted portion," it believes that the patent does not require that the transition zone have a varied inner diameter. *Id.* BD counters by arguing that the phrase "most constricted part of the transition zone" pertains to the whole invention and requires a varied inner diameter. Dkt. No. 112 at 28 (citing '733, 14:8-10).

Judge Davis previously construed this term in connection with the '011 and ' 077 Patents. *See RTI v. New Medical Techs.*, Civil Action No. 4:02-CV-34, Dkt. No. 110 at 15 (E.D.Tex. March 8, 2008). Judge Davis did not limit the term to a varied inner diameter. *Id.*

b. Court's Construction

Once again, the Court finds no reason to deviate from Judge Davis' previous construction. *See RTI v. New Medical Techs.*, Civil Action No. 4:02-CV-34, Dkt. No. 110 at 13-14 (E.D.Tex. March 8, 2008). In addition, the Court finds no reason to limit the term to the preferred embodiment. Accordingly, this Court finds that term "transition zone" means "portion of the syringe located between the barrel and the nose."

5. "inwardly facing surface"

a. Parties' Positions

The parties propose the following constructions for "inwardly facing surface," which is present in each asserted claim. Dkt. No. 114.

RTI	BD
A surface that faces the inside of the syringe	A surface in the wall that faces toward the center of the syringe and is parallel to the direction of the plunger motion

RTI contends this term should not be restricted to a surface that is parallel to the motion of the plunger, as such would improperly restrict the term to a preferred embodiment. Dkt. No. 111 at 29. RTI contends that the '733 specification attaches no significance to the fact that the preferred embodiment's surfaces happen to be parallel to the plunger's motion. *Id*. Additionally, RTI contends that claim differentiation precludes such a limitation, as the patentee chose to specifically align these surfaces in certain claims of the '011 Patent. Id. (citing '011, 13:40-43 (claim 3)).

In response, BD contends that every embodiment described or depicted in the ' 733 Patent demonstrates surfaces that are parallel to the vertical direction of the plunger motion. Dkt. No. 112 at 23-24. In addition, the Summary of the Invention within the '733 Patent also aligns these surfaces with the plunger motion. Id. (citing '733, 2:64-65 (inwardly and outwardly facing surfaces meet "along an interface oriented in the direction of retraction")). Alternatively, BD argues that during prosecution RTI took a narrower view of the scope of this term to overcome prior art. Id. As such, BD argues that RTI has surrendered broader, non-parallel coverage. Id.

b. Court's Construction

As discussed above, limitations from the preferred embodiment generally should not be imported into the claim language, unless the claims and the embodiments in the specification were meant to be strictly coextensive. Phillips, 415 F.3d at 1323. While the descriptions and depictions of the invention in the '733 Patent generally show an inwardly facing surface that is parallel to the plunger motion, this Court finds no evidence that such embodiments are strictly coextensive with the claimed invention. Indeed, the ' 011 Patent, from which the '733 Patent is a continuation-in-part, expressly claims such an orientation. '011, 13:40-43 (claim 3: "The tamperproof retractable syringe of claim 2 wherein said frictional holding [inwardly and outwardly facing] surfaces comprise a linear interface aligned in the direction of retraction."). Thus, when the patentee wished to limit the alignment of surfaces, he expressly claimed such. Accordingly, this Court finds that it would be improper to import an alignment limitation into claims where such is not expressly present.

Accordingly, this Court finds that the term "inwardly facing surface" means "a surface that faces toward the center of the syringe."

6. "retraction mechanism sealingly disposed in the nose"

The parties have agreed on a meaning for the term "retraction mechanism sealingly disposed in the nose," which appears in claim 1. The proposed construction is "a retraction mechanism sealed in the nose." Dkt. No. 110 at 1. The Court has no reason to disagree and therefore adopts the parties' construction.

7. "retainer member"

a. Parties' Positions

The parties propose the following constructions for "retainer member," which is present in each asserted claim and the '224 Patent. Dkt. No. 114. The primary dispute between the parties is whether the retainer

member must operate by means of a frictional force.

RTI	BD
A nonretractable part of the retraction mechanism that retains the retraction mechanism	A nonretractable part of the retraction mechanism, separate from the needle holder, that retains the retraction mechanism by frictional force with the wall of the syringe

RTI contends that BD's construction would not only limit the patent to a preferred embodiment, but would also limit the patent to RTI's particular commercial product, the VanishPoint(R)-syringe. Dkt. No. 111 at 8-10. The construction proposed by BD would read a frictional holding force limitation into the term. RTI believes this improper because some claims do not require any engagement or holding force, much less some kind of frictional force. *Id.* at 10 (citing '224, 20:46-54 (claim 43)). Moreover, RTI contends that the patentee explicitly stated in some claims that frictional forces were required, raising the implication that claims without such explicit statements are not limited to friction. *Id.* (comparing '733, 14:32-37 (claim 1) with 17:18-21 (claim 24) and 18:38-41 (claim 36)). RTI also contends that the specification expressly contemplates embodiments that operate using something other than friction to hold the retainer member in place. *Id.* at 11-13. Specifically, the patents teach that the holding force used in the invention, while preferably frictional, may instead rely on tack welding, sonic welding, adhesive, or clamping forces. *Id.* at 12-13 (citing '733, 9:50-53, 10:4-8, 6:47-55, and 11:49-52).

RTI also believes that BD's proposed construction is improper in another regard, it requires that the retainer member and needle holder be separate parts. *Id.* at 16-18. While one preferred embodiment teaches that the two components are separate parts, RTI argues that there is nothing in either the claims or the specification that requires such. *Id.* To the contrary, an alternative embodiment suggests that the two are welded together to form a single structure. *Id.* at 17 (citing '733, 9:7-27). Therefore, RTI contends that-despite being two components-the patents contemplate that the retainer member and needle holder may be formed into a single structure. *Id.*

In response, BD contends that the specification repeatedly describes the invention as a retracting syringe in which the needle holder is engaged and released by sliding surfaces, and therefore, friction. Dkt. No. 112 at 17. BD identifies numerous points in the specification where the holding force used in the invention is identified as a frictional force. *Id.* at 17-18 (citing ' 733, 2:67-3:6, 3:11-13, and 3:61). BD also contends that the specification uses the terms 'holding force' and 'frictional holding force' interchangeably, thus demonstrating that they are intended to have the same meaning. *Id.* (citing Tate Access Floors, Inc. v.. Maxcess Techs., Inc., 222 F.3d 958, 968 (Fed.Cir.2000)). Moreover, BD argues that the specification criticizes syringes in the prior art that operate without friction and rely instead on flexing, breaking, or penetration. *Id.* at 18 (citing '733, 1:48-54, 2:18-35). Specifically, BD contends the specification asserts that the invention was new and different because it "relies entirely on clamping force or friction...." *Id.* (quoting '733, 2:20-21).

In connection with the second issue regarding this term, that is whether the needle holder and retainer member must be separate parts, BD argues that the ' 733 claims suggest that the two components are inherently separate parts. *Id.* at 25. BD argues that a single, unitary structure cannot couple with itself or surround itself. *Id.* In addition, BD contends that the patent specification, specifically the Summary of the Invention, explains that the retraction mechanism has a "two part head." *Id.* (citing '733, 3:25-26). Finally, BD argues that melting or tacking two parts together do not make them a single part; instead, such coupling is further evidence that they are indeed two separate parts. *Id.* at 25-26.

b. Court's Construction

First, this Court finds that nothing in the specification requires the needle holder and retainer member be two separate parts. The specification states that in " *one embodiment,* the head of the holder is a two part head

comprising an inner head surrounded by a separable retainer ...." '733, 3:19-22 (emphasis added). This statement is explicitly limited to a single, preferred embodiment, thus suggesting that other embodiments of the invention may utilize a unitary structure. Such a structure is contemplated in an alternative embodiment in which the two components are initially welded together and later "ruptured or separated." *Id* . at 9:7-13.

Second, this Court finds that the invention operates through the use of a frictional or clamping force, and that the retainer member must utilize these forces. Although the claims by themselves may seem broad enough to encompass other methods of operation, the patent as a whole disavows such methods and limits itself to frictional or clamping forces. The Federal Circuit has stated that where "the general summary or description of the invention describes a feature of the invention ... and criticizes other products ... that lack the same feature, this operates as a clear disavowal of these other products...." Astrazeneca AB v. Mutual Pharm. Co., 384 F.3d 1333, 1340 (Fed.Cir.2004), *see also* SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1341 (Fed.Cir.2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims ... even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question.").

RTI is correct in asserting that some claims of the '733 Patent are explicitly limited to a frictional force while others do not. Claim differentiation would ordinarily require that all claims not be so limited. The specification, however, makes clear that the invention does not include the use flexing, breaking, or penetration as methods of operation. It does so by expressly criticizing other methods used in retractable syringes:

Other problems with the prior art are dependence on flexing or breaking of internal parts by the plunger in order to release the retraction mechanism and use of a diaphragm at the end of the plunger which must be penetrated by a needle holding member and spring. These structures present serious quality control and assembly problems.

'733, 1:48-54. In contrast to these less preferable methods, the specification asserts that the present invention is superior because it relies entirely on clamping or frictional forces: "The prior art has not recognized a retraction mechanism with separable parts that *relies entirely* on clamping force or friction...." '733, 2:18-20. By distinguishing itself from the prior art in such absolute terms, the patent has limited itself to a certain type of holding force-clamping or friction.

Finally, the varied embodiments in the invention demonstrate that this holding force may be utilized in different manners within the syringe. In one embodiment, a pair of frictional holding forces function to retain the needle in the projecting position: a frictional force between the wall of the syringe and the retainer member, and another between the retainer member and the needle holder. *See* '733, 6:56-67, 3:8-24. In another embodiment, the needle holder and retainer member are welded or tack molded together as discussed above. *See* ' 733, 9:50-53, 10:4-8, and 11:49-52. Although this weld or tack mold holds the needle holder and retainer member together, there is still a clamping or frictional force between the wall of the syringe and the retainer member. Without this force between the wall of the syringe and the retainer member, the syringe would be inoperable-it would be unable to retain the needle in a projecting position. Thus, the retainer member can only function through the use of a frictional or clamping force.

Accordingly, this Court finds that the term "retainer member" means "a non-retractable part of the retraction mechanism that uses some clamping or frictional force to keep the needle in the projecting position until released."

8. "bridging portion"

a. Parties' Positions

The parties propose the following constructions for "bridging portion," which is present in claim 1 and in the '224 Patent. Dkt. No. 114. The primary dispute between the parties is whether the bridging portion must be limited to a ridge-like structure.

RTI	BD
The structure that joins the retainer member and the head of the needle holder	A ridge on one of the facing surfaces that joins the retainer member and the head of the needle holder

RTI contends that BD's construction improperly limits the invention to a preferred embodiment. Dkt. No. 111 at 28. While the embodiment in Figure 8 admittedly depicts a raised ridge between facing surfaces, RTI argues that nothing in the specification limits the bridging portion to such a structure. *Id.* Instead, the specification states that the bridging portion may be joined to needle holder by a tack weld, or "by providing any other form of frangible bridging portion that holds the separable ring member and needle holder together." *Id.* at 28-29 (citing '733, 9:37-40).

In response, BD argues that the specification defines the bridging portion as a "small ridge" or "raised portion" joining facing surfaces. Dkt. No. 112 at 27 (citing '733, 3:43 and '077, 10:38-39). While the bridging portion may admittedly be made of various materials, BD contends that it must have some definable structure, which the patent identifies as a ridge on one of the facing surfaces. *Id.*

b. Court's Construction

The specification describes the bridging portion as a ridge-like structure that may take the form of a single "very small raised portion" or a "series of horizontally spaced apart raised portions ." While the preferred embodiment describes the bridging portion as such ridge-like structures, the Court finds no evidence that the patentee intended to limit the term to that structure. *See* Phillips, 415 F.3d at 1323 (claims should not be limited to particular embodiments unless the inventor has indicated such a narrow construction). Additionally, the bridging portion is part of an embodiment depicted in Figure 8, which the specification distinguishes from those embodiments depicted in Figures 1-3. *See* '733, 9:7-17. It is thus apparent that Figures 1-3 do not contain the claimed bridging portion, as the adjoining surfaces of the retainer member and needle holder in those embodiments are flush with one another. Thus, if two surfaces are completely flush with one another they cannot logically be joined by a bridging portion. As such, the claimed bridging portion, whatever the form it takes, must be a distinguishable structure that both joins the two components and provides some separation between them. The separation may take the form of a "small gap between them all around" ('733, 9:30-31) as depicted in Figure 8. Conversely, the bridging portion could take the form of a "frangible web" (Dkt. No 111 at 29), the gaps of which separate the two surfaces.

Accordingly, as the Court previously ruled, the term "bridging portion" means "a structure that spans the gap between and connects the retainer member and needle holder."

9. "releaseably installed by sliding engagement of said retainer member and said inwardly facing surface"

a. Parties' Positions

The parties propose the following constructions for "releaseably installed by sliding engagement of said retainer member and said inwardly facing surface," which is present in claim 1. Dkt. No. 114.

RTI	BD
Releaseably installed by sliding the retainer member along the inwardly facing surface to engage it with the wall of the syringe	Installed and released by sliding the retainer member along the inwardly facing surface to create and the release a frictional force with the wall of the syringe

As above, this term concerns the nature of the force involved in the invention. In addition, however, the parties also dispute the meaning of the words "releaseably installed" in this term. BD contends that "releaseably installed by sliding engagement" has two functional meanings. Dkt. No. 112 at 20. First, the phrase refers to the creation of a frictional force. *Id.* Second, the word "releaseably" requires that the retainer member be releaseable in the same way that it was installed. *Id.* at 20-21. BD contends that if the retraction mechanism is "installed by sliding engagement," then it must be released in the same manner-by sliding the retainer member away from the inwardly facing surface. *Id.* at 21.

RTI disagrees and contends that the term is not so limited. Dkt. No. 111 at 14. Instead, RTI argues that one of the alternate methods of release taught by the patent could achieve the release-namely by spreading the syringe wall and allowing a one-piece needle holder to retract. *Id.* at 14-15 (citing '733, 11:49-52).

b. Court's Construction

For the reasons stated above, this Court finds that the invention operates through the use of a clamping or fictional force. This Court, however, is not persuaded that the claimed release must be accomplished in the same manner as the installation. The patent teaches alternative methods for providing release of the holding force. Specifically, the patent allows the holding force to be released by spreading the barrel apart slightly, thus releasing the retraction mechanism. *See* '733, 11:49-52 ("The barrel is flexible and is spread outwardly a slight among to the position of FIG. 6 just prior to retraction. Here the mating surfaces are separated an amount which reduces the clamping force on the needle holder."). Therefore, although the holding force is created by sliding engagement in this claim, the Patent contemplates another method of its release.

Accordingly, the Court finds that the term "releaseably installed by sliding engagement of said retainer member and said inwardly facing surface" means "installed by sliding the retainer member along the inwardly facing surface to engage it with the wall of the syringe, which creates a clamping or frictional force that can be released at a later time."

10. "sliding engagement producing a holding force"

The parties propose the following constructions for "sliding engagement producing a holding force," which is present in claim 1. Dkt. No. 114.

RTI	BD
Sliding the retainer member along the inwardly facing surface of the body to produce a force that maintains the needle holder in the projected position	Sliding the retainer member along the inwardly facing surface of the body produces a frictional force that maintains the needle holder in the projected position

Once again, the dispute between the parties center on whether the holding force must be a frictional force. RTI and BD proffer the same arguments as those discussed above in connection with the term "retainer member." Dkt. Nos. 111 at 18 & 112 at 16-20.

For the reasons stated above, this Court finds that the invention operates through the use of a clamping or fictional force. Accordingly, the Court finds that the term "continuous retainer member surrounding the inner head" means "sliding the retainer member along the inwardly facing surface of the body produces a clamping or frictional force that maintains the needle holder in the projected position."

11. "outwardly facing surface"

The parties propose the following constructions for "outwardly facing surface," which is present in claims

24 and 36. Dkt. No. 114.

RTI	BD
A surface that faces toward the outside of the syringe	A surface that faces away from the center of the syringe and is parallel to the direction of the plunger motion

The parties present arguments similar to those presented in connection to the term "inwardly facing surface." For the same reasons as stated above in connection with inwardly facing surfaces, the Court finds that the claimed outwardly facing surfaces should not be limited to a direction parallel to the plunger motion.

Accordingly, this Court finds that the term "outwardly facing surface" means "a surface that faces away from the center of the syringe."

V. U.S. PATENT NO. 6,090,077

A. Overview

RTI has asserted claims 10 and 25 of the '077 Patent against BD in this lawsuit. Dkt. No. 114. For reference, the asserted claims are reproduced below (terms to be construed emphasized):

10. A syringe plunger handle assembly and syringe barrel combination for use in a retractable syringe for injecting fluids, comprising:

a hollow syringe **body** having an elongated tubular wall comprising an elongated **barrel** portion having an open back end;

an elongated plunger disposed for reciprocation in sliding sealed contact with the **barrel** portion of the **body,** the plunger having a tubular wall defining a head portion in front, a back end portion carrying a thumb cap and hollow interior comprising a retraction cavity located between the head portion and thumb cap;

the thumb cap having an outer side adapted to reside in close association with the open back end of the plunger **barrel** when the plunger is nearly fully depressed; and

the plunger having a **vent** in fluid communication with the retraction cavity, to allow airflow from the retraction cavity.

25. A tamperproof retractable syringe structure designed for one use, comprising:

a hollow syringe **body** comprising a syringe **barrel** having an open back end, **the barrel having a front end portion containing a retraction mechanism configured for operation by a plunger;**

a plunger reciprocatably mounted in sliding sealed contact with the **barrel,** the plunger having a thumb cap at its back end for working the plunger relative to the **barrel** and **a front end configured to operate the retraction mechanism;**

the plunger having a tactile first position felt by a user pressing the thumb cap at the end of free travel of the plunger in the **barrel** when the plunger is moved forward to a stop, the plunger having a length relative to the length of the **barrel** whereby in the tactile first position of the plunger a portion of the plunger and the thumb cap extend behind the **barrel** for grasping in order to draw fluid into the **barrel** by partially withdrawing the plunger from the **barrel;**

the plunger having a retraction position obtained by pressing the thumb cap to move the plunger forward beyond the tactile first position and thereby operating the retraction mechanism and simultaneously lodging the thumb cap in the open back end of the **barrel** thereby rendering the thumb cap inaccessible for grasping.

'007 Patent, 19:33-50, 20:48-21:7 (emphasis added).

B. Claim Construction

1. "body"/"barrel"

The Court construed these terms as part of its analysis of the '733 Patent, of which the '077 Patent is a continuation-in-part. The Court finds no reason to deviate from its prior constructions.

2. "vent"

The parties have agreed on a meaning for the term "vent," which appears in claim 10. The proposed construction is "an aperture that provides an opportunity or means of escape, passage, or release ." Dkt. No. 110 at 1-2. While the Court has does not disagree with the overall construction, it does believe that the word "aperture" would be unnecessarily confusing to the jury. Thus, the Court finds that the term "vent" should be construed as "an opening that provides an opportunity or means of escape, passage, or release."

3. "the barrel having a front end portion containing a retraction mechanism configured for operation by a plunger"

The parties have agreed on a meaning for the term "the barrel having a front end portion containing a retraction mechanism configured for operation by a plunger," which appears in claim 25. The proposed construction is "the section of the barrel at the injection end has a retraction mechanism that is configured to be operated by a plunger." Dkt. No. 110 at 1-2. The Court has no reason to disagree and therefore adopts the parties' construction.

4. "a front end configured to operate the retraction mechanism"

The parties have agreed on a meaning for the term "a front end configured to operate the retraction mechanism," which appears in claim 25. The proposed construction is "portion of the plunger closer to the injection end of the syringe that operates the retraction mechanism." Dkt. No. 110 at 1. The Court has no reason to disagree and therefore adopts the parties' construction.

VI. U.S. PATENT NO. 7,351,224

A. Overview

RTI has asserted claims 43, 47, 55, 60, and 61 of the '224 Patent against BD in this lawsuit. Dkt. No. 114. Claim 43 is an independent claim, upon which claims 47, 55, 60, and 61 depend. For reference, the asserted claims are reproduced below (terms to be construed emphasized):

43. A syringe assembly having a retractable needle that is rendered unusable after a single injection of fluid into a patient, the assembly comprising:

a hollow syringe **body** comprising a **barrel** and having a front end portion and a back end portion, the back end portion further comprising at least one radially extending member providing finger grips for the syringe **body;**

a retraction mechanism disposed in the front end portion, the retraction mechanism further comprising a

needle holder having a head portion, an elongated needle holding portion, and a longitudinally extending fluid passageway through the head portion and the elongated needle holding portion, the head portion further comprising an inner head, **a continuous retainer member surrounding the inner head,** and a **bridging portion** disposed between the continuous **retainer member** and the inner head, wherein said **bridging portion** couples the continuous **retainer member** and the inner head to form a fluid seal between the fluid passageway and the **barrel** prior to retraction, and a compressed retraction spring surrounding at least part of the elongated needle holding portion and biasing the inner head toward the back end portion prior to retraction;

a retractable needle extending into the front end portion of the **body** through an opening in the front end portion of the **body,** the retractable needle being held in fixed relation to the elongated needle holding portion of the needle holder and in fluid communication with the longitudinally extending fluid passageway through the head portion and the needle holding portion;

a plunger reciprocally disposed inside the **barrel** and forming a variable chamber between the plunger and the needle holder prior to and during injection, the plunger being receivable into the **barrel** through the back end portion of the **body** and comprising an outer wall, a retraction cavity disposed inwardly of the outer wall, a plunger seal element providing sliding, sealed engagement between the plunger and the **barrel** and preventing fluid leakage between the plunger and the **barrel,** the plunger seal element being restrained from sliding longitudinally along the outer wall of the plunger, and a back end with an **end cap** having an outer periphery; and

a barrier disposed in the front end portion of the **body** that limits forward motion of the needle holding portion and the retractable needle relative to the **body** as the plunger is depressed inside the barrel during injection and retraction;

wherein the continuous retainer member is releasable from the inner head of the needle holder when the plunger is further depressed inside the barrel following injection.

47. The syringe assembly of claim 43 wherein the **body** further comprises a collar having an open back end, the collar extending rearwardly behind the at least one radially extending member and longitudinally separating the at least one radially extending member from the open back end, and wherein the outer periphery of the **end cap** is in close proximity to the back end of the collar following injection and during retraction.

55. The syringe assembly of claim 43 wherein the retraction cavity is **vented** behind the plunger seal element.

60. The syringe assembly claim 43 wherein the continuous retaining member has an outside mating surface making a fluid seal with the **barrel.**

The syringe assembly of claim 43 wherein the **body** and the elongated needle holder cooperate as a spring guide during compression of the retraction spring.

'224 Patent, 22:35-23:19, 23:32-39, 24:18-19, 24:33-35, 24:36-38 (emphasis added).

B. Claim Construction

1. "body"/"barrel"/"bridging portion"/"retainer member"

The Court construed these terms as part of its analysis of the '733 Patent, of which the '224 Patent is a continuation-in-part. The Court finds no reason to deviate from its prior constructions.

2. "continuous retainer member surrounding the inner head"

The parties propose the following constructions for "continuous retainer member surrounding the inner head," which is present in claim 43. Dkt. No. 114.

RTI	BD
A nonretractable part of the retraction mechanism that encircles the inner head of the needle holder, and retains the retraction mechanism	A nonretractable part of the retraction mechanism, separate from the needle holder, that encircles the inner head of the needle holder, and retains the retraction mechanism by frictional force with the wall of the syringe

RTI and BD proffer the same arguments as those discussed above in connection with the term "retainer member." Dkt. Nos. 111 at 13-14. Once again, the dispute between the parties is two-fold: (1) whether the holding force must be a frictional force, and (2) whether the needle holder and retainer member must be separate parts.

For the reasons stated above, this Court finds that the invention operates through the use of a clamping or fictional force and that there is no requirement that two components be separate parts. Accordingly, the Court finds that the term "continuous retainer member surrounding the inner head" means "a non-retractable part of the retraction mechanism that encircles the inner head of the needle holder and uses some clamping or frictional force to keep the needle in the projecting position until released."

3. "end cap"

a. Parties' Positions

The parties offer the following constructions for "end cap," which is present in claims 43 and 47. Dkt. No. 114.

RTI	BD
Back end of the plunger	A separate piece that caps the open end of the plunger

RTI contends that BD's proposed construction improperly limits this term. Dkt. No. 111 at 30-31. RTI believes that nothing in the specification requires the end cap be a separate piece or that it cap the open end of the plunger. *Id*. Instead, RTI contends that the "force fit plug" is the separate piece that caps the end of the plunger, while the end cap is a part of the plunger itself. *Id* . (citing '224, 7:22-24 & Figs. 1-7). In addition, one claim specifically recites that "the end cap has an opening and a closure is installed in the opening." *Id*. (citing '224, 24:16-17 (claim 54)).

In response, BD contends that RTI's proposed construction does not make sense in light of the claim language. Dkt. No. 112 at 32. Specifically, the claims require a "back end with an end cap," and BD believes that RTI's construction would make this requirement nonsensical-a back end with a back end. *Id*. (citing '224, 22:65-23:9 (claim 43)).

b. Court's Construction

The Patent figures depict the end cap as a part of the plunger rather than a separate piece. *See* '224, Figs. 1-7. The Federal Circuit has held that an interpretation of a claim, which would not include a preferred embodiment disclosed in the specification, is "rarely, if ever, correct." Vitronics, 90 F.3d at 1583. This Court finds no reason to require the end cap to be a separate piece, as such a construction would not include the

embodiments depicted in Figures 1-7. This Court, however, also finds no reason to limit the term to these embodiments, in which the end cap is a part of the plunger. The Patent could conceivably cover an alternative embodiment in which the end cap was a separate piece.

In addition, the Patent states that it is the "force fit plug" rather than the end cap that closes the retraction cavity-the open end-at the back of the plunger. '224, 7:33-36. The end cap itself has a "central opening for permanently receiving [the] force fit plug." *Id.* As such, the end cap, in contradiction with the plain meaning of the word "cap," does not necessarily close the open end of the plunger. Instead, it allows the force fit plug to accomplish that function once it is permanently installed within the end cap's opening. This Court, however, also finds no reason to limit the term to this one preferred embodiment-it is possible that the Patent could cover a syringe in which the end cap and force fit plug were a single piece, rather than two separate parts.

Finally, because it is located at the back of the plunger, the Patent describes the end cap as a portion of the plunger with which the thumb contacts during depression. *Id.* ("Plunger has an end cap for depression of the plunger by the thumb.").

Accordingly, the Court finds that the term "end cap" means "a component at the back of the plunger, which may be contacted by the thumb during depression."

4. "wherein the continuous retainer member is releasable from the inner head"

a. Parties' Positions

The parties offer the following constructions for the term "wherein the continuous retainer member is releasable from the inner head," which appears in claim 43. Dkt. No. 114.

RTI	BD
The plunger releases the continuous retainer member from the inner head as the plunger is further depressed in the barrel	The plunger releases the continuous retainer member from the inner head by pushing the continuous retainer member off of the inner head as the plunger is depressed in the barrel to reduce the frictional force with the wall of the syringe

The parties' arguments in connection with this term closely mirror those proffered in connection with the term "releaseably installed by sliding engagement of said retainer member and said inwardly facing surface" construed above. *See* Dkt. Nos. 111 at 19-20 & 112 at 26-27.

b. Court's Construction

For the reasons stated above, this Court finds that the invention operates through the use of a clamping or fictional force. However, since the clamping or frictional forces are already part of this Court's construction of "continuous retainer member," this Court finds that it would be unnecessarily confusing and duplicative to include a reference to those forces in this term's construction. As also discussed above, this Court finds that that the holding force may be released by some other manner than that with which it was installed.

Accordingly, the Court finds that the term "wherein the continuous retainer member is releasable from the inner head" means "the plunger releases the continuous retainer member from the inner head as the plunger is further depressed in the barrel."

VII. CONCLUSION

The Court hereby **ORDERS** the claim terms addressed herein construed as indicated. The table below summarizes the Court's constructions:

Term	Court's Construction
	'773 Patent
body	"a hollow outer structure that houses the syringe's components." A hollow outer structure that houses the syringe's components
barrel	The elongated part of the syringe body including a portion through which the plunger moves during injection
nose	The portion of the syringe at the injection end that has a reduced diameter relative to the barrel.
nose portion	Section of the syringe body that has a reduced diameter relative to the barrel portion of the body.
transition zone	Portion of the syringe located between the barrel and the nose
inwardly facing surface	A surface that faces toward the center of the syringe
retraction mechanism sealingly disposed in the nose	A retraction mechanism sealed in the nose.
retainer member	A non-retractable part of the retraction mechanism that uses some clamping or frictional force to keep the needle in the projecting position until released
bridging portion	A structure that spans the gap between and connects the retainer member and needle holder
releaseably installed by sliding engagement of said retainer member and said inwardly facing surface	Installed by sliding the retainer member along the inwardly facing surface to engage it with the wall of the syringe, which creates a clamping or frictional force that can be released at a later time
sliding engagement producing a holding force	Sliding the retainer member along the inwardly facing surface of the body produces a clamping or frictional force that maintains the needle holder in the projected position
outwardly facing surface	A surface that faces away from the center of the syringe
	'077 Patent
body	Same as above
barrel	Same as above
vent	An opening that provides an opportunity or means of escape, passage, or release
the barrel having a front end portion containing a retraction mechanism configured for operation by a plunger	The section of the barrel at the injection end has a retraction mechanism that is configured to be operated by a plunger.
a front end configured to operate the retraction mechanism	Portion of the plunger closer to the injection end of the syringe that operates the retraction mechanism.
	'224 Patent
body	Same as above
barrel	Same as above
retainer member	Same as above
bridging portion	Same as above
continuous retainer member surrounding the inner head	A non-retractable part of the retraction mechanism that encircles the inner head of the needle holder and uses some clamping or frictional force to keep the needle in the projecting position until released
end cap	A component at the back of the plunger, which may be contacted by the thumb during depression
wherein the continuous retainer member is releasable from the inner head	The plunger releases the continuous retainer member from the inner head as the plunger is further depressed in the barrel

IT IS SO ORDERED.

E.D.Tex.,2009.
Retractable Technologies, Inc. v. Becton Dickinson & Co.

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Literature display help

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wrap up close

(57) [Summary]
The present invention is a bifurcated capillary tube (10) including closed system blood sampli
ng devices. A second branch (32) of the bifurcated capillary tube is connected to and in fluid c
ommunication with the blood collection area. It terminates in an opening adapted to receive a
blood withdrawal device.

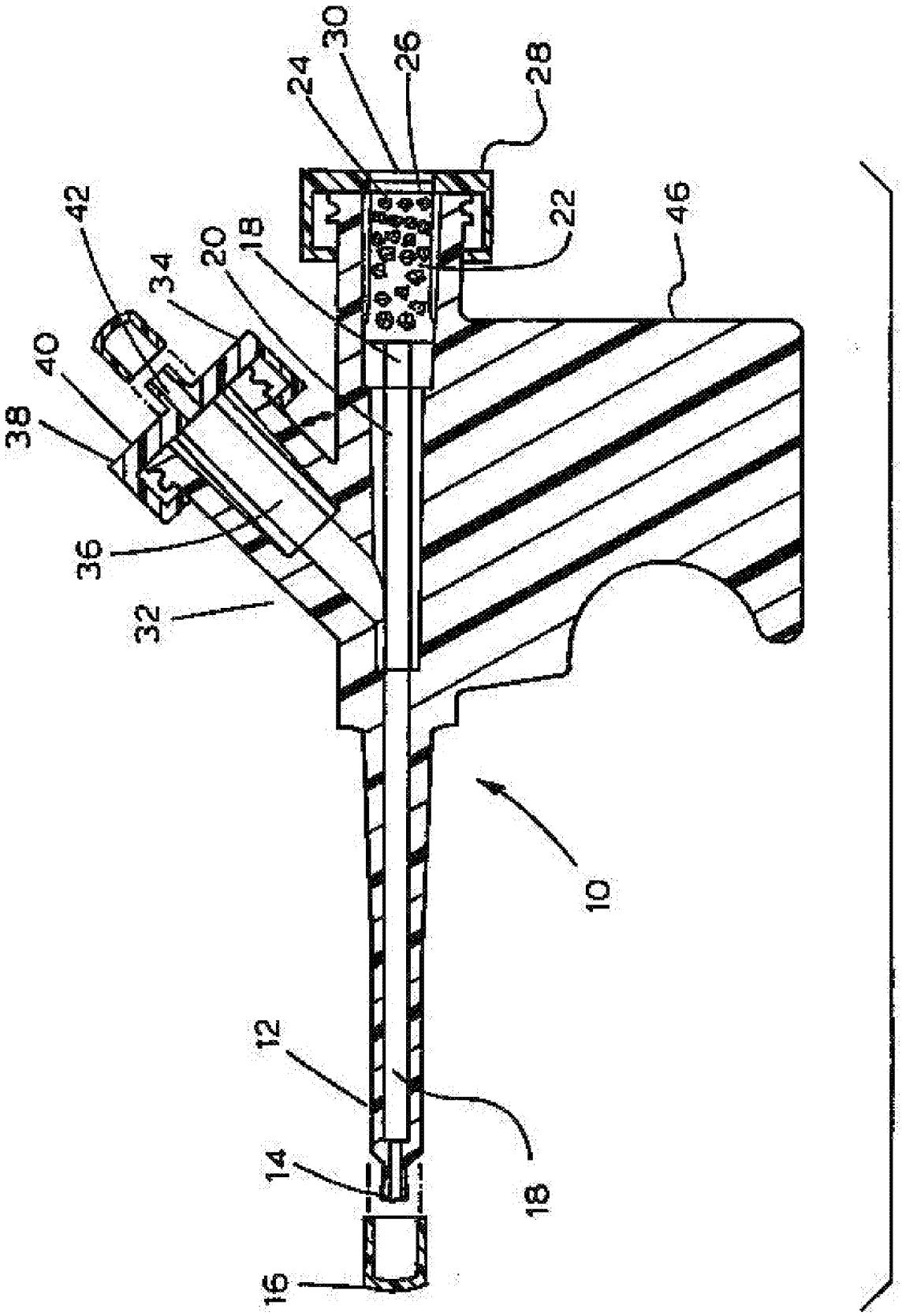


FIG. 1

The scope of the claims open ----

[Claims]

1. A closed system blood sampling device comprising a bifurcated capillary tube comprising:

a. a first branch having a cannulated

end ;

b. a blood collection area for storing an amount of withdrawn blood and supplying a first to the communicating channel;

c. a blood disposal chamber having an air permeable liquid closed end; and

d.

a second device connected to and in fluid communication with said blood collection area terminating in an opening adapted to

receive a blood extraction device.

2. 4. The cannula-shaped end is blunt, the blood waste chamber has a cap containing an air permeable hydrophobic membrane

on the end, and the blood waste chamber contains a porous blood

adsorbent 1 closed system blood sampling device.

3.

2. The closed system blood sampling device of claim 1, wherein the second branch has an internal angle of no greater than 90 degrees .

4. 4. The closed system blood sampling device of Claim 3, wherein the second branch has an angle of about 60 degrees

.

5. 3. The closed system blood

sampling .

6. 3. The closed system blood sampling device of Claim 2 , wherein said blunt cannulated distal end is

adapted to be received by an injection site including a resilient resealing means. 7. 7. The closed . 8. 3. The closed system blood sampling device of claim 2, wherein said blood collection area has a volume greater than the volume of said blood waste chamber . 9. A method of sampling blood from a patient having an artery connected to a venipuncture device attached to an injection site comprising the closed system blood sampling device of claim 1.

A law comprising:

a.

drawing blood through the cannulated end of the closed system blood sampling device , there by subsequently

filling the blood waste chamber and then the blood collection area;

b. withdrawing the blood contained within the blood collection area

through the opening in the second branch for subsequent processing; and then

c. and discarding the closed system blood sampling device

.

10. 10. The method of claim 9, wherein said cannula is blunt, said blood disposal chamber is c apped at its end with an air permeable hydrophobic

membrane and comprises a porous blood adsorbent. 11. 10. The method of claim 9, wherein t he second branch has an internal angle of no greater than 90 degrees . 12. Claim 1, wherein t he second branch has an angle of about 60 degrees.

1 method.

13. 11. The method of claim 10, wherein the cannulated end is tapered.

14.

11. The method of claim 10, wherein the blunt cannula-shaped distal end is adapted to be rec eived by an injection site including a resilient resealing means

.

15. 15. The method of claim 14, wherein the injection site is a pre-slit injection site

.

16.

11. The method of Claim 10, wherein the blood collection area has a volume greater than the volume of the blood waste chamber .

detailed description open —

Description:

CLOSED SYSTEM BLOOD SAMPLING APPARATUS

FIELD OF THE INVENTION The

present invention relates to closed system blood sampling apparatus.

BACKGROUND OF THE INVENTION

Arterial blood gas sampling is a standard procedure often used to . In some cases, samples . For a typical neonatal patient weighing 1000 grams and having a total blood volume , blood sample volume becomes a critical factor. A technique called the "three drops method" is gaining substantial clinical acceptance in neonatal units throughout the country . This method requires inserting a blunt hypodermic needle as far as possible into a standard sleeved T-connector . Three drops of blood, estimated at about 0.06 cc , are drawn onto the gauge pad, thereby removing heparinized or non-circulating blood from the cannula while providing a fresh arterial blood sample on its surface. Three more drops are then collected in the microcontainer after which the cannula is withdrawn. The blood cannula contents within the cannula lumen and the immediately prior collected microcontainer sample are then blood tested for testing.

Aspirated into a tuberculin-type syringe for transport to the chamber. A wash of the T-connector is then subsequently performed to remove residual blood. This procedure uses a controlled blood volume (0.06 cc as required to discard, and actual It provides the ability to draw 0.12 cc to possibly 0.20 cc) for blood gas testing on-the-fly.

There are several opportunities for procedure refinement. One problem is that the collection method is an open environment, which could facilitate the spread of blood contamination and/or communicable diseases . Second, the acquisition process is difficult to control with respect to volumetric accuracy and is highly sensitive to variations in physician technique, catheter placement and arterial pressure. In the treatment of neonatal patients where blood volume levels are critical, if a device could be designed for closed system collection that would also ensure sample volume consistency every time.

, improved accuracy could be of great clinical benefit.

BRIEF

DESCRIPTION OF THE DRAWING FIG. 1 is a horizontal cut away side .

FIG. 2 is an upright, partial schematic showing a closed system blood sampling device conne

cted to an injection site, which is then connected
into a venipuncture device used to draw arterial blood.
is a diagram.

In the drawings, similar parts have similar numbers.

The Invention The present invention is a closed system blood sampling device that includes a bifurcated capillary tube having a first branch

with a
cannulated .
A blood collection area is
for .
It also supplies the first fraction of blood withdrawn to a communicating blood waste chamber having an air permeable liquid closed end.

A second branch of the bifurcated capillary is connected to and communicates with the blood collection area.
liquid communication. It
terminates .

In a preferred embodiment, the cannulated
end blunt, the blood waste chamber
is capped at its end with an air permeable hydrophobic membrane, and the blood waste chamber is porous. of blood adsorbents. The second branch
has an interior angle no greater than 90 degrees, and preferably the interior angle is 60 degrees.
It is also desirable that the cannulated end be tapered
so that fully below .

Preferably, the closed system blood sampling device
is
withdrawn from the injection site before the blood sample is withdrawn therefrom by means such as by direct aspiration into a tuberculin syringe or blood gas analyzer.

Although closed system blood sampling devices are particularly well suited for obtaining neonatal blood samples
, the devices are readily adaptable for obtaining samples from a variety of patient types.
be done.

Detailed Description of the Invention

In FIG
.
It is preferably formed of a transparent, chemically inert, non-toxic plastic such as polycarbonate or the like . It includes a blood withdrawal
cannula shaped end 12 . The cannula tip 14 is blunt and
narrowed to prevent backflow of blood at the injection site during arterial blood sampling.

A blood sampling device is used at the cannula tip to maintain sterility
It is fitted with a removable cap 16, which is removed just before.

FIG. 1 shows a cannulated distal end 12 that is tapered.
This particular configuration was chosen so that the cannula could engage and
generally later . The internal bore 18 at the cannulated distal end is sized
by capillary action driven by normal positive arterial blood pressure . The internal capillary 1 8 connects with and leads into a larger diameter lumen 20 . The continuous bore 18 and lume n 20 of the cannula 12 constitute the blood collection area. Hole 18 where it exits lumen 20 tr ansitions into blood waste chamber 22 . In a preferred embodiment of the invention , blood di sposal chamber 22 includes blood retention means such as absorbent material 24, which may be rayon or cellulose wadding or the like. The open end 26 of the blood waste chamber 22 has a cap 28 fitted on top of it with a liquid impervious, air permeable hydrophobic membrane 30 that allows air to escape from the blood sampling device 10 of the present invention. is closed by A suitable thin film material is sheet polytetrafluoroethylene . Connected to the lumen 20 and in fluid communication therewith is a second branch or port 32 . It is arranged to have an internal angle 34 not exceeding 90 degrees. The interior angle is

Preferably it is about 60 degrees. Hole 36 connects with hole 18 and matches it in dimensions . The port 32 is terminated at its distal end with an adapter cap 38 (at its top 40 a capillary lu er
Joint 42 is connected
is sealed by The capillary luer is protected from contamination
by a protective cap 44 that is removed just before blood is drawn from the closed blood sampl ing device.
Port 32 and its hole 36 form
part . For convenience of use, the closed blood sampling device is connected with
a pistol grip handle 46.

The blood collection area has a liquid volume greater than the liquid volume of the blood dis posal chamber. If
the closed blood sampling device described is to be used
in , the fluid volume of the blood collection area
may be 0.12 cc, and the fluid volume of the blood waste chamber 22 may be It would be abo ut 0.06cc.

The use of the closed blood
sampling is illustrated in FIG
. A communicating artery 48 is shown. Neck 54 of venipuncture device 50
is adapted to receive injection site 56 . Although a conventional injection site may
be used as such or adapted for use in the practice of the present invention, the injection site i s preferably pre-slit with a resilient reseal. It is desirable to be of a type having a possible par tition. This type of injection site is available from Baxter Healthcare Corporation and is availab le from Baxter Healthca.

Neonatal Tee Connector Luer Fitting sold under the trademark InterLink, a registered tradema rk of re Corporation .

Such pre-slit, resilient, resealable injection
sites and methods of their manufacture are described in US Pat. No. 5,188,620.
, the disclosure of which is incorporated herein by reference.
The pre-slit, resilient, resealable injection site described in this patent
is designed to accept a blunt cannula.
Another injection site related to the injection site detailed in US Pat. No. 5,188,620
is described in US Pat. No. 5,300,034. This patent is also a preferred embodiment used in the practice of this invention.
The plethora of publications and references describing various injection sites are elaborated
. This patent and publications cited therein are also
incorporated .

Injection site 56 is connected to a T-connector 58 which in turn is connected to
microbore tubing which is connected through female luer fitting 62 to intravenous line 64
. The distal end of injection site 56 is connected to neck 54 of venipuncture device 50 . A prox imal end 66 of injection site 56 is a pre-slit, resilient member adapted to receive blood withdr awal cannula 12 sized to fit snugly into
the injection site. , is connected with the resealing septum 68 . Inserted into the second branc h or port 32 is a conventional syringe 70 such as a tuberculin blood aspiration syringe or an ar terial blood gas loss resistant syringe. The cannula 12 of the device is inserted through the s

eptum 68 of the injection site 56 and positioned so that the tip 14 of the cannula 12 is fully in serted into the injection site adjacent the venipuncture device. be. Doing so would remove the residual from the blood draw volume as a measurable factor. Arterial pressure causes blood to enter and flow up the device through capillary action.

will let As blood rises to the hydrophobic membrane 30 of the device, air
will escape through the upstream hydrophobic membrane 30 . Original blood originally presen t in the catheter will be forced up past
the luer fitting branch for retention and eventual disposal in the device . The device will be wit hdrawn from the T-connector as soon as visual confirmation
of a blood-filled lumen is formed.
The vent
removal cap 44 will be removed from the bifurcated luer fitting 42 and replaced by a syringe 7 0 that will be aspirated to remove the arterial blood
sample
. Residual blood volume upstream of the bifurcation will remain in the device for subsequent d isposal
.

drawing open —

[Fig. 1]

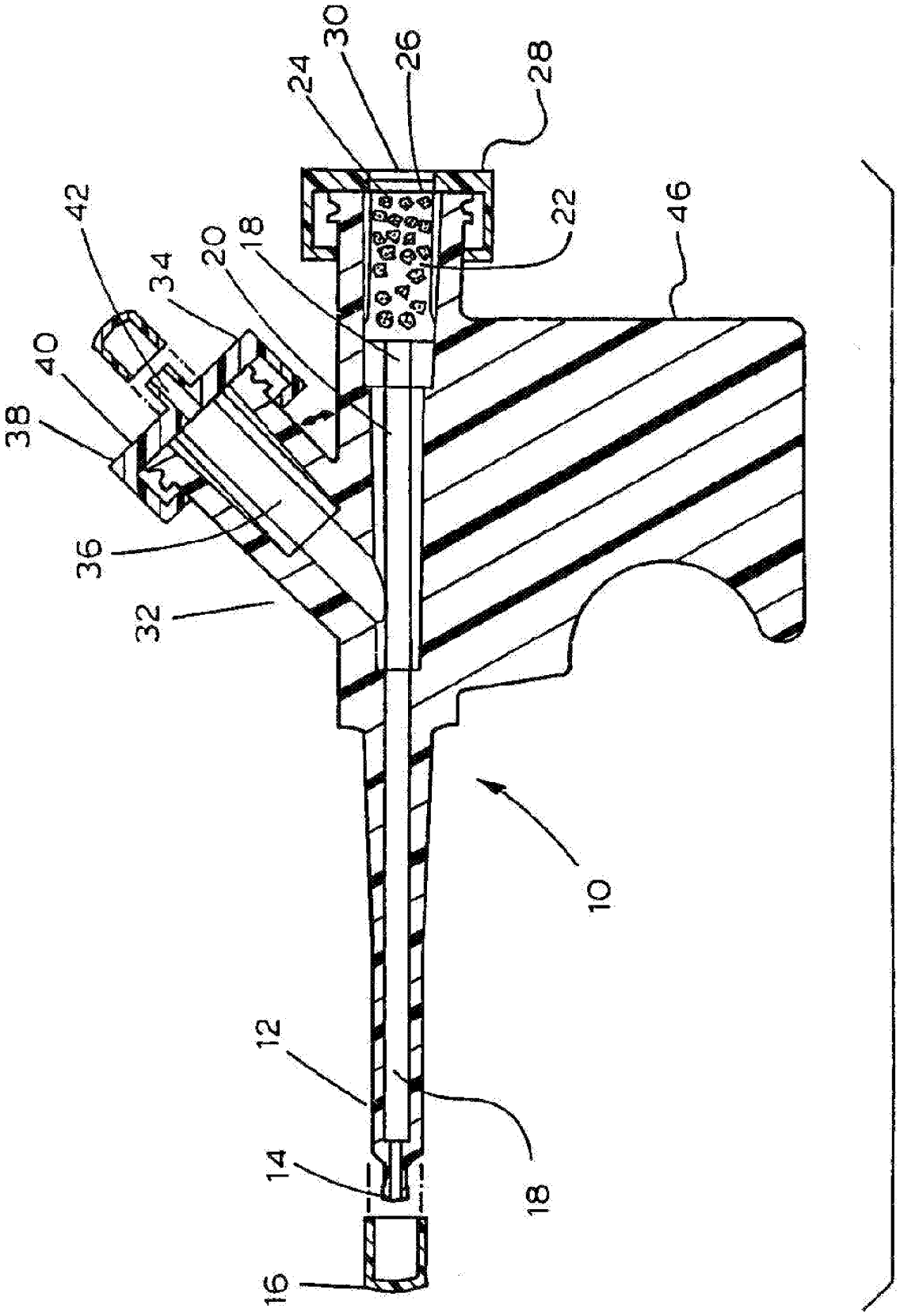


FIG. 1

[Figure 2]

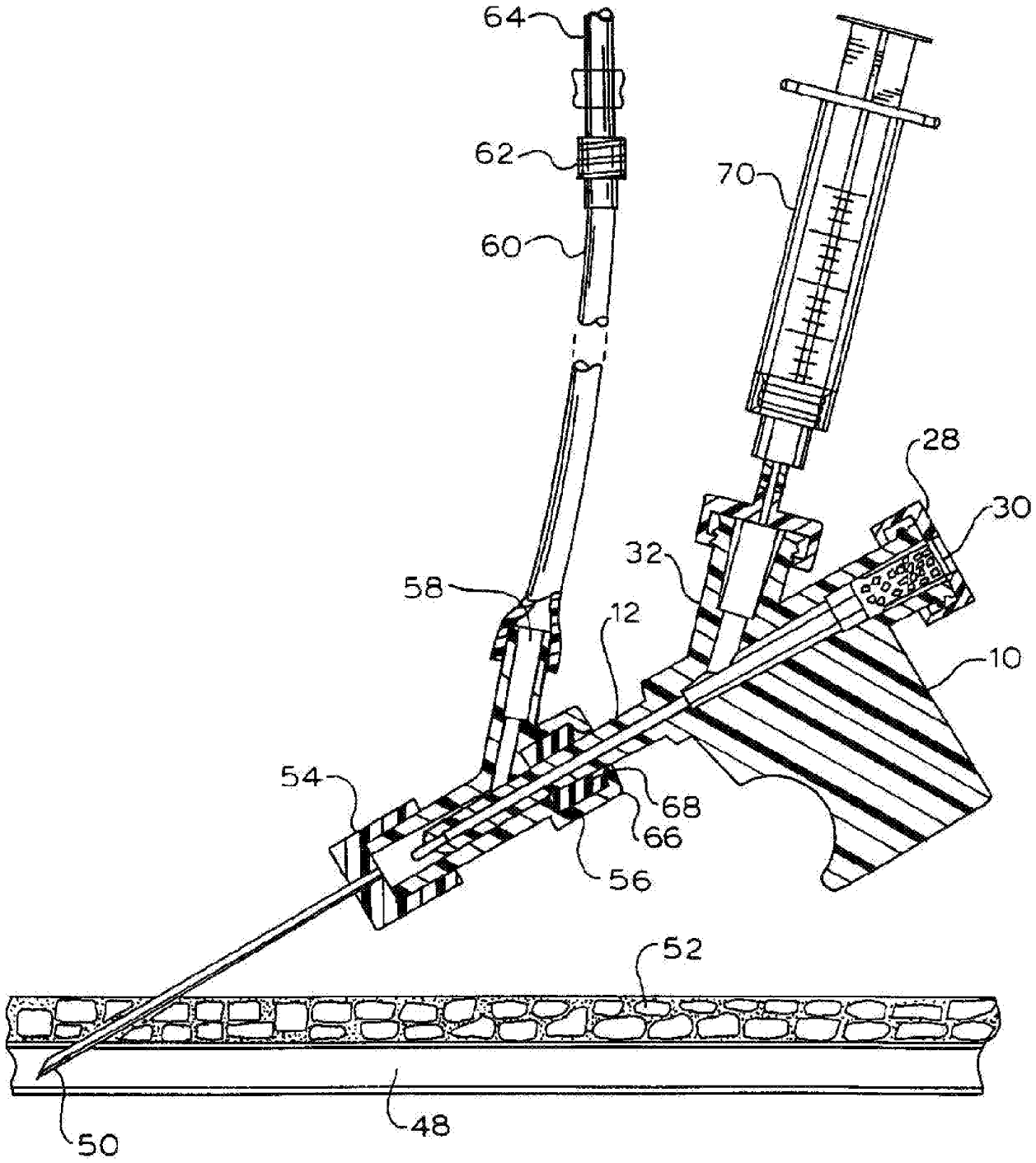


FIG. 2

search report open —

[International search report]

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A 61M 5/00
US CL : 604/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/122, 35, 125, 126, 128, 256, 258, 283, 284
128/ 760, 762, 767, 768

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 4,531,937 (Yates) 30 July 1985, See Entire Reference	1-7,9-15 --- 8,16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 DECEMBER 1995	Date of mailing of the international search report 04 JAN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT	Authorized officer ANDRE ROBERT

Washington, D.C. 20231
Facsimile No.

SAM KIMELL
Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet)(July 1992)★

drawing open

Representative drawing 1 2

Magnify and Rotate

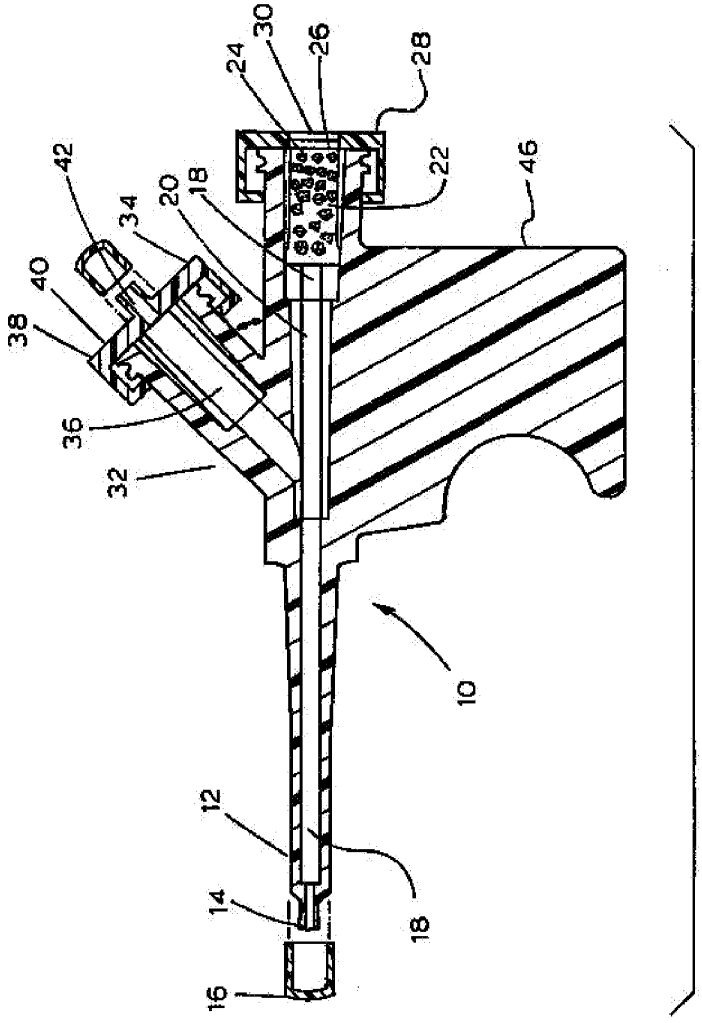


FIG. 1

Representative drawing

1 / 1 display

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Espacenet

Bibliographic data: JPH09504726 (A) — 1997-05-13

CLOSED SYSTEM BLOOD SAMPLING DEVICE

Inventor(s):

Applicant(s):

Classification:
- **international:** *A61B5/15;* (IPC1-7): A61B5/14
- **cooperative:** A61B5/15003 (EP); A61B5/150213 (EP); A61B5/150259 (EP); A61B5/150992 (EP); A61B5/155 (EP)

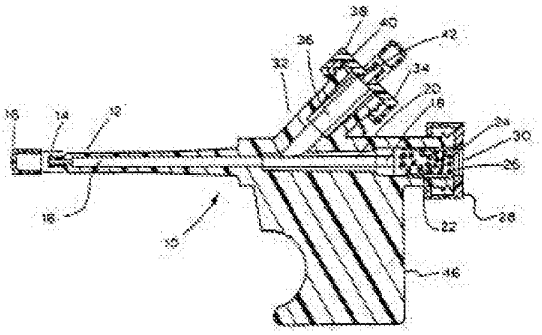
Application number: JP19950508283 19950822

Priority number(s): WO1995US10702 19950822 ; US19940296207 19940825

Also published as: AT208640 (T) AU3412795 (A) AU686450 (B2) CA2173331 (A1) DE69523887 (T2) more

Abstract not available for JPH09504726 (A)
Abstract of corresponding document: WO9605875 (A1)

The invention comprises a closed system blood sampling device comprising a bifurcated capillary tube (10) which has a first branch (12) having a cannula shaped end (14) for withdrawing and conveying blood to a communicating blood collection zone. The second branch of the bifurcated capillary tube (32) is connected to and is in fluid communication with the blood collection zone. It terminates in an opening adapted to receive a blood withdrawal device.



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審査請求　未請求　　予備審査請求　未請求(全 11 頁)

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(87)国際公開日　平成８年(1996)２月29日
(31)優先権主張番号　０８／２９６，２０７
(32)優先日　1994年８月25日
(33)優先権主張国　米国（ＵＳ）
(81)指定国　ＥＰ(ＡＴ，ＢＥ，ＣＨ，ＤＥ，ＤＫ，ＥＳ，ＦＲ，ＧＢ，ＧＲ，ＩＥ，ＩＴ，ＬＵ，ＭＣ，ＮＬ，ＰＴ，ＳＥ)，ＡＵ，ＣＡ，ＪＰ

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(54)【発明の名称】　閉鎖系血液サンプリング装置

(57)【要約】
本発明は、血液を抜き取りそして連通した血液収集区域へ血液を移送するための、カニューレ形の末端(14)を有する第一の枝(12)を有する、分岐した毛細管(10)を含む閉鎖系血液サンプリング装置を含む。該分岐した毛細管の第二の枝(32)は、該血液収集区域へと連結され、そしてそれと液体連通している。それは、血液抜き取り装置を受け入れるのに適合させた開口に終わっている。

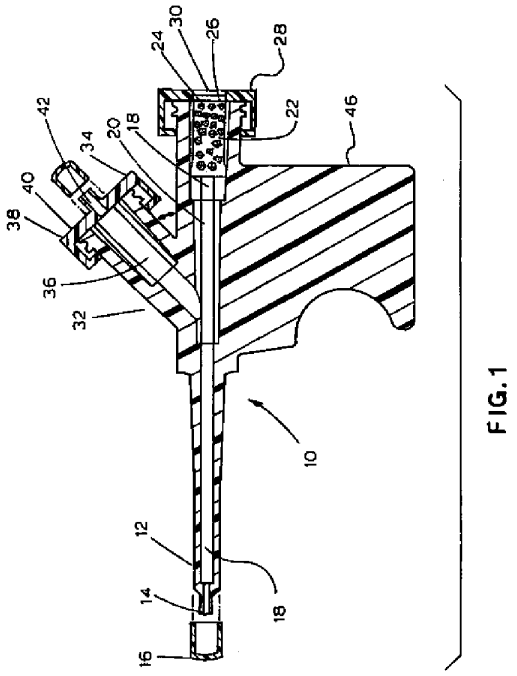


FIG. 1

【特許請求の範囲】

１．　分岐した毛細管を含む閉鎖系血液サンプリング装置であって、

ａ．血液を抜取って連通路へと血液を移送するためのカニューレ形の末端を有する第一の枝と、

ｂ．ある量の抜き取られた血液を貯蔵し、そして抜き取られた血液の最初の画分を連通路へと供給するための血液収集区域と、

ｃ．空気透過性の液体閉鎖性の末端を有する血液廃棄室と、そして、

ｄ．血液抜き取り装置を受け入れるのに適合させた開口に終わる該血液収集区域に連結されそしてこれと液体連通している第二の技と、

を含む閉鎖系血液サンプリング装置。

２．　該カニューレ形の末端が鈍く、該血液廃棄室が空気透過性の疎水性薄膜を含むキャップをその末端に嵌めてあり、そして該血液廃棄室が多孔性の血液吸着剤を含むものである、請求項１の閉鎖系血液サンプリング装置。

３．　第二の枝が９０度よりも大きくない内角を有するものである、請求項１の閉鎖系血液サンプリング装置。

４．　第二の枝が約６０度の角度を有するものである、請求項３の閉鎖系血液サンプリング装置。

５．　該カニューレ形の末端が先細っている、請求項２の閉鎖系血液サンプリング装置。

６．　該鈍いカニューレ形の末端が、弾力のある再シールする手段を含む注射部位によって受け入れられるのに適合させてあるものである、請求項２の閉鎖系血液サンプリング装置。

７．　該注射部位が予めスリットを入れてある注射部位である、請求項６の閉鎖系血液サンプリング装置。

８．　該血液収集区域が、該血液廃棄室の体積よりも大きな体積を有するものである、請求項２の閉鎖系血液サンプリング装置。

９．　請求項１の該閉鎖系血液サンプリング装置を含む注射部位に取付けられた静脈穿刺装置と連結された動脈を有する患者から、血液をサンプリングする方

法であって、

ａ．該閉鎖系血液サンプリング装置の該カニューレ形の末端を通して血液を抜き取り、それによってその後該血液廃棄室そして次いで該血液収集区域を満たすステップと、

ｂ．その後の処理のために、該血液収集区域内に含まれた該血液を該第二の枝にある該開口を通して抜き取るステップと、そして、次いで、

ｃ．該閉鎖系血液サンプリング装置を捨てるステップと、

を含む方法。

１０．　該カニューレが鈍く、該血液廃棄室がその末端に空気透過性の疎水性薄膜を含むキャップを嵌めてあり、そして多孔性の血液吸着剤を含むものである、請求項９の方法。

１１．　第二の枝が９０度よりも大きくない内角を有するものである、請求項９の方法。

１２．　第二の枝が約６０度の角度を有するものである、請求項１

１の方法。

１３．　該カニューレ形の末端が先細っている、請求項１０の方法。

１４．　該鈍いカニューレ形の末端が、弾力のある再シールする手段を含む注射部位によって受け入れられるのに適合させてあるものである、請求項１０の方法。

１５．　該注射部位が予めスリットを入れてある注射部位である、請求項１４の方法。

１６．　該血液収集区域が、該血液廃棄室の体積よりも大きな体積を有するものである、請求項１０の方法。

【発明の詳細な説明】

閉鎖系血液サンプリング装置

本発明の分野

本発明は、閉鎖系血液サンプリング装置に関する。

本発明の背景

動脈血のガスサンプリングは、重態の疾病において呼吸機能の評価を助けるためにしばしば使用される標準的な手順である。場合により、一日に20回ものサンプルが抜き取られることができる。1000グラムの体重でそして約85ccの全血液体積を有する典型的な新生児患者にとって、血液サンプルの体積は重大な要素になる。

「３滴法」と呼ばれる技術が、国中の新生児ユニットにおいて実質的に臨床上受入れられつつある。この方法は標準のスリーブで止められたＴ字形コネクターの中へとできる限り遠く、鈍い皮下針を挿入することを要求する。約０06ccと推定される三滴の血液が、ゲージパッド上へとたらされ、それによってその表面に新鮮な動脈血サンプルを提供する間にヘパリン加血液又は非循環血をカニューレから取り除く。次いで、更なる三滴がマイクロコンテナー中に集められ、その後にカニューレが引き抜かれる。カニューレ管腔内の血液カニューレ内容物へ及び直前に収集されたマイクロコンテナーサンプルは、次いで検査のために血液試験室へと輸送するためにツベルクリンタイプの注射器中へと吸引される。次いで残りの血液を除去するためにＴコネクターの洗浄がその後行われる。この手順は制御された血液体積（捨てるのに必要なものとして０06cc、及び実

際の血液ガス検査のために０12cc乃至多分０20cc）を抜き取る能力を提供する。

手順の改良のための幾つかの機会が存在する。一つの問題は、血液汚染及び／又は伝染病の拡散を促進し得るであろうその収集方法が開放した環境であることである。第二には、体積の正確さに関しては収集過程が制御しにくく、そして医者の技術、カテーテル配置及び動脈圧の変化に対して非常に影響されやすい。もし、毎回サンプル体積の一貫性も保証することができるであろう閉鎖系の収集のための装置が設計できれば、血液体積レベルが重大である新生児患者の治療では

、正確さの改善は大きな臨床上の利益になりうる。

図面

図１は、本発明の閉鎖系血液サンプリング装置を示す水平方向の切り取った側面図である。

図２は、注射部位に連結され、次いで、該注射部位が動脈血を抜き取るために使用される静脈穿刺装置中へと連結されている閉鎖系血液サンプリング装置を示す直立の部分的に概要的な図である。

該図面中では、類似の部品は類似の番号を有する。

本発明

本発明は、血液を抜き取って連通した血液収集区域へ移送するためのカニューレ形の末端を有する第一の枝を有する分岐した毛細管を含む閉鎖系血液サンプリング装置である。血液収集区域はある量の抜き取られた血液を貯蔵するためのものである。それは、抜き取られた血液の最初の画分を空気透過性の液体閉鎖性の末端を有する連通した血液廃棄室へ供給をもする。

分岐した毛細管の第二の分岐は血液収集区域に連結されてこれと

液体連通している。それは血液抜取り装置を受け入れるのに適合させた開口に終わっている。

好ましい具体例においては、閉鎖系血液サンプリング装置のカニューレ形の末端は鈍く、血液廃棄室はその末端に空気透過性の疎水性薄膜を含むキャップがはめてあり、そして血液廃棄室は多孔性の血液吸着剤を含む。第二の枝は90度より大きくない内角を有し、そして好ましくは該内角は60度である。後に一層完全に記述される好ましい注射部位中へと、カニューレ形の末端がぴったり嵌合するように、カニューレ形の末端が先細りであることも同様に望ましい。

好ましくは、閉鎖系血液サンプリング装置は、血液サンプルがツベルクリン注射器又は血液ガス分析器中へと直接的に吸引される等のような手段によってそこから抜き取られる前に、注射部位から抜き取られる。

閉鎖系血液サンプリング装置は、新生児の血液サンプルを得るのに特に適しているが、該装置はさまざまな患者のタイプからサンプルを得るために直ちに適合

される。

本発明の詳細な記述

図１において、閉鎖系血液サンプリング装置は全体として数字10によって指示されている。それは、ポリカーボネート等のような透明で化学的に不活性な毒性のないプラスチックによって好ましくは形成される。それは血液抜取りカニューレ形の末端12を含む。カニューレ先端14は鈍く、そして動脈血サンプリングの間注射部位の血液逆流を防止するようにくびれて細まっている。無菌性を維持するために、カニューレ先端には、血液サンプリング装置が使用される

直前に取り外される、取外し可能なキャップ16が嵌められている。

図１は、先細りにされるカニューレ形の末端12を示している。その詳細は後に一層完全に記述されるであろうが、カニューレが特有の注射部位と係合そして一般的に嵌合することができるように、この特有の構成が選ばれた。カニューレ形の末端の内部穴18は、正常な正の動脈血圧によって駆動される毛管作用によって、抜き取られた血液が該穴に沿って移動することを許容するように寸法が与えられている。

内部毛細穴18は、一層大きな直径の管腔20と連結しその中へと続いている。該カニューレ12の連続した穴18及び管腔20は血液収集区域を構成する。それが管腔20を出るところの穴18は、血液廃棄室22内へと移行している。本発明の好ましい具体例では、血液廃棄室22は、レーヨン又はセルロース詰め綿等であってよい吸着材料24のような血液保持手段を含む。血液廃棄室22の開口末端26は、本発明の血液サンプリング装置10から空気が排出されることを許容する、液体を通さない、空気透過性の疎水性薄膜30をその頂部に嵌めてあるキャップ28によって閉じられている。適した薄膜材料は、約０８ミクロンの厚さを有するシート状のポリテトラフルオロエチレンである。

該管腔20に連結されてそれと液体連通しているのは第二の分岐又はポート32である。それは、90度を越えない内角34を有するように配置されている。該内角は好ましくは約60度である。穴36は穴18と連結し、そして寸法においてそれと一致する。ポート32は末端においてアダプターキャップ38(その頂部40に毛管ルアー

継手 42が連結

されている）によってシールされている。毛管ルアーは、血液が閉鎖された血液サンプリング装置から抜き取られる直前に取り外される保護キャップ 44によって、汚染から保護される。ポート 32とその穴 36は前に記述された血液収集区域の一部を形成する。使用の便宜のために、閉鎖された血液サンプリング装置はピストル握り把手 46と連結される。

血液収集区域は、血液廃棄室の液体容積よりも大きな液体容積を有する。もし、記述された閉鎖された血液サンプリング装置が新生児の血液サンプリングにおいて用いられるためであれば、血液収集区域の液体容積は 0 12ccであるかもしれず、そして血液廃棄室 22の液体容積は約 0 06ccであろう。

血液を抜き取ってサンプリングするための本発明の閉鎖された血液サンプリング装置の使用が図 2 中に図解されており、該図には皮下組織 52を突き通して挿入された静脈穿刺装置 50と連通した動脈 48を示している。静脈穿刺装置 50の首 54は注射部位 56を受け入れるよう適合させてある。慣用の注射部位がそのようなものとして使用されてよく、又は本発明の実施において用いられるのに適合させてよいが、該注射部位は好ましくは予めスリットを入れてある弾力性のある再シール可能な隔壁を有するタイプであることが望ましい。このタイプの注射部位は Baxter Hea1thcare Corporationから入手可能であり、そしてこれは Baxter Healthcare Corporationの登録商標である InterLinkという商標の下に販売される新生児 T 字形コネクタールアー継手である。

そのような予めスリットを入れてある、弾力性のある、再シール可能な注射部位及びそれらの製造の方法が米国特許 5 188 620中に

記述されており、その開示が参照によってここに導入される。この特許中に記述されている予めスリットを入れてある、弾力性のある、再シール可能な注射部位は鈍いカニューレを受け入れるように設計されている。米国特許 5 188 620中に詳しく述べられた注射部位に関係した他の一つの注射部位が米国特許 5 300 034中に記述されている。この特許も同じく、この発明の実施中で使用される好まし

い注射部位を記述するおびただしい数の刊行物及び参照文献を詳しく述べている。この特許及びその中に挙げられた刊行物も同じく参照によってここに導入される。

注射部位 56はＴ字形コネクター 58と連結され、Ｔ字形コネクター 58が今度は、雌のルアー継手 62を通じて静脈内ライン 64へと連結される微細穴チューブと連結される。注射部位 56の先端側末端は静脈穿刺装置 50の首 54へと連結されている。注射部位 56の根元側末端 66は、該注射部位中へぴったり嵌合するように寸法が与えられた、血液抜取りカニューレ 12を受け入れるよう適合させた、予めスリットを入れてある、弾力性のある、再シールする隔壁 68と連結されている。第二の枝又はポート 32中へと挿入されているのは、ツベルクリン血液吸引注射器のような慣用の注射器 70又は動脈血ガス損失抵抗性注射器である。

装置のカニューレ 12は、注射部位 56の隔壁 68を貫通して挿入され、そしてカニューレ 12の先端 14が静脈穿刺装置に隣接した注射部位中へと完全に挿入されるように配置されるであろう。そのように実施すると、実際のＴ字形ハウジングの残余の体積が血液吸引体積中から、測定可能な要素としては除かれるであろう。動脈圧が、血液をして毛細管作用を通じて該装置へと入りそして該装置を流れ登らせるであろう。血液が該装置の疎水性薄膜 30へと上昇するにつれて、空気が上流の疎水性の薄膜 30を通して散逸するであろう。該カテーテル中に最初に存在した元々の血液は、該装置中における保持及び最終的な廃棄のためにルアー継手分岐を通り越して押し上げられるであろう。該装置は、血液が満たされた管腔の視覚的確認が形成されるとすぐにＴ字形コネクターから引き抜かれるであろう。ガス抜き除去キャップ 44が分岐したルアー継手 42から除去され、そして動脈血サンプルを取り除くために吸引されるであろう注射器 70によって置き換えられるであろう。分岐の上流の残余血液体積が、その後の廃棄のために該装置中に残るであろう。

【図１】

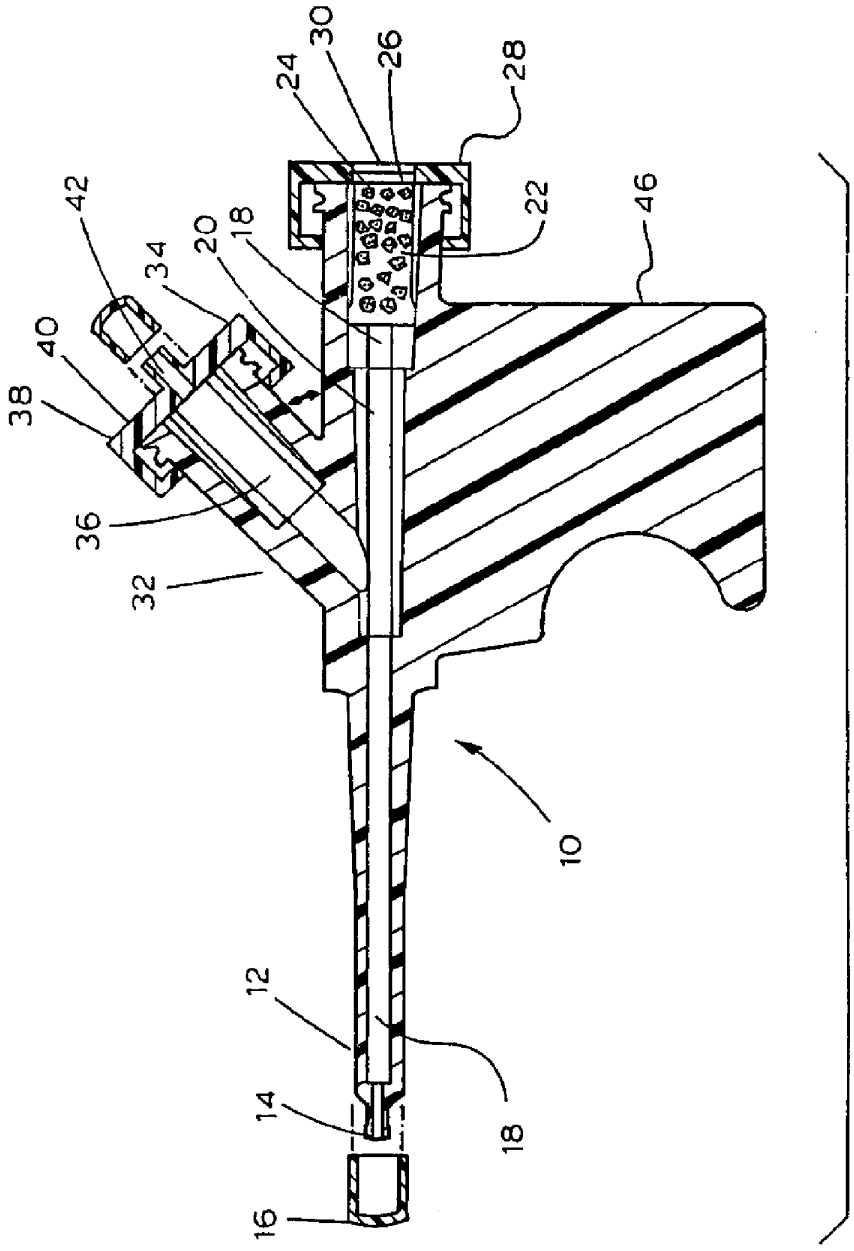


FIG. 1

【図２】

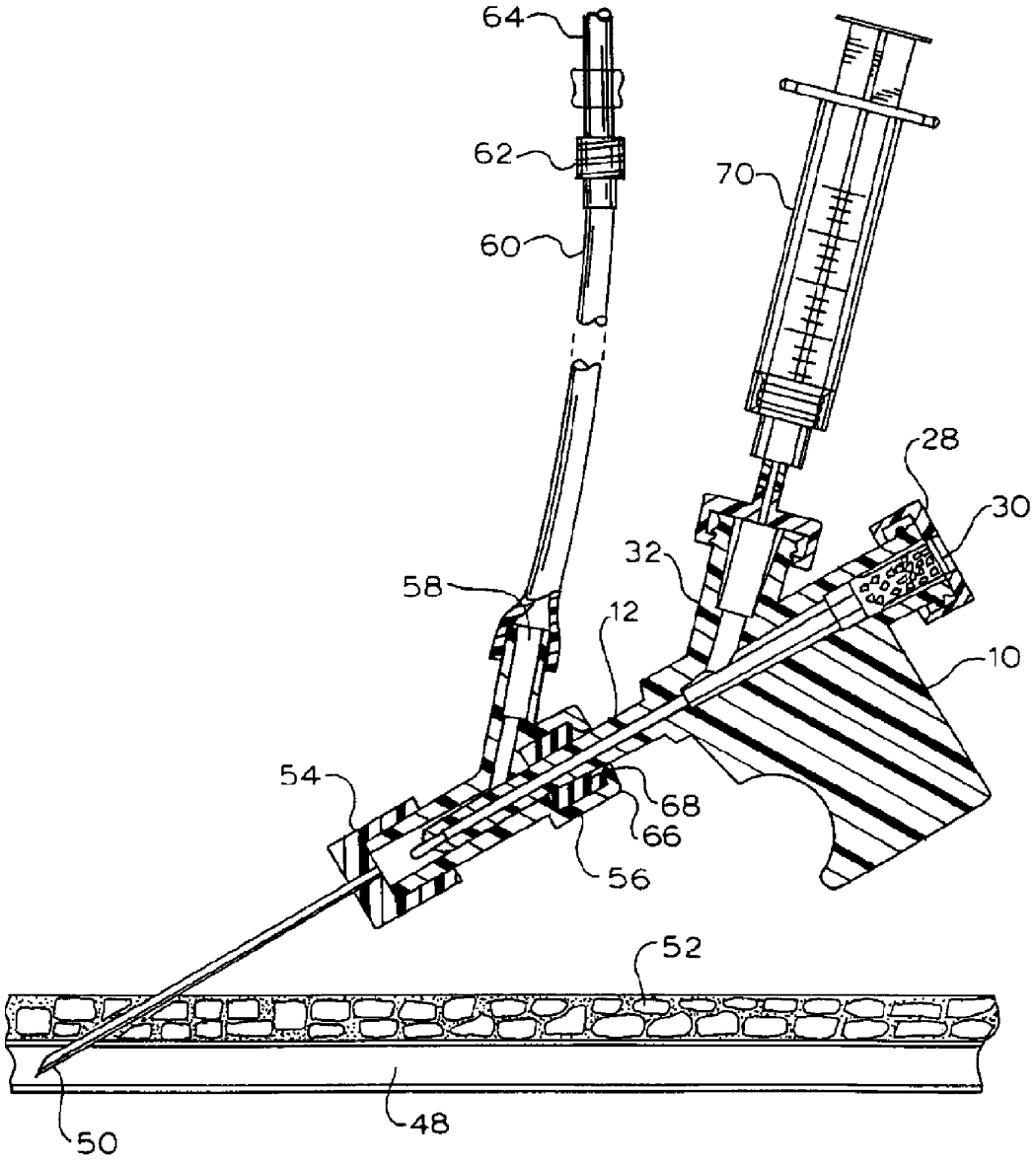


FIG. 2

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A 61M 5/00
US CL. : 604/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/122, 35, 125, 126, 128, 256, 258, 283, 284
128/ 760, 762, 767, 768

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 4,531,937 (Yates) 30 July 1985, See Entire Reference	1-7,9-15 --- 8,16

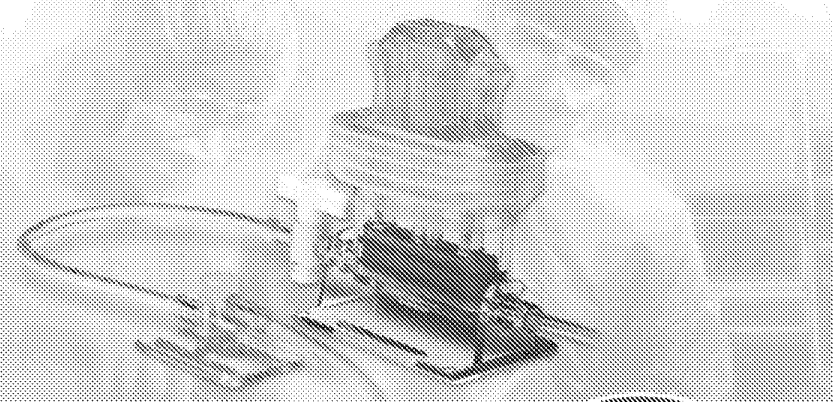
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

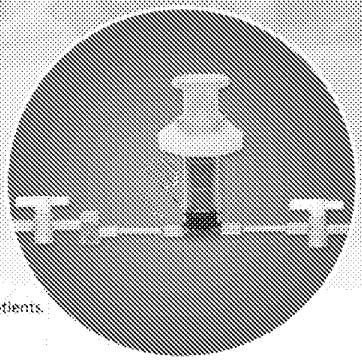
Date of the actual completion of the international search 08 DECEMBER 1995	Date of mailing of the international search report 04 JAN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No.	Authorized officer SAM RIMELL Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet)(July 1992)*

Conservation. Safety. Simplicity. Edwards VAMP and VAMP Jr. Systems.



VAMP System
Venous Arterial blood Management Protection System



VAMP Jr. System
for pediatric and neonatal patients

Edwards

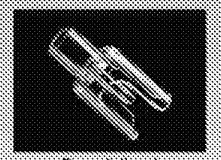


Figure 1 Luer-lok

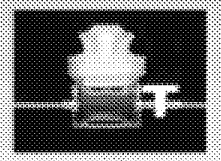


Figure 2 VAMP Reservoir

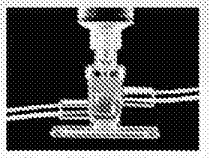


Figure 3 Z-site sampling port

VAMP Kits

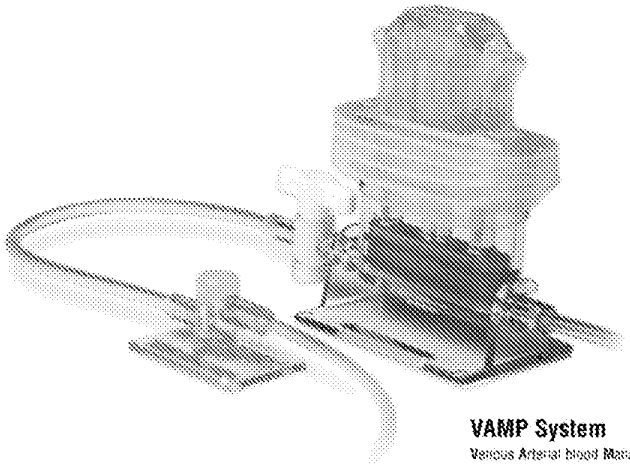
The closed blood sampling system that protects patient to the Edwards TruWave Disposable Pressure Transducer. The Edwards VAMP system provides the safest and easiest method of needleless blood sampling. The blunt cannula design (Figure 1) provides safety by eliminating the needlesticks associated with blood sampling.

It's the only system with the VAMP reservoir – a unique design that conserves blood and ensures consistent blood sampling (Figure 2).

Another unique design that enables the collection of undiluted samples while greatly reducing residual blood holding, is our Z-site sampling port (Figure 3). The VAMP system was designed with the benefits of a closed system in mind. From the self-sealing sampling port that replaces stopcocks to our patented reservoir and shut-off valve, we're dedicated to providing safe and convenient blood sampling for your patients.

The VAMP system is easy, safe, and convenient for your patient. And it works best with TruWave Disposable Pressure Transducers.

An Easy, Convenient System... An Accurate Sys



VAMP System

Venous Arterial blood Management Protection System

The safe way to perform pediatric and neonatal blood sampling.

Because it's not the right size for pediatric and neonatal care, the Edwards VAMP Jr. system makes blood sampling safer and safer for you and your special patients. Completely closed, which may provide greater protection against nosocomial infections, the VAMP Jr. system reduces the loss of patient blood while providing consistent clearing volumes, safer reinfusion and unaltered accurate blood samples. The needleless system also reduces the threat of needlesticks.

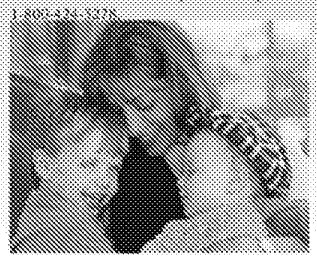
A unique in-line reservoir puts safety first.

Blood conservation and consistent sampling are critical for optimal pediatric and neonatal care. The VAMP Jr. reservoir is designed with "cc" markings to help you select the appropriate clearing volumes based on the size of your patient and the samples required. And since the volume is held in the in-line reservoir and not set aside in a syringe to be reinfused later, the potential for contamination may be reduced. After sampling, the plunger is pushed closed, wiping the walls clean and safely reinfusing all the blood to the patient. Plus, VAMP Jr.'s special contamination hood and one way in line shut-off valves may reduce the risk of sepsis from touch and/or airborne contaminants.

The VAMP Jr. system fits the special needs of your special patients.

The VAMP Jr. system is designed to require decreased volume over a smaller incision for more accurate sampling and flushing in pediatric and neonatal patients. For the added convenience of accurate pressure monitoring, the VAMP Jr. system is available preassembled with TruWave disposable pressure transducers (DPTs) in kit configurations to meet the specific needs of your specific patients.

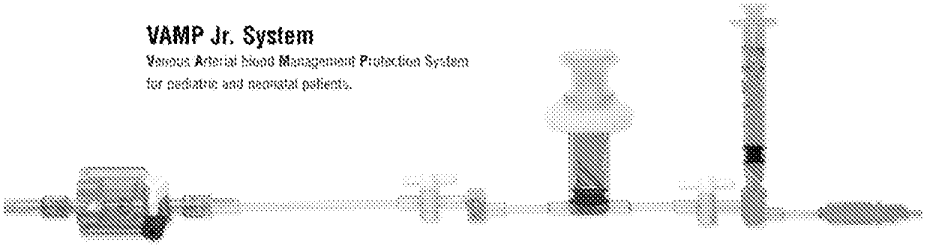
To learn more about the VAMP Jr. system, contact your Edwards Lifesciences Corporation Representative at 1-800-424-3278.



Item.. And with VAMP Kits, A Complete System

VAMP Jr. System

Venous Arterial Blood Management Protection System for pediatric and neonatal patients.



VAMP System Venous Arterial blood Management Protection

TruWave/VAMP Combination Kits	Case Qty.	Model No.
30" VAMP System with Arm-mount Reservoir	10	PXVMP130
60" VAMP System with Arm-mount Reservoir	10	PXVMP160
72" VAMP System with Arm-mount Reservoir	10	PXVMP172
84" VAMP System with Arm-mount Reservoir	10	PXVMP184
60" VAMP System with Pole-mount Reservoir	10	PXVMP260
72" VAMP System with Pole-mount Reservoir	10	PXVMP272
84" VAMP System with Pole-mount Reservoir	10	PXVMP284
60" VAMP System with Arm-mount Reservoir on the arterial line with: • Two TruWave Disposable Pressure Transducers with two 3 ml/hr flush devices • Bifurcated IV set (manifold) • One set of 48" and 12" pressure tubing • Three 3-way stopcocks	10	PXVMP2321
60" VAMP System with Pole-mount Reservoir on the arterial line with: • Two TruWave Disposable Pressure Transducers with two 3 ml/hr flush devices • Bifurcated IV set (manifold) • One set of 48" and 12" pressure tubing • Three 3-way stopcocks	10	PXVMP2322

Please contact your local sales representative for VAMP® combination kit information and model numbers.

VAMP Jr. System

VAMP Jr.	VAMP Jr./DPT Combo Kits
VMP306 3" proximal, 6" distal for neonatal application	VMP306PX 3cc TruWave DPT with 3" proximal, 6" distal VAMP Jr. for neonatal application
VMP408 3" proximal, 3" distal for pediatric application	VMP408PX 3cc TruWave DPT with 3" proximal, 3" distal VAMP Jr. for pediatric application
VMP428 12" proximal, 16" distal for pediatric application	VMP428PX 3cc TruWave DPT with 12" proximal, 16" distal VAMP Jr. for pediatric application
VMP448 19" proximal, 29" distal for pediatric application	VMP448PX 3cc TruWave DPT with 19" proximal, 29" distal VAMP Jr. for pediatric application

CE

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Caution: Rx only. For complete product warnings, contraindications, precautions, and instructions for use, consult the Instructions for Use.

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Bacterial Contamination of Blood Components: Risks, Strategies, and Regulation

Joint ASH and AABB Educational Session in Transfusion Medicine

*Christopher D. Hillyer, Cassandra D. Josephson, Morris A. Blajchman, Jaroslav G. Vostal, Jay S. Epstein, and Jesse L. Goodman**

Downloaded from http://ashpublications.org/hematology/article-pdf/2003/1/575/1713810/575_589a.pdf by guest on 08 March 2023

Bacterial contamination of transfusion products, especially platelets, is a longstanding problem that has been partially controlled through modern phlebotomy practices, refrigeration of red cells, freezing of plasma and improved materials for transfusion product collection and storage. Bacterial contamination of platelet products has been acknowledged as the most frequent infectious risk from transfusion occurring in approximately 1 of 2,000-3,000 whole-blood derived, random donor platelets, and apheresis-derived, single donor platelets. In the US, bacterial contamination is considered the second most common cause of death overall from transfusion (after clerical errors) with mortality rates ranging from 1:20,000 to 1:85,000 donor exposures. Estimates of severe morbidity and mortality range from 100 to 150 transfused individuals each year.

Concern over the magnitude and clinical relevance of this issue culminated in an open letter calling for the "blood collection community to immediately initiate a program for detecting the presence of bacteria in units of platelets." Thereafter, the American Association of Blood Banks (AABB) proposed new standards to help mitigate transfusion of units that were contaminated with bacteria. Adopted with a final implementation date of March 1, 2004, the AABB Standard reads "*The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components.*"

This Joint ASH and AABB Educational Session reviews the risks, testing strategies, and regulatory approaches regarding bacterial contamination of blood components to aid in preparing practitioners of hematology and transfusion medicine in understanding the background and clinical relevance of this clinically important issue and in considering the approaches currently available for its mitigation, as well as their implementation.

In this chapter, Drs. Hillyer and Josephson review the background and significance of bacterial contamination, as well as address the definitions, conceptions and limitations of the terms *risk, safe* and *safety*. They then describe current transfusion risks including non-infectious serious hazards of transfusion, and current and emerging viral risks. In the body of the text, Dr. Blajchman reviews the prevalence of bacterial contamination in cellular blood components in detail with current references to a variety of important studies. He then describes the signs and symptoms of transfusion-associated sepsis and the sources of the bacterial contamination for cellular blood products including donor bacteremia, and contamination during whole blood collection and of the collection pack. This is followed by strategies to decrease the transfusion-associated morbidity/mortality risk of contaminated cellular blood products

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Morris A. Blajchman, MD, FRCP(C), McMaster University and Canadian Blood Services, Hamilton, Ontario, Canada
Jaroslav G. Vostal, MD, PhD, Center for Biologics Evaluation and Research, FDA
Jay S. Epstein, MD, Center for Biologics Evaluation and Research, FDA
Jesse L. Goodman, MD, MPH, Center for Biologics Evaluation and Research, FDA

including improving donor skin disinfection, removal of first aliquot of donor blood, pre-transfusion detection of bacteria, reducing recipient exposure, and pathogen reduction/inactivation. In the final sections, Drs. Vostal, Epstein and Goodman describe the regulations and regulatory approaches critical to the appropriate implementation of a bacterial contamination screening and limitation program including their and/or the FDA's input on prevention of bacterial contamination, bacterial proliferation, and detection of bacteria in transfusion products. This is followed by a discussion of sampling strategy for detection of bacteria in a transfusion product, as well as the current approval process for bacterial detection devices, trials recommended under "actual clinical use" conditions, pathogen reduction technologies, and bacterial detection and the extension of platelet storage.

Bacterial contamination of transfusion products, especially platelets, is a longstanding problem that has been partially controlled through modern phlebotomy practices, refrigeration of red cells, freezing of plasma, and improved materials for transfusion product collection and storage. Indeed, bacterial contamination of platelet products has been acknowledged as the most frequent *infectious risk* from transfusion occurring in approximately 1 of 2,000–3,000 whole-blood derived, random donor platelets (hereafter RDP), and apheresis-derived, single donor platelets (hereafter SDP)[1-4] (see below). In the US, bacterial contamination is considered the second most common cause of death overall from transfusion (after clerical errors) with mortality rates for platelet-related sepsis ranging from 1:20,000 to 1:85,000 donor exposures.[5] Estimates of severe morbidity and mortality range from 100 to 150 transfused individuals each year.[6,7]

To address this problem, the US Food and Drug Administration (FDA) has sponsored scientific workshops to highlight and clarify relevant issues and to promote the development of technologic interventions.[8-10] Additionally, the Centers for Disease Control and Prevention (CDC) conducted a nationwide surveillance study on bacterial contamination in blood products.[11] Many publications (detailed later in this chapter) have added important data attempting to determine and define the true clinical effect of bacterial contamination of blood components, and a similar number of publications have offered data as to the ability of a variety of methods to detect and limit this contamination.

Concern over the magnitude and clinical relevance of this issue culminated in an open letter calling for the "blood collection community to immediately initiate a program for detecting the presence of bacteria in units of platelets" (see http://www.cbbsweb.org/bacterial risk.pdf). Thereafter, the American Association of Blood Banks (AABB), after publication of a number of Association Bulletins (see AB 96-06[3] at www.AABB.org), proposed new standards (December 2002) to help mitigate transfusion of units that were contaminated with bacteria. Adopted with a final implementation date of March 1, 2004, AABB Standard 5.1.5.1. now reads:

> **5.1.5.1** *The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components. Standard 5.6.2 applies. [Arm Prep]*

Thus, this Joint ASH and AABB Educational Session was conceived to review the risks, testing strategies, and regulatory approaches regarding bacterial contamination of blood components; to aid in preparing practitioners of hematology and transfusion medicine in understanding the background and clinical relevance of this important issue; and to consider the approaches currently available for its mitigation as well as their implementation.

Background and Significance

Whereas the risk of transfusion related transmission of viral diseases such as human immunodeficiency virus (HIV) and hepatitis has steadily decreased over the last 40 years, the risk of transmission of bacteria has remained about the same. Thus, due to our success with viral pathogens, bacterial contamination now has the dubious distinction of being the most common infectious risk from transfusion and has become a matter of increasing concern and attention.[12,13] Recent studies of platelets have suggested a bacterial contamination rate of about 1 per 1–3,000 units, clinical sepsis in about 1 per 20,000 transfusions and related fatality in about 1 per 60,000 transfusions[5,14,15] (reviewed in detail below). The fatality risk from bacterially contaminated red blood cells (RBCs) is much lower, about 1 per 500,000.[15]

Despite this longstanding, persistent infectious risk of transfusion, it has been tolerated by some as an "acceptable risk." However, with the significant risk reduction of transfusion-transmitted diseases attributable to viruses such as HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV), the magnitude and relative importance of platelet-induced sepsis has moved to the forefront of blood supply safety.[16] In order to appreci-

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ate the significance of the relative importance of bacterial contamination of platelets, a perspective on the safety of the nation's blood supply is necessary.

Risk

There are approximately 30 million units of blood and blood products transfused each year in the US, and perhaps an equal number internationally. The American public, the medical profession, and the government hold the transfusion of these units to the highest standards of safety.[17] Indeed, the blood supply in the US has been described as "safer than ever relative to known risks," however, "the usual notions of safety do not necessarily apply where transfusion is concerned."[17] The CDC, the AABB, and the American Red Cross[18] have echoed these statements.

In the early 1980s, the incidence of transfusion transmitted (TT) HIV was greater than 1 case per 1,000 units in some locales, whereas the current incidence of TT-HIV is less than 1 case per 2 million screened and tested units;[19] some authorities have posited that this risk may actually be closer to 1 in 5 million screened and tested units especially if there is widespread implementation of "single unit" nucleic acid testing (NAT). Similar improvements have been made for HBV and HCV, two TT-viruses carrying significant morbidity and mortality (**Figure 1**).[20] Despite these improvements, many experts argue that the potential US blood recipient demands a "zero-risk" blood supply. Unfortunately, even for HIV in 2002, this goal has not been achieved as there were two reported cases of persons allegedly contracting HIV through transfusion and subsequently suing the blood supplier. In one case, a $100 million dollar negligence lawsuit has been filed. Additionally, a number of "emerging pathogens" still exist, as does the transfusion transmission of pathogens for which testing is not required. Thus, how safe the blood supply is becomes difficult to quantitate and by some criteria the risks to the blood recipient would be considered "very low" to "negligible" (see **Table 1**).[21]

Safe and safety

The word "safe" has been defined as free from "harm or risk" or "secure from danger, harm, or evil." However, safety is a more subjective term emanating from one's understanding and perspective, as well as the amount of control one has in determining the chance of the adverse outcome occurring. Thus, while the risk of dying in a car accident significantly exceeds the risk of dying from TT-infectious disease, the latter has elements of increased dread and less control and therefore has an increasingly fear-filled association. The Paling Perspective Scale[22] provides several examples of risks with which the public is "comfortable" (see **Figure 2**) and allows comparison to the risk of TT-HIV (< 1:2M) and bacterial contamination (see discussion of risk estimates below). Indeed, research has shown that patients, and the majority of the population, have a very poor understanding of risk. It is worthwhile to compare the risk of death from influenza, cigarette smoking, motorcycle riding, or lightning with the risk of dying or acquiring variant Creutzfeldt-Jakob disease (vCJD) though there

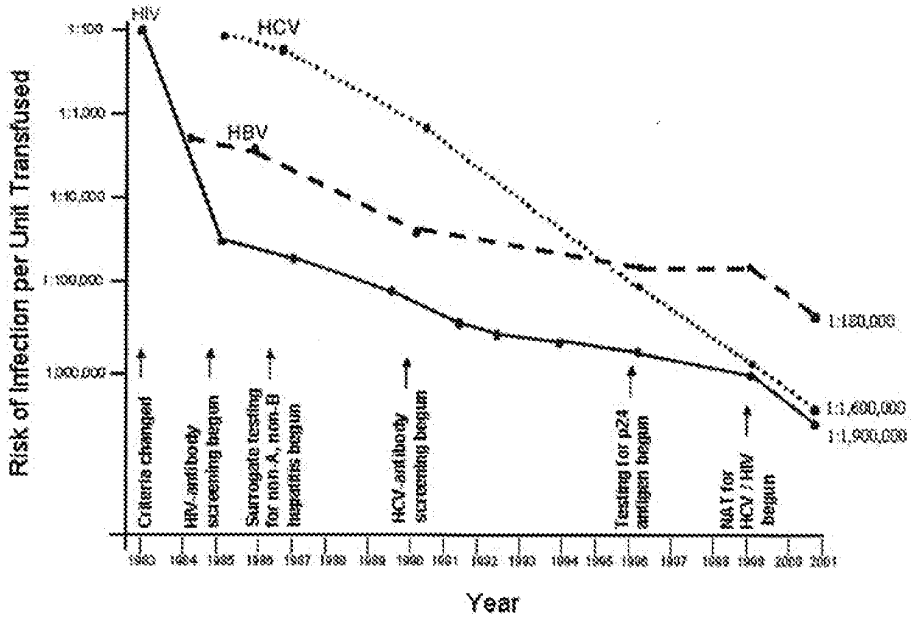


Figure 1. New test implementation and declining risk of viral infections from transfusion.[20]

Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; NAT, nucleic acid testing.

Modified by M.P. Busch from table in AuBuchon JP, Birkmeyer JD, Busch MP. Safety of the Blood Supply in the United States: Opportunities and Controversies. Ann Intern Med. 1997;127:904-909 and used with permission.

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Table 1. Risk of an individual dying (D) in 1 year or developing an adverse response (A).[21]

Term Used	Risk Range	Example	Risk Estimate
High	> 1:100	(A) Transmission to susceptible household contacts of measles and chickenpox	1:1–1:2
		(A) Transmission of HIV from mother to child (Europe)	1:6
Moderate	1:100–1:1,000	(D) Smoking 10 cigarettes per day	1:200
		(D) All natural causes, age 40	1:850
Low	1:1,000–1:10,000	(D) All kinds of violence	1:3,300
		(D) Influenza	1:5,000
		(D) Accident on road	1:8,000
Very low	1:10,000–1:100,000	(D) Leukemia	1:12,000
		(D) Playing soccer	1:25,000
		(D) Accident at work	1:43,000
Minimal	1:100,000–1:1,000,000	(D) Accident on railway	1:500,000
Negligible	< 1:1,000,000	(D) Hit by lightning	1:1,000,000
		(D) Release of radiation by nuclear power station	1:10,000,000

have been no known TT-cases of vCJD, although animal models support the possibility that vCJD may be transfusion-transmitted.[23]

Transfusion risks

It is vital to consider the other risks of transfusion such as those termed non-infectious serious hazards of transfusion (often termed NiSHOTs; see **Table 2**) which dramatically outweigh the residual risk of TT-infectious diseases.[24] However, the agents that are known to be transfusion transmitted, and those that "might be" are described in **Table 3**, for it is only upon this backdrop that a decision can be made on the relative value of new technologies and their ability to abrogate the agents,

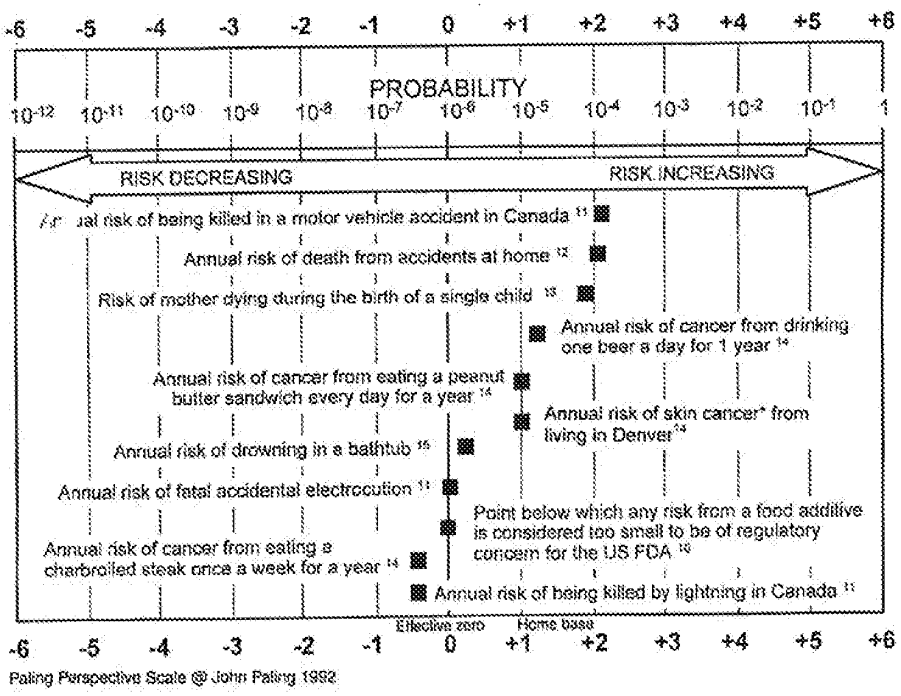


Figure 2. Risks with which the public is comfortable.

The numbers denoting references in this figure are those from the primary article and are not notations of the references found at the conclusion of this chapter.

Abbreviations: FDA, Food and Drug Administration.[22]

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Table 2. Noninfectious serious hazards of transfusion (NiSHOTs).[24]

- Mistransfusion and ABO/Rh incompatible transfusion
- Cardiopulmonary toxicity
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated graft-versus-host disease (TA-GVHD)
- Metabolic derangements in pediatric and massive transfusion
- Undertransfusion

Table 4. Criteria for transfusion transmission of viruses and other infectious agents.[25]

1. There must be an asymptomatic, viremic phase in the blood donor.
2. Virus viability must be maintained during storage.
3. There must be a seronegative recipient population.
4. The agent must be capable of inducing disease.

including bacterial contamination of platelet products.

Typically, four elements are required for an infectious disease–causing agent to be transmitted by transfusion and the criteria are listed in **Table 4**.[25] However, despite many possible agents that can be transmitted by transfusion, units are regularly tested only for HIV, HCV, HBV, HTLV, and *Treponema pallidum*. Donor demographics may bring changes in risk level of transfusion-transmitted agents and affect future choices for routine screening. For example, the incidence of malaria and Chagas disease seems to be rising due to increasing travel to endemic areas, climate changes, and immigration.

Clinical relevance

The unique aspect of most bacterial species when compared to viral pathogens is that they can readily proliferate in the nutrient-rich blood product environment during storage. This is particularly true in platelet products that are stored at room temperature, rather than in the cold. It is estimated that the level of contamination at the time of collection is generally relatively low, probably on the order of 1–10 colony forming units/mL or less.[26] Once the product is contaminated, the inoculated bacterial seed can proliferate within hours to reach levels of 10^6/mL or greater. Such quantities of bacteria infused with the transfusion product over a short period of time can cause bacteremia that may progress to sepsis and death. The outcome of a contaminated transfusion is highly dependent on the amount of bacteria transfused, the type of bacteria and its pathogenicity for humans, the rate of transfusion, and the clinical status of the recipient. Immunosuppressed patients and older individuals with poor nutritional status will be the most susceptible population. However, even healthy individuals can have a rapidly fatal outcome when transfused with a large load of endotoxin-producing Gram-negative bacteria.

Thus, there is significant concern about, and demand for, a "safe" or "safer" blood supply in order to provide the best and safest patient care. This, in turn, has the public, government, and blood suppliers' attention keenly focused on preventing bacterial contamination of platelets and subsequent sepsis due to platelet transfusions. This risk has become "unacceptable" in a climate where the blood supply remains "the safest that it has ever been."

Table 3. Agents and their likelihood of transfusion transmission in qualitative terms.

Agent	Transfusion Transmission
Parasites	
Malaria	Rare cases
Babesia	Occasional cases, endemic
T. cruzii	Occasional cases, US
T. gondii	Rare cases
Leishmania	Rare cases (< 5 worldwide)
Bacteria	
Contaminants	Approximately 1:3,000 platelet units
Specific Agents	
T. pallidum	Rare cases
B. burgdorferi	No known cases
E. chaffeensis	No known cases
E. cytophagophilia	One possible case
R. rickettsii	One reported case
Viruses	
HIV	Rare cases
HCV	Rare cases
HBV	Occasional cases
HTLV	Rare cases
CMV	Occurs, threat to specific pts
EBV	Occurs, threat to specific pts
B19	Occurs, threat to specific pts
HAV	Rare cases
HGV	Occurs, not a threat to pts
TTV	Occurs, not a threat to pts
Sen-V	Occurs, not a threat to pts
HHV-8	No known cases
WNV	Several cases reported
Enterovirus	Known donor viremia
Prions	
CJD	No known cases
vCJD	No known cases*

* Animal models support the possibility that this agent may be able to be transmitted by transfusion

Abbreviations: HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HTLV, human T-cell lymphotrophic virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HGV, hepatitis G virus; TTV, transfusion-transmitted virus; HHV-8, human herpes virus–8; WNV, West Nile virus; CJD, Creutzfeld-Jakob disease; vCJD, variant CJD.

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Table 5. Summary of the available prospective studies evaluating the prevalence of bacterial contamination in whole blood–derived platelets, apheresis platelets, and red blood cell units.

Blood Produce Type	Reference	Positives per Number of Units Tested	Contamination Prevalence per 100,000 Units
WB-plts	Morrow et al[32]	6 per 74,598	8
WB-plts	Barrett et al[33]	1 per 4,272	23
WB-plts	Yomtovian et al[34]	6 per 15,705	38
WB-plts	Chiu et al[35]	10 per 21,503	46
WB-plts	Blajchman et al[36]	16 per 31,610	51
WB-plts	Leiby et al[37]	4 per 4,995	80
WB-plts	Blajchman et al[38]	7 per 10,065	70
A-plts	Morrow et al[32]	1 per 9,519	5
A-plts	Blajchman et al[31]	14 per 6,055	230
A-plts	Barrett et al[33]	5 per 17,928	28
A-plts	Yomtovian et al[34]	0 per 2,476	0
A-plts	Dzieczkowski et al[39]	1 per 5,197	19
A-plts	Aubuchon et al[40]	1 per 2,678	37
RBCs	Barrett et al[33]	1 per 31,385	3
RBCs	Dzieczkowski et al[39]	1 per 7,080	0
Overall	*n* = 15	89 per 274,379	32.4*

* 95% confidence intervals 25.6 to 39.1

Abbreviations: A-plts, apheresis platelets; WB-plts, whole blood–derived platelets; RBCs, red blood cells; *n*, number of studies.

Prevalence of Bacterial Contamination in Cellular Blood Components

The contamination of RBCs and platelets with bacteria occurs relatively frequently.[12,15,27-31] However, the available prevalence data vary considerably from one study to the next. The data from the available prospective studies evaluating frequency of bacterial contamination of blood components are summarized in **Table 5**. The mean prevalence of bacterial contamination in whole blood–derived, RDP platelets is 33.9 per 100,000 units and for apheresis-derived, SDP platelet units is 51.0 per 100,000 units. For RBCs it is 2.6 per 100,000 units. The overall cellular blood product contamination prevalence from all of the data shown in **Table 5** is 32.4 per 100,000 units. This translates into an approximate rate of 1 bacterially contaminated cellular blood product unit per 3,000 cellular blood product units released.

In contradistinction to the available data on the bacterial contamination of cellular blood products (RBCs and platelets), the frequency of clinically apparent septic transfusion events or reactions due to such contaminated products is considerably lower. The available data on the prevalence of transfusion-associated septic events is summarized in **Table 6**. It should be noted that these summaries report only the more severe or potentially life threatening septic reactions. It is likely, therefore, that these reports represent only one end of the clinical spectrum of transfusion-associated septic transfusion reactions. Moreover, it is very likely that even severe and even fatal septic transfusion reactions go unrecognized as being transfusion-associated. Thus, the actual prevalence of septic transfusion reactions may be considerably higher than reported, due to the observational bias that occurs. For all of these reasons, it has been very difficult to determine the true morbidity and mortality risk of transfusing bacterially contaminated cellular blood products.

The variation in the reported prevalence of clinical events is shown clearly in **Table 6**. This table enumerates the risk of septic clinical events per million units transfused from 3 published studies: (1) the BaCon Study from the US, (2) the Hémovigilance system in France, and (3) the Johns Hopkins Hospital, which reports a 10-year follow-up of platelet transfusion episodes detected in that institution.[11,41,5] From the data in **Table 6**, it is impossible to define a specific prevalence of clinical transfusion-associated septic events, except to say that they probably occur with a frequency of 1 per approximately 25,000 platelet units transfused, and 1 per approximately 250,000 RBC units transfused. This latter estimate excludes the data from the BaCon study (1:5 million), as this study was likely limited by an underestimation bias.[11]

It is important to note that transfusion-associated septic reactions due to bacterially contaminated cellular blood products often go unrecognized as such, because of the high frequency of febrile non-hemolytic transfusion reactions

Table 6. Prevalence of transfusion-associated septic reactions per million (10^6) apheresis platelets, whole blood–derived platelets, and red blood cell units transfused.[17-19]

Study	Country	A-Plts	WB-Plts	Case Fatality Rate - Plts	RBCs	Case Fatality Rate - RBCs
Perez et al[41]	France	31.8	71.8	31.3%	5.8	24.0%
Kuehnert et al[11]	US	9.9	10.6	20.7%	0.2	60.0%
Ness et al[5]	US	74.5	67.0	17.4%	ND	ND

Abbreviations: A-plts; apheresis platelets; WB-plts, whole blood–derived platelets; RBCs, red blood cells; ND, not determined.

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(FNHTR) that occur following the transfusion of cellular blood products, particularly following platelet transfusions. For platelets, the FNHTR rate may be as high as 15% per unit transfused, whereas for RBCs the FNHTR rate is less than 1% per RBC unit transfused. As the symptoms of septic transfusion reactions often mimic those occurring with FNHTRs, many apparently mild septic transfusion reactions may not be recognized as such. Moreover, most of the organisms isolated from contaminated platelet and RBC units tend to be skin-associated organisms (i.e., Gram-positive cocci), which are not usually implicated in RBC-associated septic transfusion reactions, and are often considered contaminants related to procedure of taking the sample for culture (i.e., a false positive).

Signs and Symptoms of Transfusion-Associated Sepsis

The transfusion of a contaminated cellular blood product unit may be associated with variable signs and symptoms. As indicated above, not all contaminated blood products cause symptoms in the recipient; in fact, it appears that many do not.[28] The initial signs and symptoms, when they occur, include fever and chills, which usually begin shortly after (within 2 hours) the start of the transfusion. Subsequent signs may include: hypotension, nausea, vomiting, diarrhea, oliguria, and shock. Other potential presenting symptoms include: respiratory symptoms (dyspnea, wheezing, and/or cough) and bleeding due to the consequence of endotoxin-induced disseminated intravascular coagulation. It is important to note that a majority of septic transfusion reactions associated with contaminated RBCs usually occur with units that have been stored for more than 21 days, whereas septic reactions associated with contaminated platelets usually occur with units that have been stored for 3 days or more.[28]

The clinical severity of a transfusion-associated septic reaction can vary considerably, depending on: (1) the species of bacteria present in the blood product unit, with Gram-negative organisms tending to cause more severe reactions, due to the presence of endotoxin often elaborated by such organisms; (2) the total number of bacteria infused or present in the cellular blood product unit infused to a recipient; (3) the rate of propagation of the bacteria present; and (4) recipient characteristics, such as underlying disease, leukocyte count, the status of the immune system, and whether the recipient is receiving concomitant antibiotic therapy.

Sources of the Bacterial Contamination for Cellular Blood Products

Possible mechanisms of the bacterial contamination of blood components include: donor bacteremia, contamination during the whole blood collection procedure, contamination of the collection pack, and contamination during the blood processing procedure.

Donor bacteremia

Blood donors with an asymptomatic bacteremia or who are in the recovery phase of a bacterial infection, may have transient bacteremic episodes and still qualify as a blood donor. Approximately 30 cases of *Yersinia enterocolitica* sepsis associated with RBC transfusion have been reported in the literature. This Gram-negative bacillus may cause enterocolitis, characterized by diarrhea, low-grade fever, and abdominal pain in the donor. Symptoms may be very mild and asymptomatic cases have been documented. In cases of transfusion-associated *Yersinia enterocolitica* septicemia reported to the CDC, approximately 75% of the implicated blood donors recalled having had diarrhea in the days preceding or following their blood donation, on retrospective questioning.[42] Transfusion-associated *Yersinia enterocolitica* sepsis varies markedly from country to country, with an estimated incidence of 1 per 65,000 transfusions in New Zealand to 1 per 500,000 transfusions in the US.[43,44] It is important to note that *Yersinia*-related sepsis is very episodic. Thus, over longer time intervals, the rates in these two countries might be different.

Bacteremia of short duration may also occur following dental manipulation such as tooth extraction, the use of gum irrigation devices, and even tooth brushing. A case of transfusion-associated *Staphylococcus aureus* platelet contamination has been documented, likely the result of a bacteremia in a blood donor who had undergone the repair of a tooth 3 hours before the donation.[45]

Contamination during whole blood collection

Contamination at the time of blood collection is the major cause of bacterial contamination of platelet units. The majority of organisms present in both culture studies and case reports of platelet-associated sepsis is usually normal skin flora as it may be virtually impossible to totally decontaminate human skin. Blood culture results show an incidence of positive cultures, ranging from 2% to 6% after the cleansing of the skin.[46] In addition, it has been postulated that a small core of skin may enter the phlebotomy needle at the time of donation and that viable bacteria remain associated with the deep layers of skin, in spite of adequate skin disinfection.[47] In the presence of a scarred phlebotomy site, surface cultures may be negative, while blood cultures are positive.[48] Organisms not part of the normal skin flora may colonize on the skin and be associated with a septic transfusion reaction. A recent report of a fatal reaction due to *Clostridium perfringens* was linked to a

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donor who frequently changed his infant children's diapers. This organism, as well as other species, normally part of fecal flora, grew in arm swab cultures from the implicated donor.[49] Although not linked to episodes of bacterial contamination of blood products, skin disinfection materials including swab sticks containing iodine or alcohol have been reported to be contaminated by various bacterial species.[28]

Contamination of the collection pack

Leaky seals, damaged tubing, or micro-punctures in collection bags have been linked to episodes of bacterial sepsis.[50] Regularly, blood packs used to collect donor blood have been found to have micro-punctures, possibly leading to the bacterial contamination of a cellular blood product.[28] Moreover, it has been reported that blood packs in the absence of any defects may be heavily contaminated. A report published in 1999 reported 6 patients who developed septicemia with *Serratia marcescens*, following transfusions with red cells or platelets.[51] This outbreak was traced to the heavy contamination of the exterior of blood packs. Upon investigation, 0.73% of blood bags from the same lot of packs grew the same ribotype of *Serratia marcescens*. It was postulated that the bacteria probably entered the blood bag at the time of blood donation, either by suction into the needle or due to contamination of the phlebotomist's hands and subsequently the donor's skin.[51]

Strategies to Decrease the Transfusion-Associated Morbidity/Mortality Risk of Contaminated Cellular Blood Products

A variety of strategies have evolved in recent years in an attempt to decrease the morbidity and mortality risk associated with transfusion-associated bacteremic and septic episodes. These measures are aimed at reducing the risk of the transfusion of cellular blood product units that are contaminated with bacteria by: (1) reducing recipient exposure; (2) avoiding contamination (i.e., improved donor screening or better skin disinfection); (3) optimizing blood component processing and storage; and (4) implementing tests and procedures that can be used to detect the presence of bacteria in blood product units.[28] These approaches are summarized in **Table 7**.

Improving donor skin disinfection

Because most of the bacteria isolated from contaminated blood products are normal skin flora, optimal disinfection of donor venesection sites may significantly reduce the bacterial contamination of blood products.[52,53] Recent studies exploring blood culture contamination rates of blood products have demonstrated that both the quality of the antiseptic used and/or the mode of application of the antiseptic can influence the efficacy of skin disinfection. Thus, one possibility of reducing the prevalence of blood product bacterial contamination might be to improve donor skin disinfection.

Removal of first aliquot of donor blood

Even if skin disinfection is optimal, bacteria may be introduced into the blood container by means of a skin core, which is often taken inadvertently when the blood collection needle enters the skin.[31] This has been reported to occur in approximately 65% of all venepunctures.[47] Recently, studies have suggested that when a needle tip is contaminated, the majority of the contaminating bacteria can be detected in the first few millimeters of blood passing through the venepuncture needle. Several recent studies suggest that the diversion of the initial 15 to 30 mL of whole blood from the main container might be associated with reduced risk of bacterial contamination.[54-56] Several blood bag manufacturers have developed plastic software to accommodate such an option. Several countries, including Canada, have recently introduced this intervention to try to reduce the rate of transfusion-associated sepsis.

Pretransfusion detection of bacteria

The pretransfusion detection of bacteria is an important potential method to reduce the risk of transfusion-associated bacteremia and septic reactions. However, no single

Table 7. Proposed strategies to reduce transfusion-associated septic risk.

A. Reducing risk of blood product contamination:
   1. Improved donor screening.
   2. Improved venepuncture site disinfection.
   3. Removal of first aliquot of donor blood.

B. Optimizing blood component processing and storage:
   1. Optimize storage temperature.
   2. Limit storage time.
   3. Universal leukocyte reduction.

C. Reduce recipient exposure to blood donors:
   1. Optimize transfusion indications.
   2. Reduce transfusion triggers for RBCs and platelets.
   3. Increase use of apheresis-derived products.

D. Pretransfusion bacterial detection:
   1. Visual inspection of components before issue.
   2. Direct staining for bacteria.
   3. Bacterial ribosomal assays.
   4. Assays for bacterial endotoxin.
   5. NAT for bacterial DNA.
   6. Measure CO_2 production by bacteria.
   7. Measure O_2 consumption by bacteria.
   8. Direct bacterial culture (manual or automated).

E. Implement pathogen reduction methodology when available.

Abbreviations: NAT, nucleic acid test; RBCs, red blood cell units.

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currently available laboratory technique is ideal.[15] Pretransfusion detection of bacteria is much more complex than traditional transmissible disease testing, because the amount of bacteria present in a particular cellular blood component usually changes over time. Moreover, because the initial inoculum is usually very small (less than 10 organisms per mL) even a very sensitive technique will miss some contaminated units, if the testing is performed very soon after blood collection.[15]

Automated blood culture methods are being used currently in some European and US centers to test buffy-coat platelets or apheresis platelet concentrates for the presence of bacterial contamination. Because of the larger volume of these products, a 10-mL sample can be used for bacterial culture, substantially improving the sensitivity of detection. Various protocols are in use to culture platelet units: this can be done either shortly after component production, or only for platelet units that have not been transfused by day 3 of storage. A quarantine period of 24–48 hours after inoculation into a culture tube is used in some European centers, prior to issuing such platelet units. In several European countries, the regulatory authorities have accepted the extension of the platelet shelf life to 7 days, for platelet units on which bacterial cultures have been performed. Reduced platelet outdating appears to offset the cost of such bacterial testing.[40]

Because the number of bacteria present in a contaminated blood unit increases over time of storage, less sensitive methods potentially can be used in the hospital blood bank to perform bacterial screening prior to transfusion. Relatively rapid methods of bacterial detection, such as Gram-staining or the detection of metabolic changes, are being used. However, screening with such low sensitivity methods may be inadequate to prevent some transfusion-associated septic reactions.[7]

Reducing recipient exposure

One approach that has not been extensively utilized in an attempt to prevent transfusion-associated bacterial contamination is to reduce recipient exposure. In this regard, it would be possible to reduce transfusion-associated septic events by reducing transfusion triggers. Recent studies for both the use of allogeneic RBCs as well as prophylactic platelet transfusions have suggested that reduced transfusion triggers do not endanger recipients. One suggested approach to reducing the risk of transfusion-associated sepsis due to contaminated platelets is to use apheresis platelets in preference to pools of whole blood-derived platelets.[5] The universal use of apheresis platelets would significantly reduce recipient exposure to contaminated blood products by a factor of 5. Five is the number of whole blood-derived platelet units usually used per platelet transfusion episode to an adult recipient. Finally, attention should be paid to optimizing transfusion indications. Audits of cellular blood transfusion use have regularly indicated that cellular blood products are often prescribed inappropriately. The reduction of such inappropriate use of cellular blood products should significantly reduce the incidence of transfusion-associated septic reactions.

Pathogen inactivation

Over the past 10 years, a number of photodynamic or photochemical methods have been reported that could lead to the reduction of viruses, bacteria, and protozoa that are present in cellular blood products.[15] These pathogen reduction devices include: the use of a combination of a psoralen and ultraviolet A (UVA) light; riboflavin and visible light; ultraviolet B irradiation; and the addition of methylene blue or phthalocyanines with visible light.[57-60] With regard to the bacterial inactivation of contaminated platelet concentrates, Lin et al reported that the novel psoralen amotosalen (S-59), combined with UVA light exposure has effective bacterial inactivation capability.[61] Thus, a combination of 150 μmol/L of the psoralen S-59 and 3 joules/cm UVA light result in significant bacterial reduction of contaminated apheresis platelets, as well as whole blood–derived platelets. Such methodologies are undergoing regulatory review in both North America and Western Europe.

Regulation and Regulatory Approaches

Prevention of bacterial contamination

Several approaches have been instituted by the transfusion community and the FDA to help minimize the chances of bacterial contamination of transfusion products at the time of collection. However, the improvement of collection techniques cannot prevent product contamination when the source is occult bacteremia in the donor; this risk may potentially be reduced by more careful and specific questioning of donors to identify recent medical procedures or symptoms that could indicate the onset of an infectious process. For sources of contamination associated with the collection method, steps can be taken that are more likely to decrease the risk.

An obvious first step is more effective sterilization of the phlebotomy site. The FDA has publicly discussed education about proper application of disinfectants and the problems with scar tissue.[62] More effective disinfectants have been recommended to sterilize the collection sites and the use of ineffective disinfectants, such as green soap, have been discouraged.[62] However, a careful review of the literature by FDA revealed that certain skin disinfection procedures using isopropyl

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alcohol followed by tincture of iodine that have been thought to be superior to those using povodone iodine actually are comparably effective in studies using hospitalized patients.[62] Sterilization of the skin surface also has limits when the phlebotomy needle cores out a skin plug as it passes through the skin. This inherently nonsterile skin plug can be carried into and seed the collected blood.

Recently, two studies have suggested that diversion of the initially collected blood to a separate container (referred to as a diversion pouch) away from the rest of the collected product that is to be used in transfusion could reduce the contamination rate. In a European study of actual transfusion products, diverting the first 15 mL of whole blood appeared to reduce the contamination rate of the final container.[63] Similar findings were also shown in an artificial model of blood collection.[56] The diversion pouch approach, using two recently FDA approved collection systems, is now being adopted by many blood centers as a way to lower the contamination risk. However, the ability of initial aliquot diversion to prevent clinical cases of transfusion-associated sepsis has not, as yet, been reported. It is important to note that this approach will only reduce the level of skin contaminants in blood products.

Prevention of bacterial proliferation—Refrigeration of platelets?

For red cells that are stored at 4°C, bacterial growth is slow and limited to a few psychrophilic bacteria such as *Yersinia enterocolitica*, *Pseudomonas* species and *Serratia liquefaciens*.[64] In comparison, platelets are stored at room temperature and provide a good medium for growth of both Gram-negative and Gram-positive bacteria. For most bacterial species, growth in platelet units can occur, rapidly reaching log phase within 24-48 hours.[12,26] An exception is the common skin contaminant, *Staphylococcus epidermidis* which is a slower growing organism and usually reaches the log phase in 48–72 hours. Since this and similar organisms account for a large proportion of the bacterial species found to contaminate blood units, such slower growth characteristics need to be considered when optimizing sampling strategies for bacterial detection.[65]

Rapid proliferation of bacteria during storage of transfusion products could be decreased if cold temperatures were used. For red cells, this is generally a standard practice and reduces the growth of most bacterial species and the risk of transfusion related sepsis. On the other hand, platelets do not maintain adequate function when stored at cold temperatures. Even relatively short exposures to cold are associated with irreversible changes in platelets that significantly decrease their ability to remain in circulation.[66] Attempts to understand the basis of the temperature sensitivity of platelets have only recently been productive.

A new study has suggested that platelets may respond to cold by clustering of GpIb on their surface which is then recognized by macrophages as a signal for clearance.[67] Better understanding of the molecular changes in platelet physiology after cold exposure could lead to alternate storage conditions that would allow cold temperature storage and a reduction of bacterial proliferation while preserving platelet function and viability. Evaluation of novel storage conditions would involve in vitro experiments to demonstrate that the platelets have not been extensively activated or damaged by the conditions. Since in vitro tests have a poor predictive value for clinical performance of platelets, the gold standard for platelet evaluation remains the recovery and survival of radiolabeled transfused platelets.[68] Platelets, collected from a single donor by apheresis, are divided into two products and stored under either conventional or novel conditions. At the end of storage a small portion of the cells is labeled with either ^{51}Cr or ^{111}In and the radiolabeled cells are reinfused into the original donor. Serial blood samples are then taken to monitor clearance of the cells from circulation. The double label allows for a direct comparison of the same platelets stored under different conditions in the same recipient.

Detection of bacteria in transfusion products

Ultimately, the reduction of bacterial contamination of transfusion products will require routine testing of the products for the presence of bacteria. Attempts to detect bacteria in transfusion products have spanned the range of simple to highly sophisticated state-of-the-art methodologies. On the low tech side, changes in the appearance of the product, such as platelet swirling or the color of the red cell units, have been utilized but with low specificity and sensitivity.[69] Other tests such as determining pH or glucose levels, or direct bacterial staining with Gram's stain or acridine orange have similarly not been very useful due to relatively low sensitivity when compared with bacterial concentrations that can cause sepsis. Tests with bacteria-specific nucleic acid probes or fluorescent dyes or antibodies are currently being developed.[70,71] However, the most useful detection systems currently available appear to be automated, culture-based methods similar to what has been used for clinical detection of bacteremia in blood cultures obtained from patients.[65]

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Sampling strategy for detection of bacteria in a transfusion product

Currently utilized platelet products are either random donor or apheresis units. Both types of units may be stored individually for up to 5 days at room temperature. Approximately 4–6 random donor units are pooled prior to transfusion to achieve a transfusion product with sufficient platelet content. The major factor in sampling either a random donor unit or an apheresis unit is the difference in volume. A typical apheresis unit contains approximately 200–250 mL while the random donor unit contains only 45–55 mL. Thus, the volume of the sample taken for bacterial detection can have a significant impact on the amount of product left for transfusion, particularly for random donor units. On the other hand, a larger sample volume increases sensitivity and thus a balance has to be reached to optimize sensitivity and minimize the impact on the product.

The timing of sampling is highly dependent on the method of detection. For culture-based methods, the product sample is inoculated into a container (bottle or bag) that allows for bacterial growth. Usually this occurs at 37°C and in the presence of sodium polysulfone (SPS), a bacteria growth-potentiating substance, that allows the bacteria to grow faster in the device than in the transfusion product. As the bacteria proliferate in the device, there is a fixed amount of time before a positive signal can be detected. The time to detection, dependent on the initial inoculum and the growth characteristic of the bacteria, is usually 24-48 hours when employing currently available detection methods. Because of this time required, the ideal sampling time for culture-based devices is as early as possible in the storage period so that a test-based decision about the clinical usefulness of the product can be made prior to its use. However, since the level of contamination at the time of collection is low and bacteria could be missed by a sampling error (especially with a low sample volume) at the beginning of storage, a certain amount of presampling storage time is usually allowed for the bacteria to begin to proliferate in the product. For platelets this is usually 24–48 hours.

The length of this presampling incubation period also depends on the sensitivity of the detection device. A more sensitive device can utilize a sample collected earlier in the product storage period while a less sensitive device would require a sample that contains more bacteria as occurs later in storage. The sampling strategy can be altered for a detection method that detects bacteria in real time. These approaches utilize probes, antibodies or nucleic acid–based detection system and can produce an answer within hours of sampling. The sensitivity of culture-based assays should be in the range of 10–100 CFU/mL and the sensitivity of methods that could be used at the point of transfusion would most likely be in the range of 100–1000 CFU/mL.[26]

Current approval process for bacterial detection devices

The FDA has encouraged manufacturers to submit applications for devices that will detect bacteria in transfusion products. The most urgent need is for bacterial screening of platelet products. Two devices have recently been cleared by the FDA for use in quality control monitoring of the platelet collection process that, in the past, was performed by manual culture (BioMeriuex, Inc. BK 000042; Pall Corp. BK 020014). The current devices allow sampling of the platelet product and automation of the quality control culture process. One device detects bacteria based on elaboration of CO_2 in the sample culture, while the other detects a decrease in pO_2. *However, these devices have not yet been specifically approved for use in release of platelets for transfusion because the effectiveness of the devices to detect bacterial contamination in the clinical setting has not been established.*

For the quality control indication, the validation was based on in vitro "spiking" experiments. A unit of platelets, either whole blood–derived, random donor, or apheresis-derived, single donor, was deliberately contaminated with a known amount of a single bacterial species. The unit was then repeatedly sampled 10 times and each time the sample was inoculated into the device. Thus, 10 separate readings were performed by the device for each bacterial species. The manufacturers were encouraged to validate their devices for as many bacterial species as possible and a list of the most common relevant bacteria was agreed on based on literature search, FDA advisory committee input and public workshops input.[10,65]

Trials recommended under "actual clinical use" conditions

The FDA has proposed that validation of bacterial detection devices for release of platelets for transfusion would require a field trial of the device under actual clinical use conditions.[62] The design of such a trial would be to obtain a sample for bacterial detection by a culture-based device early in the storage period. A second sample would then be taken at the end of the storage period or at the time of release of platelets. The results of both cultures would be compared to determine if the first culture was predictive of the result of the second culture. If the unit is contaminated at collection, then the bacteria will have time to grow between the first and second sampling. The bacterial load

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should be higher and detection of bacteria should be easier at the second sampling.

The needed studies should demonstrate that a sample taken early in the storage period and screened by the automatic culture device is predictive of the culture results up to the time of outdate of the product. Although some aspects of the study could be modeled in vitro it is not clear what is the expected level of bacterial contamination under actual clinical conditions, whether the devices will have sufficient sensitivity or whether sampling errors may occur when low levels of bacteria are present early in the storage period. In addition, such studies will also demonstrate the false positive rate and rate of contamination, if any, from bacteria introduced by sampling and inoculation procedures.[72] An excessive false positive rate would lead to an unnecessarily high discard rate for transfusion products.

Such issues raise the level of safety and efficacy concerns for devices intended for release of blood products for transfusion and are the basis for the current FDA practice of requesting clinical or field study data prior to approval of the devices. The field trials of the bacterial detection devices could be combined, under an IND or IDE application, with an extension of storage to day 7 or with pre storage pooling, allowing some costs to potentially be offset by savings from decreasing platelet product loss due to expiration and/or from pre storage leukoreduction of a pool instead of individual units.

Pathogen reduction technologies

As an additional measure of safety, transfusion products could potentially be treated with a pathogen reduction process to decrease or eliminate pathogens, including bacteria, which were not detected by testing. Methods are being developed that allow selective targeting of pathogens in blood products. The selectivity is based on absence of nucleic acids in platelets and red cells. A chemical compound is added to the transfusion product that interacts with the nucleic acids of pathogens and, upon spontaneous or light energy–induced activation, cross links nucleic acids and prevents their transcription and replication. Efficacy of these methods is usually established by in vitro studies where various pathogens are "spiked" into a platelet or red cell unit and then treated using the pathogen reduction methodology. The efficacy of these treatments should be in the range of 6–10 log reduction of common bacterial pathogens.[10]

However, from an FDA perspective, evaluation of the safety aspects of these methods is more complex and challenging. It includes assessment of possible damage caused by the treatment to the transfusion product (including functionality and survival of transfused cells) and evaluation of the potential toxicities of any residual chemicals to the recipients of the product. In fact, concerns about the safety of these products may arise because of mutagenicity of some of the chemical agents employed and thus their potential to be carcinogenic and genotoxic. In addition, the reactions of the chemical agent(s) with plasma and cellular proteins and lipids can create novel chemical entities that may have unexpected toxicities and increased immunogenicity when administered to certain patient populations. Because of the uncertainties that surround the treated products, even after extensive preclinical and clinical evaluation, it is likely that postmarketing studies will be needed to identify any low frequency adverse events associated with their use in a broader patient population. Another issue is whether the therapeutic efficacy of the treated transfusion products has been fully preserved after treatment with the pathogen reduction process. This is again being evaluated both in vitro and in Phase 2 and 3 clinical trials designed to follow efficacy endpoints, such as hemostasis in the case of platelet transfusions.

The final analysis of the documented and theoretical risks of the pathogen reduction process to the recipient of treated transfusion products will need to be weighed against the risk of the transfusion-transmitted diseases they could prevent, a risk which currently is relatively low. Thus, the clinical use of these products will ultimately depend on the appropriate risk benefit analysis for proposed uses and upon the data submitted for evaluation.

Transfusion product substitutes

The risk of transmitting pathogens by transfusion has been a major driving force for the development of manufactured substitutes for transfusion products. Such products would ideally be free of pathogens, have a long shelf life and may also not present the requirement of having to be serologically typed for each recipient. However, initial results of efforts to engineer red cells or platelets have so far fallen short of matching the natural cells. For example, initial efforts using the hemoglobin molecule to carry oxygen has been associated with a variety of toxicity issues.[73] Additional research and clinical testing will need to be done to fully evaluate and, hopefully, realize the potential of these types of products.

Bacterial detection and the extension of platelet storage

Increased risk of bacterial contamination has been the major concern regarding prestorage pooling of platelets and extension of platelet storage beyond the currently allowed 5 days. For pooled platelets it has been demonstrated that a platelet pool created by combining

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1 contaminated unit with 3–4 other units permits greater levels of bacteria at stationary phase.[74] Until 1986, platelets could be stored for up to 7 days at room temperature. However, due to concerns over a rise in clinically significant transfusion-associated infections from an increased bacterial load at the end of an extended storage period, this was shortened to 5 days on the advice of an FDA scientific advisory committee.

Returning to platelet storage beyond 5 days and allowing prestorage pooling of platelets would require an appropriately validated effective bacterial detection system. Such validation would involve in vitro testing with pooled products and a field trial in a clinical setting. In addition to bacterial detection the storage conditions for pooled platelets and platelets stored beyond 5 days will need to be validated to demonstrate that platelet quality is preserved under these conditions.[75] Use of FDA-approved sterile connection devices otherwise allows pooling and sampling of platelets without introducing bacterial contamination through the pooling process itself.[62]

Regulatory summary

Bacterial contamination of transfusion products, especially platelets, is a significant clinical problem with multiple causes. Based on recognition of this issue, the FDA and the blood industry have taken steps to improve control of bacterial contamination at multiple steps during blood collection and processing. Dealing effectively with this problem will involve continued and enhanced education of phlebotomy, technical, nursing, and medical staff with regard to sources of contamination and the importance of the problem. Using approved products and procedures, blood collection centers can implement practices that may decrease bacterial contamination, including better skin disinfection, collection of blood with a diversion pouch set, testing for bacteria, and, potentially, the use of safe and effective pathogen reduction technologies if and when available. Promising technologies for bacterial detection appear to be close at hand and offer significant potential to screen out contaminated units. The FDA and the blood community share a common goal that increased efforts focused on the problem of bacterial contamination will be translated into successes comparable to those we have already achieved in decreasing risks from most transfusion transmitted viral diseases.

Concluding Comments

Septic transfusion reactions associated with the use of contaminated blood products remain a very significant adverse event. Nonetheless, clear-cut approaches to reduce the frequency of such events are appearing. A wide variety of measures have been proposed in order to reduce the frequency of transfusion-associated septic reactions and many of these measures are being actively investigated, and in some countries being instituted.[15,76] Thus, the potential reduction in the risk of transfusion-associated septic reactions is a realistic possibility in the foreseeable future.

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FEATURES

Better Blood Transfusion

There has been renewed interest in the safety and effectiveness of transfusion practice in recent years because of:-

- data from the Serious Hazards of Transfusion (SHOT) scheme showing that the safety of transfusion practice in hospitals should be improved,
- increases in the cost of blood associated with the introduction by Blood Services of safety measures such as universal leucocyte-depletion of blood components and nucleic acid testing,
- concerns about the transmission of variant Creutzfeldt-Jakob disease (vCJD) by blood transfusion and the potential effect that measures to minimise this risk might have on the blood supply.

Research is being carried out both on new approaches for the safety of the transfusion process, and to determine the appropriate indications for transfusion. The use of blood components only when there is a real clinical need is arguably the best way of avoiding the risks of transfusion. These issues apply to critical care as much if not more than to other clinical areas where transfusions are regularly used.

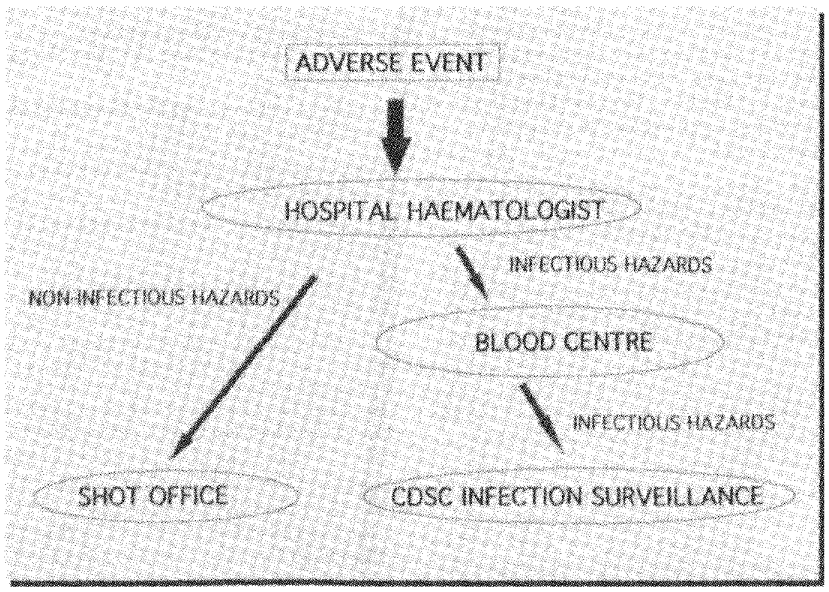
Risks of transfusion and new approaches to reducing the risks

The Serious Hazards of Transfusion (SHOT) scheme was established in 1996 to collect reports of major adverse events associated with the transfusion of blood components in the UK (1). Figure 1 shows the mechanism for reporting. 92% of eligible hospitals participated in 2001/02.

It is striking that the most frequent event is incorrect blood transfused (IBCT). Immune complications of transfusion are all represented to varying degree, but episodes of transfusion-transmitted infection are infrequent. Recent figures from the National Blood Service indicate that the risk of HIV transmission has been reduced to less than 1 in 8 million (less than the risk of being struck by lightning), the risk of hepatitis B transmission is 1 in 900,000, and the risk of HCV has decreased to less than 1 in 30 million since the introduction of nucleic acid testing.

The increase in reports over the 5 years of the SHOT scheme is due to an increase in incidents of IBCT. This may be due to better reporting or a real increase in the number of incidents; the latter is thought to be less likely, but cannot be excluded. IBCT is defined as an episode where a patient was transfused with blood which did not meet the appropriate requirements or was intended for another patient. Out of the 699 incidents reported between 1996/97 and 2000/01, there were 161 ABO incompatible transfusions (resulting in 9 deaths and 37 cases of major morbidity), 73 RhD incompatible transfusions, and 37 cases involving other red cell incompatibilities. 195 wrong transfusions were by chance ABO and RhD compatible. Analysis of the distribution of errors causing IBCT shows that they occur throughout the transfusion process. The most frequent site of error is at the time of collection and/or

Figure 1. Mechanism of SHOT reporting. (CDSC- Communicable Disease Surveillance Centre)



KUR-MAG-DE005167

administration of blood (55%), followed by errors in the laboratory (28%), and errors at the time of request, sampling or prescription of blood (13%). The SHOT data have clearly demonstrated that multiple errors often contribute to IBCT; in 2001/02, 54% of IBCT cases involved multiple errors. IBCT was found to occur in all sites where blood is used, with both elective and emergency transfusion, and to involve many types and grades of staff.

In over 70% of cases, there was minor or no morbidity. However, 14% of incidents were associated with major morbidity e.g. admission to an intensive care unit, renal dysfunction, or confirmed infection. The death of the patient was definitely attributed to transfusion in 37 cases (3%), and was possibly associated with transfusion in a further 32 cases (2%). The most frequent cause of death was transfusion-associated graft-versus-host disease (TA-GvHD) (13 cases). The most frequent cause of death or major morbidity was IBCT (71 cases) followed by transfusion-related acute lung injury (TRALI) (67 cases).

TRALI is a complication of transfusion particularly relevant to critical care. It is severe acute reaction characterized by respiratory distress, hypoxia and pulmonary infiltrates soon after transfusion with no other apparent cause. In many cases, preformed leucocyte antibodies have been found in the plasma of the donors, and these are thought to cause pulmonary leucostasis and leucocyte activation resulting in capillary leak and pulmonary damage. TRALI has been reported to occur after the transfusion of all types of blood components, but is particularly likely to occur with those with a large volume of plasma such as fresh frozen plasma (FFP). TRALI is clinically indistinguishable from acute respiratory distress syndrome (ARDS), and the occurrence of ARDS with a possible association with transfusion provides grounds to consider TRALI as the cause. Unlike ARDS, TRALI is self-limiting, and there is usually clinical improvement within 48–96 hours provided prompt respiratory support is provided. The production of FFP from only male donors, and reducing the volume of plasma in platelet concentrates are under consideration as measures to reduce the risk of TRALI.

The SHOT scheme has no mechanism for implementing its recommendations, and is reliant on other organisations to do so. Some parallel initiatives have supported the work of the SHOT scheme, including the development of national guidelines for transfusion practice by the British Committee for Standards in Haematology (BCSH), for example on the administration of blood (2). The SHOT scheme has recommended that further research should be carried out into information technology solutions for safer transfusion. An example is the use of barcode technology for patient identification and for the confirmation that the right blood will be transfused. A barcode patient identification system was recently found to simplify the clinical transfusion process and improve practice (3). Further work is required on the development of such systems for transfusion, and also for other hospital procedures requiring patient identification such as drug administration. These systems are particularly relevant for clinical areas such as critical care where the patient cannot verbally confirm their identification.

SHOT has also recommended the introduction of new strategies for reducing the risk of bacterial contamination. New methods are being introduced for cleaning the arms of blood donors and for diverting the initial 20ml of donor blood into a pouch for laboratory testing, and bacterial testing of platelet concentrates is being considered.

Measures to encourage the appropriate use of blood components and blood products

Concerns about blood safety have probably been the main driver for changes in transfusion practice in recent years. The threat of transfusion-transmitted infection has outweighed other risks of transfusion, and maybe it is time to 'realign transfusion safety with risks' using data from schemes such as SHOT about the observed risks of transfusion (4). At a clinical level, evidence does influence practice, but the level of evidence is critical. Guidelines and recommendations from experts appear to have limited impact, but level 1 evidence from systematic reviews or randomised controlled trials can have a major impact. For example, in the field of critical care, the publication of a systematic review on the absence of benefit of the use of albumin and possible increased mortality rapidly reduced its use (5), and a randomised controlled trial on transfusion triggers for red cell transfusion resulted in a change in practice in many centres (6). Greater efforts are needed to develop a sound evidence-base for the use of blood components and blood products in critical care as well as other clinical areas.

Better Blood Transfusion is an initiative led by the UK Chief Medical Officers to improve the safety and effectiveness of transfusion practice. Its output has been two Health Service Circulars (HSCs) setting out a number of recommended actions to hospital Chief Executives (7 8). An audit of the implementation of the HSC 1998/224 Better Blood Transfusion showed that most hospitals had established Hospital Transfusion Committees (HTCs), were participating in the SHOT scheme, and had protocols for the administration of blood (9). However, there was evidence of poor provision of training for clinical staff and patient information, few protocols for the appropriate use of blood, few

FEATURES

audits of transfusion practice, and limited use of autologous transfusion. The HSC 2002/009 Better Blood Transfusion – Appropriate Use of Blood was published in July 2002, and it included an action plan and an ongoing programme for Better Blood Transfusion to be taken forward in each Trust. It recommended the establishment of a Hospital Transfusion Team (HTT) in each Trust. The HTT is tasked with implementing the agreed actions recommended by the HTC; it should be led by a senior doctor interested in transfusion medicine (not necessarily a haematologist) and include one or more Transfusion Nurses (depending on the size of the Trust), senior blood bank laboratory staff and specialists who work in clinical areas with large or high risk blood usage. It should be provided with managerial, information technology, and administrative support. The main work of the HTT and HTC is directed to:-

- the development and implementation of local policies for safe and appropriate transfusion based on national guidelines, and the use of alternatives to blood where appropriate,
- the provision of training for the many staff involved in transfusion,
- the provision of better information for patients.

The Chief Medical Officer's National Blood Transfusion Committee (NBTC) was established in England in 2001 (for details, see www.doh.gov.uk/blood/nbtcommittee.htm). It provides a potentially powerful framework through its Regional Transfusion Committees for improving transfusion practice and supporting the work of the HTCs. It oversees the national Better Blood Transfusion initiative, and acts as the Steering Group for an initiative for national comparative audit of clinical transfusion practice based on an earlier pilot scheme (10). The NBTC reviews the findings of the SHOT scheme, and supports its recommendations. One of its main roles is to provide educational material for hospitals and patients, for example it has recently developed a national patient information leaflet, recommendations on the resources to implement Better Blood Transfusion, and an audit tool for the use of blood (available on www.doh.gov.uk/bbt2). Recommendations on strategies for the avoidance of transfusion are in preparation. Specific measures which could be considered in critical care practice include better compliance with evidence-based triggers for transfusion, greater use of near patient testing to determine the need for transfusion, and minimising blood loss due to sampling. ■

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BLOOD DRAWING DEVICE WITH FLASH DETECTION

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A device for drawing fluid from a lumen, and particularly blood from a blood vessel, is disclosed. The device may provide indication of the entry of an intravenous cannula into the lumen. The device may include a guide tube for receiving a blood sample container and which may be connected to a needle for drawing blood from a lumen. A rear cannula may extend into the guide tube from the well. A flexible sleeve may be mounted on a barb connected to the guide tube. The flexible sleeve may extend into the guide tube from the well and surround at least a tip portion of the rear cannula. A venting member may be provided between the interior of the sleeve and the ambient.

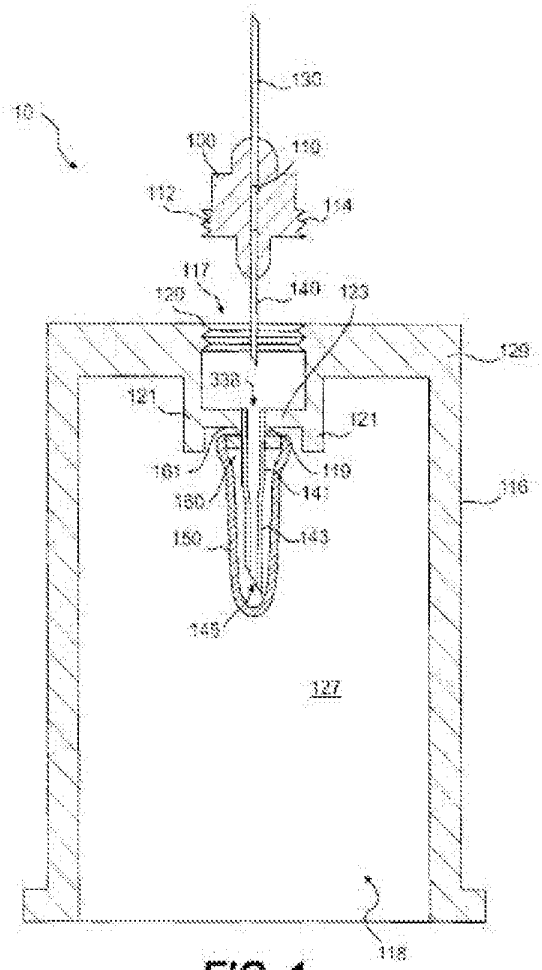

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FIG. 1

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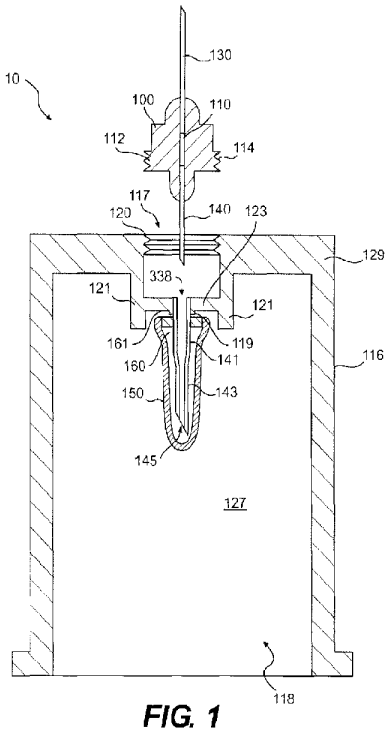


FIG. 1

(57) Abstract: A device for drawing fluid from a lumen, and particularly blood from a blood vessel, is disclosed. The device may provide indication of the entry of an intravenous cannula into the lumen. The device may include a guide tube for receiving a blood sample container and which may be connected to a needle for drawing blood from a lumen. A rear cannula may extend into the guide tube from the well. A flexible sleeve may be mounted on a barb connected to the guide tube. The flexible sleeve may extend into the guide tube from the well and surround at least a tip portion of the rear cannula. A venting member may be provided between the interior of the sleeve and the ambient.

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BLOOD DRAWING DEVICE WITH FLASH DETECTION

FIELD OF THE INVENTION

[0001] The present invention relates to an apparatus for drawing bodily fluids, and particularly blood, from an animal.

BACKGROUND OF THE INVENTION

[0002] Intravenous blood collection assemblies have long been used to draw bodily fluids, such as blood, from patients. With respect to drawing blood in particular, the vessel or lumen from which the blood is drawn is often rather small and or not visible. If the needle tip is not in communication with the interior of the blood vessel during the procedure, the procedure is likely to be unsuccessful, causing error, undermining the integrity of the specimen, and the patient may be harmed additionally by the penetration of delicate underlying structures. Accordingly, confirmation of accurate placement of the needle tip into a blood vessel is desirable for blood drawing procedures.

[0003] Past intravenous blood collection assemblies have included mechanisms for indicating when a needle tip is in communication with the interior of a blood vessel. These needle kits have included a transparent portion in the needle body from which the presence of blood can be observed. The observation of blood in the needle body is known as "flash." Flash detection has been less than satisfactory for many such collection assemblies. In some instances, the flow of blood into the transparent portion of the needle body is impeded by air backpressure in the needle, and thus flash confirmation is not visible or delayed. This delay can impede the determination of the precise moment at which the needle tip enters the blood vessel, which may cause the healthcare worker inserting the needle to miss or perforate the vessel and penetrate into delicate surrounding structures. In other instances, while flash occurs, the visual indication of flash is not easily detected because the amount of flash is small or obscured due to the positioning of the collection assembly. Accordingly, there is a need

for a blood-drawing device that provides flash relatively rapidly and to an extent that a user may readily detect it.

[0004] There are also many needles that are currently used that do not provide for flash detection. It would be advantageous to be able to retrofit such needles so that they may be used to draw blood and provide detection of flash.

SUMMARY OF THE INVENTION

[0005] Responsive to the foregoing challenges, Applicant has developed a guide tube assembly for connection to a device for drawing fluid from a lumen, comprising: a guide tube (116) having an open end (118) and a well (117); a flexible sleeve (150, 151) having an interior space in fluid communication with the well (117) and extending into the guide tube (116); one or more passages (332, 334, 336, 338) extending through the guide tube (116) which are in fluid communication with the flexible sleeve (150) interior space; and a venting member (160) connected to the guide tube (116) or incorporated into the flexible sleeve (150, 151), said venting member in fluid communication with the one or more passages (332, 334, 336, 338) and disposed between the flexible sleeve (150, 151) interior space and an ambient.

[0006] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only, and are not restrictive of the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] In order to assist the understanding of this invention, reference will now be made to the appended drawings, in which like reference characters refer to like elements.

[0008] Figure 1 is a side view in cross-section of a blood drawing needle and guide tube having a venting member in accordance with a first embodiment of the present invention prior to connection with a blood drawing needle.

[0009] Figure 2 is a side view in cross-section of the guide tube shown in Figure 1

after connection to the blood drawing needle.

[0010] Figure 3 is a side view in cross-section of a guide tube having a venting member in accordance with an second embodiment of the present invention prior to connection with a blood drawing needle.

[0011] Figure 4 is an end view of the raised dimple surface of a well bottom wall provided in the guide tube in accordance with an alternative embodiment of the invention shown in Figures 1-3.

[0012] Figure 5 is an end view of the raised radial line surface of a well bottom wall provided in the guide tube in accordance with an alternative embodiment of the invention shown in Figures 1-3.

[0013] Figure 6 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening in accordance with a third embodiment of the present invention.

[0014] Figure 7 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening with well bottom extensions surrounding the venting member in accordance with a fourth embodiment of the present invention.

[0015] Figure 8 is a side view in cross-section of a blood drawing device with a guide tube having a venting member and viewing window located in a guide tube side wall in accordance with a fifth embodiment of the present invention.

[0016] Figure 9 is a side view in cross-section of a blood drawing device with a guide tube having a venting member and viewing window located in a guide tube side wall in accordance with a sixth embodiment of the present invention.

[0017] Figure 10 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening in accordance with a seventh embodiment of the present invention.

[0018] Figure 11 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening and a viewing

window located in a guide tube side wall in accordance with an eighth embodiment of the present invention.

[0019] Figure 12 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening surrounded by well bottom extensions and having a viewing window located in a guide tube side wall in accordance with a ninth embodiment of the present invention.

[0020] Figure 13 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube opening with well bottom extensions surrounding the venting member in accordance with a tenth embodiment of the present invention.

[0021] Figure 14 is a side view in cross-section of a blood drawing device with a guide tube having a sealing membrane in a guide tube well and a venting member and viewing window located in a guide tube side wall in accordance with an eleventh embodiment of the present invention.

[0022] Figure 15 is a side view in cross-section of a blood drawing device with a guide tube having a venting member and viewing window located in a guide tube side wall in accordance with a twelfth embodiment of the present invention.

[0023] Figure 16 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a guide tube well in accordance with a thirteenth embodiment of the present invention.

[0024] Figure 17 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a sleeve tubulation and a viewing window located in a guide tube side wall in accordance with a fourteenth embodiment of the present invention.

[0025] Figure 18 is a side view in cross-section of a blood drawing device with a guide tube having an air-permeable sleeve and a viewing window located in a guide tube side wall in accordance with a fifteenth embodiment of the present invention.

[0026] Figure 19 is a side view in cross-section of a blood drawing device with a

guide tube having a sleeve with a venting portion and a viewing window located in a guide tube side wall in accordance with a sixteenth embodiment of the present invention.

[0027] Figure 20 is a side view in cross-section of a blood drawing device with a guide tube having a venting member located in a sleeve tubulation and a viewing window located in a guide tube side wall in accordance with a seventeenth embodiment of the present invention.

[0028] Figure 21 is a side view in cross-section of a blood drawing device with a guide tube having an air-permeable sleeve and a viewing window located in a guide tube side wall in accordance with an eighteenth embodiment of the present invention.

[0029] Figure 22 is a side view in cross-section of a blood drawing device with a guide tube having a sleeve with a venting portion and a viewing window located in a guide tube side wall in accordance with a ninteenth embodiment of the present invention.

[0030] Figure 23 is a side view in partial cross-section of a first Luer-adapter type butterfly needle attachment which may be used to connect with the guide tubes shown in Figures 1-22.

[0031] Figure 24 is a side view in cross-section of a second butterfly needle attachment that may be used to directly connect to the guide tubes shown in Figures 1-22.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0032] Reference will now be made in detail to a first embodiment of the present invention, an example of which is illustrated in the accompanying drawings. With reference to Figs. 1 and 2, a guide tube **116** is shown. The guide tube **116** is provided for connection to a central body **100** which may include one or more constituent elements, such as a threaded connector **112** with interlocking threads **114** or other connection means, for connecting the central body to the guide tube. The threaded connector **112** may be integrally formed with, or connected to the central body using

adhesive, male-female interfaces, threaded interfaces, or any other connection means. It is appreciated that the guide tube **116** may be connected to the central body **100** by any connection means, including without limitation the threaded interfaces shown, male-female interfaces, pressure-fit connectors, slot and key connectors, snap-on connectors, and the like. The type of connection between the guide tube **116** and the central body **100** is not intended to be limiting to the scope or use of any of the present embodiments of the invention.

[0033] A fluid passage **110** within the central body **100** may communicate with, and in the embodiment shown, be connected to the front cannula **130** and the first rear cannula **140**, respectively, using adhesive, threaded interfaces, pressure fit, or other connection means. Alternatively, the central body **100** may be integrally formed with the front and/or first rear cannulae **130** and **140**. It is further appreciated the front and first rear cannulae **130** and **140** may be formed of a continuous material and eliminate the need to fluid passage **110**. It is also appreciated that the front and/or rear cannulae may be transparent or translucent, in whole or part, to provide flash detection in alternative embodiments of the present invention. If included, the fluid passage **110** may be defined by the opening within the central body between the front and rear cannulae when the cannulae are directly connected to the central body. The fluid passage **110** may be adapted to receive a sufficient amount of fluid to allow observation of the fluid (*i.e.*, "flash") from outside the blood-drawing device **10**. At the same time, the fluid passage **110** may have a sufficiently small volume so as to rapidly fill with fluid during the use of the blood-drawing device.

[0034] Preferably, the central body **100** may be constructed of plastic material suitable for medical use. Further, in any embodiment of the present invention, all, or portions, of the central body **100** may be transparent, translucent, connected to transparent or translucent I.V. tubing, or otherwise adapted to permit detection of fluids passing through the central body and/or I.V. tubing from a vantage point outside of the blood-drawing device **10**. For example, with reference to Fig. 1, the central body **100**

may include a transparent wall that is adapted to permit the observation of "flash" when it occurs. In an alternate embodiment of the present invention, the side wall of the central body **100** also may be adapted to magnify or otherwise enhance the detection of fluid passing through the central body, although it is appreciated that a magnifying or enhancement feature is not necessarily required.

[0035] It is further appreciated that the front cannula **130** may be replaced with or connected to a flexible butterfly connection tube **182** that is part of a butterfly needle **180** as shown in Fig. 23. When connected to a flexible butterfly connection tube **182**, the front cannula **130** extending from the central body **100** may be eliminated and replaced with a Luer-adapter including a female connector **102** and male connector **103** which is connected via the butterfly connection tube **182** to a butterfly cannula **184** which substitutes for the front cannula **130**. The flexible butterfly connection tube **182** may be translucent or transparent when combined with the embodiments shown in Figs. 1-22 so that the "flash" of blood that enters the device **10** may be visible first in the butterfly connection tube. In a further alternative, shown in Fig. 24 and applicable to the embodiments shown in Figs. 1-22, the female connector **102** of the Luer-adapter may connect directly to a specially formed mating male connector **103** integrally formed with the guide tube **116.** It is appreciated that the placement of the male and female connectors could be reversed or replaced with other connector types in alternative embodiments of the invention.

[0036] With renewed reference to Figs. 1-2, the front cannula **130** may extend from the front end of the central body **100** and terminate at a tapered or pointed end **132** which is adapted to be inserted into a lumen. The first rear cannula **140** may extend from the rear of the central body **100** and terminate at a tapered or pointed end.

[0037] A generally cylindrical guide tube **116** is adapted to be connected to the central body **100**. Preferably, the guide tube **116** may be made in whole or part of transparent or translucent material that permits viewing of the interior space of the guide tube. The guide tube **116** may include a substantially closed end **129**, an open

end **118** at one end communicating with an interior opening **127**, and a well **117** at the opposite end defined in part by a well bottom wall **123**. The open end **118** may be adapted to receive a blood or fluid sample container. The upper edge of the well **117** may include threads or other connection means **120** adapted to mate with the threads **114** of the threaded connector **112** provided on the central body **100**.

[0038] The well bottom wall **123** may include a centrally located opening through which a second rear cannula **141** extends towards the guide tube open end **118**. The second rear cannula **141** may be sufficiently fastened to the well bottom wall **123** by any means such that the application of pressure from a fluid sample container pressed against the second rear cannula will not dislodge the second rear cannula. The guide tube **116** may extend coaxially with the second rear cannula **141** sufficiently beyond the tapered end **145** to provide some degree of protection against inadvertent "needle sticks" by a user of the blood-drawing device **10** as well as to guide the reception of a fluid sample container.

[0039] The bottom surface of the well bottom wall **123** located within the interior of the guide tube **116** may include a shoulder **119** against which a venting member **160** may be disposed. The shoulder **119** may create an air space **161** between the bottom surface of the well **117** and the venting member **160**. In one alternative embodiment of the invention, shown in Fig. 4, the shoulder **119** may be replaced by or incorporate a surface having raised dimples **217**, or in another alternative embodiment, as shown in Fig. 5, the shoulder may be replaced by or incorporate a surface having raised radial lines **219**, or some other surface which both supports the venting member **160** and provides for air flow between the venting member and the interior of the guide tube **116**. In still other alternative embodiments of the present invention, an air-permeable spacer may be provided between the venting member **160** and the bottom surface of the well bottom wall **123** to provide the required air flow in place of any raised features on the bottom of the well bottom wall.

[0040] The second rear cannula **141** may include a stepped diameter **143** or other

narrowing feature that results in the second rear cannula having a narrower diameter at the pointed end **145** compared with the end extending from the well **117**. The end of the second rear cannula **141** nearest to the well **117** may have a diameter sufficient to receive the first rear cannula **140** within it. In alternative embodiments of the invention, the second rear cannula **141** may have a uniform diameter over its entire length.

[0041] One or more well bottom extensions **121** may also extend from the well bottom wall **123** into the guide tube opening **118** adjacent to the venting member **160**. The well bottom extensions **121** may surround the venting member **160** in whole or in part and may be formed so as to leave an air space for air to flow from the interior of the sleeve **150** through the venting member **160** to the ambient in the guide tube interior opening **127**. The well bottom extensions **121** may be semi-circular, or prong shaped, and surround the venting member **160**. Further, the well bottom extensions **121** may extend into the guide tube **116** a distance sufficient to protect the venting member **160** from being impacted against, damaged or dislodged by, the stopper of a container inserted into the guide tube. The well bottom extensions **121** may be formed of plastic material which is integral with the rest of the guide tube **116** and well bottom wall **123**. The well bottom extensions **121** may also contact the venting member **160** and/or flexible sleeve **150** so as to assist in retaining the sleeve and venting member in the guide tube **116**.

[0042] The venting member **160** may be constructed out of any material which is capable of substantially preventing blood from passing through it while permitting air to vent through it. Preferably, for purposes of ease of manufacturing, the venting member **160** may be formed as a stamped disk with a central opening from a sheet of venting member material for the embodiment shown in Figs. 1-2.

[0043] The venting member **160** may be constructed of any of a number of materials that provide the desired level of porosity, which may include, but are not limited to sintered, layered, rolled, foamed, perforated, or impregnated, hydrophyllic/hydrophobic compositions, porous polyethylene, porous polypropylene,

porous polyfluorocarbon, absorbent paper, materials impregnated with dilute Russell Viper venom molded fiber, fiberglass, felt, granular starch, cellulose, polyacrylamide gel, hydrogel, a molded admixture of porous hydrophobic/hydrophyllic granules and sufficiently low density silicone, molded open cell polyurethane, and like polymeric materials. Examples of materials that may be used to construct the venting (i.e., porous) member **160** are discussed in U.S. Patent No. 4,207,870 to Eldridge, and U.S. Patent No. 4,340,068 to Kaufman, each of which are hereby incorporated by reference.

[0044] The venting member **160** (*i.e.*, a means for venting air) may be inserted over the second rear cannula **141** and pressed against or near to the rear portion of the well bottom wall **123**. The venting member **160** may form a seal against the second rear cannula **141** that is sufficient to prevent blood from escaping past the venting member. In the embodiments of the present invention, the venting member **160** may be gas, and particularly air, permeable, but at least partially, and preferably wholly, impermeable to a liquid, such as blood. Preferably, the venting member **160** may be substantially porous for gas constituents less than about 5 microns in size, and substantially non-porous for liquid constituents about 5 microns or greater in size, however, it is appreciated that these approximate sizes should not be limiting for the invention.

[0045] For each of the embodiments discussed in connection with Figs. 3-24, the venting member **160** may be constructed in accordance with the description of the venting members described in connection with the embodiment of the invention described in connection with Figs. 1-2.

[0046] A flexible sleeve **150** may be disposed over and around the second rear cannula **141**. The sleeve **150** may isolate the second rear cannula **141** from the ambient, wherein the ambient includes any space outside of the sleeve **150**, irrespective of whether or not the space is contained within the guide tube **116** or any other structure. The flexible sleeve **150** may be stretched over all or part of the side wall of the venting member **160**, or in alternate embodiments, otherwise contact the venting member **160**. The flexible sleeve **150** may be made of a shape memory

material, such as elastic rubber or elastomeric silicone or latex, or the like, which will return to the shape shown in Fig. 1 as long as no other structure obstructs it. Examples of materials that may be used to construct the flexible sleeve **150** are discussed in U.S. Patent No. 3,877,465 to Miyake, U.S. Patent No. 5,086,780 to Schmitt, U.S. Patent No. 6,110,160 to Farber, U.S. Patent No. 6,533,760 to Leong, U.S. Patent Pub. No. US 2002/0004647 A1 to Leong, and U.S. Patent Pub. No. US 2003/0078544 A1 to Chen, each of which is hereby incorporated by reference. It is appreciated that any suitable material may be used for the flexible sleeve without departing from the intended scope of the present invention.

[0047] The flexible sleeve **150**, also known as a multiple sample sleeve, may preferably be transparent or translucent such that the presence of blood within the flexible sleeve may be visually detected. When the flexible sleeve **150** is transparent or translucent in any of the embodiments shown in Figs. 1-24, the guide tube **116** may also be transparent or translucent so that the "flash" of blood may be visible through both the guide tube and the flexible sleeve to the person drawing blood. The length of the flexible sleeve **150** may be sufficient to accommodate the second rear cannula **141** but not so long as to present serious risk of the second rear cannula piercing the side wall of the flexible sleeve when a fluid sample container is pushed into the guide tube **116**.

[0048] Prior to using the device **10** to draw blood, the central body **100** may be connected to the guide tube **116** at the threaded end **112** as shown in Fig. 2, in which like reference characters refer to like elements. When so connected, the combination of the guide tube **116** with a venting member **160** and the flexible sleeve **150** may be used to effectively "retrofit" a non-venting blood drawing device to become a venting blood drawing device. It is appreciated that each of the embodiments of the present invention shown in Figs. 1-24 may be used to retrofit existing non-venting blood drawing devices to become devices which vent air without substantially venting blood. The well **117** may be designed to provide sufficient space to accommodate the rear portion of

the central body **100** of a conventional or known blood drawing device within it to provide retro-fitting.

[0049] The function of the first embodiment of the blood-drawing device **10** will now be described with reference to Figs. 1-2. With reference to Figs. 1-2, the tapered end **132** of the front cannula **130** (or some extension thereof) may be inserted into a fluid containing body lumen prior to the insertion of a fluid sample container into the guide tube **116**. In a preferred embodiment of the present invention, the front cannula **130** is inserted into a lumen containing a visually detectable fluid, such as blood. At the time that the front cannula **130** is inserted into the body lumen, it is assumed that the internal passages within the blood-drawing device (*i.e.*, the passage through the front cannula **130**, the fluid passage **110**, the passage through the rear cannula **140**, and the space inside the flexible sleeve **150**) may be filled with atmospheric air or some other gas. When the front cannula **130** establishes communication with the fluid in the body lumen, fluid pressure in the lumen may force the fluid through the front cannula **130** towards the fluid passage **110**.

[0050] The flow of fluid through the front cannula may begin to compress the air in the fluid passage **110**, the rear cannula **140**, the second rear cannula **141**, and the space between the rear cannulae and the flexible sleeve **150**, driving the air towards the venting member **160**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the flexible sleeve **150** and the venting member **160** to the ambient within the guide tube **116**. The air may vent from the venting member **160** through the air space **161** that may be created by the shoulder **119** or the dimples **217** (Fig. 4) or radial lines **219** (Fig. 5). As a result, there may be insufficient air pressure within the fluid passage **110** to resist the flow of the fluid, where it may be detected or observed as "flash" by a user.

[0051] Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle) or through a transparent or translucent flexible sleeve **150** and/or a

transparent or translucent guide tube **116**. The visual detection of blood indicates positive vein entry, known as flash. It is appreciated that "flash" may be detected at any point along the device that includes a transparent or translucent member, which may include, but not be limited to, a transparent or translucent cannula, central body, I.V. tubing, flexible sleeve, or other constituent member.

[0052] Once flash is detected, a fluid sample container may be pressed into the open end **118** of the guide tube **116**, the second rear cannula **141** may pierce the flexible sleeve **150**, and the flexible sleeve is pushed back towards the base of the second rear cannula. As shown in Fig. 2, the first rear cannula **140** may slide into the second rear cannula **141** and the second rear cannula may extend into the guide tube **116** a distance which is sufficient to pierce the stopper provided on the top of a fluid sample container. The one or more well bottom extensions **121** may prevent the fluid sample container from crushing, dislodging or otherwise damaging the venting member **160**. A sample of blood may then be received in the fluid sample container.

[0053] An alternative embodiment of the present invention is shown in Fig. 3, in which like reference characters refer to like elements in the other drawing figures. The embodiment shown in Fig. 3 differs from that shown in Figs. 1-2 in that the second rear cannula **141** is truncated. In this embodiment the first rear cannula **140** is of sufficient length to pierce a fluid sample container. It is also appreciated that the second rear cannula **141** could be replaced with an integral portion of the well bottom wall **123** shaped to receive the venting member **160**. In all other respects the embodiment shown in Fig. 3 operates like the embodiment shown in Figs. 1-2.

[0054] With reference to Fig. 6, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The well bottom wall upper surface **125** may prevent blood from flowing into the well **117** when the central body **100** is seated against the well bottom wall **123**.

[0055] With continued reference to Fig. 6, the second rear cannula **141** may have a

venting member **160** disposed about it at a base portion against the inner end wall of the guide tube **116**. The venting member **160** may have a base **300** and a barb portion **302**. The base **300** may be adhered to the end wall of the guide tube **116**, pressure fit onto the second cannula **141**, or otherwise fixed into position within the guide tube **116** without being directly connected to the central body **100** or any element of the central body, such as the first rear cannula **140**. The venting member **160** base **300** may be defined in part by an annular recess which separates the base from the barb portion **302** that is adapted to have the open end of a flexible sleeve **150** mounted thereon. Alternatively, the venting member **160** need not have any annular recess so long as the flexible sleeve **150** has a base portion **300** which provides an air path for air to flow from inside the flexible sleeve **150** to the interior of the guide tube **116**. The air path may be provided in whole or in part by well bottom wall **123** features such as dimples **217** (Fig. 4), radial lines **219** (Fig. 5) or the like. The embodiment shown in Fig. 6, as well as the embodiments of the invention shown in Figs. 1-5 and 7-24, may be used to retrofit an existing and non-air venting needle central body **100** into an air venting blood drawing device after being connected to the guide tube **116**.

[0056] With continued reference to Fig. 6, when the front cannula **130** (or butterfly cannula **184** with respect to Figs. 23-24) is introduced to a lumen, such as a vein, to draw fluid, such as blood, the blood may readily flow through the front cannula, the first rear cannula **140**, the second rear cannula **141** and into the interior of the flexible sleeve **150**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the flexible sleeve **150** and the venting member **160** through the venting member base **300** to the ambient within the guide tube **116**. The venting member base **300** may provide a surface for air to escape from the venting member **160**. Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle) or through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**. The visual detection of blood indicates

positive vein entry, known as flash. Once flash is detected, a fluid sample container may be pressed into the open end **118** of the guide tube **116**, the second rear cannula **141** may pierce the flexible sleeve **150** and the flexible sleeve is pushed back towards the base of the second rear cannula. The shape of the venting member **160** with a wide base **300** and barb portion **302** may be such as to withstand the force of a fluid sample container being inserted into the guide tube and against the venting member without the venting member being crushed or otherwise damaged. This is necessary so that multiple sample containers can be filled with blood without the risk of leakage past a damaged venting member.

[0057] With reference to Fig. 7, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 7 is identical in all respects to that shown in Fig. 6 with the following exception. With respect to Fig. 7, one or more well bottom extensions **121** may extend from the well bottom wall **123**. The well bottom extensions **121** may surround the venting member **160** in whole or in part and may be formed so as to leave an air space for air to flow from the interior of the sleeve **150** through the venting member **160** to the ambient in the guide tube opening **118**. The well bottom extensions **121** may be semi-circular or prong shaped and surround the venting member **160**. Further, the well bottom extensions **121** may extend into the guide tube **116** a distance sufficient to protect the venting member **160** from being impacted against, damaged or dislodged by, the stopper of a container inserted into the guide tube. The well bottom extensions **121** may be formed of plastic material which is integral with the rest of the guide tube **116** and well bottom wall **123**. The well bottom extensions **121** may also be used to secure the venting member **160** and more particularly, the base portion **300** of the venting member so that the venting member is retained in place without the need to use an adhesive or other connection means to the guide tube **116**.

[0058] With reference to Fig. 8, another embodiment of the present invention is

shown in which all reference characters refer to like elements shown in the previous drawing figures. As noted above with respect to Figs. 6-7, the well bottom wall upper surface **125** may prevent blood from flowing into the well **117** when the central body **100** is seated against the well bottom wall **123**.

[0059] With continued reference to Fig. 8, the flexible sleeve **150** may be mounted or fitted onto a sleeve connector **330** which is integrally formed with the guide tube **116** within the guide tube opening **118**. A sleeve connector passage **332** may extend through the sleeve connector **330** and connect with a lateral passage **334** that extends from the sleeve connector passage **332** to a guide tube aperture **342** located along the guide tube outer wall. The guide tube aperture **342** may have a venting member **160** disposed in it, and an optional viewing window **340** disposed in it. The viewing window **340** may be transparent or translucent and may permit blood to be viewed by a user through the viewing window so as to detect flash. The viewing window **340** may be disposed next to, circumferentially about, or within the venting member **160** without departing from the intended scope of the invention. In fact, the viewing window **340** and the venting member **160** may be disposed in separate apertures in alternative embodiments. The viewing window **340** also may be unnecessary if flash is detected elsewhere, such as through a translucent or transparent butterfly connection tube, central body, flexible sleeve and/or guide tube.

[0060] The blood drawing device shown in Fig. 8 may be used as follows. The central body **100** may be connected to the guide tube **116** such that the rear portion of the central body seals against the well bottom wall upper surface **125**. Such sealing is not required in this or any other embodiments discussed, but is preferred to limit the amount of blood that may flow into the well space **117** if the central body **100** is disconnected from the guide tube **116**.

[0061] Once the central body **100** is connected to the guide tube **116**, the front cannula **130** or butterfly cannula **184** may be introduced into a lumen, such as a vein, to draw fluid, such as blood. The blood may readily flow through the front cannula **130**,

the first rear cannula **140**, the second rear cannula **141** and into the interior of the flexible sleeve **150**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the flexible sleeve **150**, the sleeve connector passage **332**, the lateral passage **334**, and the venting member **160** to the ambient outside the guide tube **116**. Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**. The visual detection of blood indicates positive vein entry, known as flash. Once flash is detected, a fluid sample container may be pressed into the open end **118** of the guide tube **116**, the second rear cannula **141** may pierce the flexible sleeve **150** and the flexible sleeve is pushed back towards the base of the second rear cannula.

[0062] With reference to Fig. 9, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 9 is identical in all respects to that shown in Fig. 8 with the following exception. With respect to Fig. 9, a well passage **336** extends from the well **117** to the aperture **342**. Air may vent from the rear cannula **140** up through the second rear cannula **141** and into the well **117**. The air may then flow through the well passage **336** and the venting member **160**. Blood may fill the well passage **336** and the aperture **340**. Blood may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**.

[0063] With reference to Fig. 10, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. A venting member **160** may be disposed against the well bottom wall **123** of the guide tube **116**. The venting member **160** base portion **300** may be adhered

to the well bottom wall of the guide tube **116**, pressure fit onto the cannula **140**, or otherwise fixed into position. A central well opening **338** may extend through the venting member **160** and the well bottom wall **123** to permit air and blood to flow into the well **117**. Alternatively, the central well opening **338** may be reduced in diameter so that the cannula **140** seals against the well bottom wall **123** and/or the venting member **160**. The venting member **160** may have a base **300** separated from a barb portion **302** by an annular recess. The barb portion **302** may be adapted to have an open end of a flexible sleeve **150** mounted thereon. Alternatively, the venting member **160** need not have any annular recess so long as the flexible sleeve **150** has a base portion **300** which provides an air path for air to flow from inside the flexible sleeve **150** to the interior of the guide tube **116**. The air path may be provided in whole or in part by well bottom wall **123** features such as dimples **217** (Fig. 4), radial lines **219** (Fig. 5) or the like.

[0064] With continued reference to Fig. 10, when the front cannula **130** or butterfly cannula **184** is introduced to a lumen, such as a vein, to draw fluid, such as blood, the blood may readily flow through the front cannula, the first rear cannula **140** and into the interior of the flexible sleeve **150**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the flexible sleeve **150** and the venting member **160** through the venting member base **300** to the ambient within the guide tube **116**. The venting member base **300** may provide a surface for air to escape from the venting member **160**. Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle) or through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**. The visual detection of blood indicates positive vein entry, known as flash. Once flash is detected, a fluid sample container may be pressed into the open end **118** of the guide tube **116**, the rear cannula **140** may pierce the flexible sleeve **150** and the flexible sleeve is pushed back towards the base of the second rear cannula.

[0065] With reference to Fig. 11, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 11 is identical in all respects to that shown in Fig. 10 with the following exception. With respect to Fig. 11, a well passage **336** extends from the well **117** to the aperture **342**. After air vents through the venting member **160**, blood may flow from the rear cannula **140** up through the central well opening **338** and into the well **117**. The blood may then flow through the well passage **336** and to the viewing window **340**. Blood may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**. The well **117** may be formed with sufficient space to permit blood to flow to the viewing window without creating significant air back-pressure in the well passage **336** and aperture **342**.

[0066] With reference to Fig. 12, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 12 is identical in all respects to that shown in Fig. 11 with the following exception. With respect to Fig. 12, one or more well bottom extensions **121** may extend from the well bottom wall **123**. The well bottom extensions **121** may surround the venting member **160** in whole or in part and may be formed so as to leave an air space for air to flow from the interior of the sleeve **150** through the venting member **160** to the ambient in the guide tube opening **118**. The well bottom extensions **121** may be semi-circular or prong shaped and surround the venting member **160**. Further, the well bottom extensions **121** may extend into the guide tube **116** a distance sufficient to protect the venting member **160** from being impacted against, damaged or dislodged by, the stopper of a container inserted into the guide tube. The well bottom extensions **121** may be formed of plastic material which is integral with the rest of the guide tube **116** and well bottom wall **123**. The well bottom extensions **121** may also be used to secure the venting member **160** and more

particularly, the base portion **300** of the venting member so that the venting member is retained in place without the need to use an adhesive or other connection means to the guide tube **116**.

[0067] With reference to Fig. 13, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 13 is identical in all respects to that shown in Fig. 10 with the following two exceptions. With respect to Fig. 13, one or more well bottom extensions **121** may extend from the well bottom wall **123**. The well bottom extensions **121** may surround the venting member **160** in whole or in part and may be formed so as to leave an air space for air to flow from the interior of the sleeve **150** through the venting member **160** to the ambient in the guide tube opening **118**. The well bottom extensions **121** may be semi-circular or prong shaped and surround the venting member **160**. Further, the well bottom extensions **121** may extend into the guide tube **116** a distance sufficient to protect the venting member **160** from being impacted against, damaged or dislodged by, the stopper of a container inserted into the guide tube. The well bottom extensions **121** may be formed of plastic material which is integral with the rest of the guide tube **116** and well bottom wall **123**. The well bottom extensions **121** may also be used to secure the venting member **160** and more particularly, the base portion **300** of the venting member so that the venting member is retained in place without the need to use an adhesive or other connection means to the guide tube **116**. Further, in Fig. 13 the central body **100** may be connected to the guide tube **116** such that the rear portion of the central body seals against the well bottom wall upper surface **125**. Such sealing is not required in this or any other embodiments discussed, but is preferred to limit the amount of blood that may flow into the well space **117** if the central body **100** is disconnected from the guide tube **116**.

[0068] With reference to Fig. 14, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The well bottom wall **123** may have a sealing membrane **310** made of

material similar to or the same as the flexible sleeve **150** which may prevent blood from flowing into the well **117** when the cannula **140** is inserted through and/or withdrawn from it.

[0069] With continued reference to Fig. 14, the flexible sleeve **150** may be mounted or fitted onto a sleeve connector **330** which is integrally formed with the guide tube **116** within the guide tube interior opening **127**. A central well opening **338** may extend through the sleeve connector **330** and connect with a lateral passage **334** that extends from the central well opening **338** to a guide tube aperture **342** located along the guide tube outer wall. The guide tube aperture **342** may have a venting member **160** disposed in it, and an optional viewing window **340** disposed in it. The viewing window **340** may be transparent or translucent and may permit blood to be viewed by a user through the viewing window so as to detect flash. The viewing window **340** may be disposed next to, circumferentially about, or within the venting member **160** without departing from the intended scope of the invention. In fact, the viewing window **340** and the venting member **160** may be disposed in separate apertures in alternative embodiments. The viewing window **340** also may be unnecessary if flash is detected elsewhere, such as through a translucent or transparent butterfly connection tube, central body, flexible sleeve and/or guide tube. The blood drawing device shown in Fig. 14 may be used in the same manner as that described above in connection with Fig. 8.

[0070] With reference to Fig. 15, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 15 is identical in all respects to that shown in Fig. 9 with the following exception. With respect to Fig. 15, the central well opening **338** is defined by the well bottom wall **123** and the sleeve connector **330**. The second rear cannula (shown in Fig. 9) is not provided. When the front cannula **130** is introduced to the vein of a patient air may vent from the rear cannula **140** up through the central well opening **338** and into the well **117**. The air may then flow through the well passage **336** and the venting member **160**. After the air is vented, blood may fill

the well passage **336** and the aperture **340**. Blood may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**.

[0071] With reference to Fig. 16, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The flexible sleeve **150** may be mounted or fitted onto a sleeve connector **330** which is integrally formed with the guide tube **116** within the guide tube opening **118**. A central well opening **338** may extend through the sleeve connector **330** and connect with a well **117**. A venting member **160** which may be a flexible membrane or other porous material may be disposed along the interior of the well bottom wall **123** so as to provide a blood barrier between the central well opening **338** and the well **117**. A well passage **336** may extend from the well **117** to the outside of the guide tube **116** outer wall. One or more raised features **344** may be provided adjacent to the end of the well passage **336** to assist a user in tactically sensing the location of the well passage so as not to block it with the user's fingers or hand.

[0072] The blood drawing device shown in Fig. 16 may be used as follows. The central body **100** may be connected to the guide tube **116** such that the rear cannula **140** extends through the venting member **160**. Once the central body **100** is connected to the guide tube **116**, the front cannula **130** or butterfly cannula **184** (in alternative embodiments that utilize a butterfly needle) may be introduced into a lumen, such as a vein, to draw fluid, such as blood. The blood may readily flow through the front cannula **130**, the rear cannula **140** and into the interior of the flexible sleeve **150**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the flexible sleeve **150**, the central well opening **338**, the venting member **160** and the well passage **336** to the ambient outside the guide tube **116**. Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly

needle), or through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**. The visual detection of blood indicates positive vein entry, known as flash. Once flash is detected, a fluid sample container may be pressed into the open end **118** of the guide tube **116**, the second rear cannula **141** may pierce the flexible sleeve **150** and the flexible sleeve is pushed back towards the base of the second rear cannula.

[0073] With reference to Fig. 17, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The flexible sleeve **150** may be mounted or fitted onto a sleeve connector **330** which is integrally formed with the guide tube **116** within the guide tube opening **118**. A central well opening **338** may be defined by a second rear cannula **141** and provide fluid communication between the interior of a flexible sleeve **150** and a well **117** provided in the guide tube **116**. A well passage **336** may extend from the well **117** to a guide tube aperture **342** located along the guide tube **116** outer wall. The guide tube aperture **342** may have a viewing window **340** disposed in it. The viewing window **340** may be transparent or translucent and may permit blood to be viewed by a user through the viewing window so as to detect flash. The flexible sleeve **150** may include a side tubulation **154** in which a venting member **160** is inserted.

[0074] The blood drawing device shown in Fig. 17 may be used as follows. The central body **100** may be connected to the guide tube **116**. Once the central body **100** is connected to the guide tube **116**, the front cannula **130** or butterfly cannula **184** may be introduced into a lumen, such as a vein, to draw fluid, such as blood. The blood may readily flow through the front cannula **130**, the first rear cannula **140**, the second rear cannula **141** and into the interior of the flexible sleeve **150**. Air within the blood drawing device **10** that would otherwise prevent or slow the flow of blood into it, may vent through the venting member **160** provided in the side tubulation **154** in the flexible sleeve **150** to the ambient inside the guide tube **116**. Blood that flows into the blood drawing device may be viewed either through the central body **100**, the butterfly

connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**. The viewing window **340** may be unnecessary if flash is detected elsewhere, such as through a translucent or transparent butterfly connection tube, central body, flexible sleeve and/or guide tube.

[0075] With reference to Fig. 18, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 18 is identical in all respects to that shown in Fig. 17 with the following exception. In Fig. 18, an air-permeable, blood impermeable flexible sleeve **151** replaces the flexible sleeve **150** shown in Fig. 17. The air-permeable, blood-impermeable sleeve **151** serves as a venting member.

[0076] The air-permeable, completely or partially blood-impermeable flexible sleeve **151** may be constructed of a material that is largely air-permeable, but partially, largely or entirely impermeable to blood. The air-permeable sleeve **151** may be used to isolate the rear cannula **140** of a blood drawing device from the ambient in the same manner as conventional sleeve may isolate rear cannulae. During a blood drawing procedure using a device not equipped with a means for venting air from the sleeve, blood from a lumen may be slowed or prevented from entering the device due to air back pressure in the device. In these devices the air in the device may be trapped because there is no vent provided. In the present embodiment, an air-permeable sleeve **151** replaces a conventional sleeve in the guide tube **116**. The air-permeable sleeve **151** may provide a pathway to vent air from the device interior, through the sleeve wall, to the ambient. As the air is vented, the blood filling the device may contact the air-permeable sleeve **151**. However, the air-permeable sleeve **151** may prevent or retard the flow of blood through its wall because the pore size of the air-permeable sleeve may be large enough to allow the passage of air, but too small to allow much or any blood to pass. This air passage-blood blockage may permit blood to fill the needle and/or the sleeve **151** more readily because there is reduced or no air back pressure inhibiting the flow of blood into

the blood drawing device. As a result, a blood drawing device equipped with the air-permeable sleeve **151** may indicate flash (the visual indication of blood flow into the needle) more readily. The air-permeable sleeve **151** may be used with conventional needle drawing or infusion sets (such as butterfly needles), hypodermic needles, or the like, to enhance flash indication.

[0077] The air-permeable sleeve **151** may be made of any suitable material that is completely or at least partially air-permeable and substantially blood impermeable, such as for example, low density polyethylene or low density rubber. One example of a method of making such material is described in U.S. Patent No. 5,641,442. A second example may be made of crumbed material of sufficiently low density/high flexibility to allow the required flexibility in spite of the use of thermal binders like polyethylene. Low density material such as low density silicone may be sifted using a #80 mesh and mixed with #100 mesh low density polyethylene. This mixture may be heated at approximately 280° F and injected into a cavity mold to form the selectively porous sleeve **151**.

[0078] An air-permeable sleeve may be constructed of porous material formed from the combination of a hydrophobic porous material with a hydrophilic porous agent. The hydrophobic porous material, for example, may be a polymeric matrix of either thermoplastic resins such as polyvinyl chloride or copolymers thereof, or synthetic or natural thermosetting rubber-like polymers. In a second example, the polymeric matrix may be rubber-like polymers combined with additives such as anti-degradants, cross-linking agents, cure inhibitors, platinum and other type catalysts, inert fillers, or like materials used to compound thermosetting compounds, and intimately mixed with a hydrophilic porous agent such as silica hydrogel, precipitated hydrated silica, for example such as that sold under the trademark Hi-Sil from PPG Industries, or polyacrylamide gel, cross-linked homopolymer of acrylamide, for example such as that sold under the trademark Agrosoake from Agrosoake International, inert fillers and/or water or solvent soluble porosics. In a third example, the polymeric matrix may be

made of a synthetic or natural thermosetting polymer or copolymer, such as those that may be made in accordance with the methods disclosed in U.S. Patent No. 4,548,835 to Takahashi, et al. and U.S. Patent No. 4,153,760 to Sundberg et al, for example, each of which is hereby incorporated by reference.

[0079] The porous agent may be prepared by polymerizing acrylamide in the presence of an aqueous sodium carbonate to produce a partially hydrolyzed, lightly cross-linked, polyacrylamide gel in accordance with the method disclosed in U.S. Patent No. 3,022,279 to Proffitt, for example, which is hereby incorporated by reference. The polyacrylamide gel may be produced in bead or granular form using an inverse suspension polymerization method for water-soluble monomer, which is disclosed in U.S. Patent No. 2,982,749 to Friedrich et al., for example, and which is hereby incorporated by reference.

[0080] In one embodiment, for example, the hydrophilic granules may be added to the hydrophobic material in sufficient quantities to create a hydrophilic/hydrophobic porous material. The porosity of the hydrophobic material may be manifested by a network of voids/pores extending throughout the matrix or binder, between neighboring particles of the dispersed filler and portions of the polymeric matrix, which may be achieved by the shrinking of the swollen hydrophilic granules during the dehydration/curing phase. The resultant degree of porosity may be controlled by the amount of water or water substitute added to the polymeric matrix binder material during the mixing phase, the vulcanization of the polymeric matrix (such as for example, under hydrostatic conditions in a steam autoclave to a state of cure using the pressurized steam as a source of heat), the proportion and size of the hydrophilic granules added, the duration of the mixing phase, and the wall thickness of the elastomeric sleeve. The hydrophilic granules may be mixed with a normally hydrophobic binder (and water or a water substitute may be added to control porosity) in a mixing type extruder.

[0081] When this material is formed into an air-permeable flexible sleeve **151**, water-

based liquids such as blood may rapidly soak into the pores/voids containing the granular material, causing the granules to swell and seal the pores/voids contained within the polymeric matrix. Thus, the air-permeable flexible sleeve, which is initially permeable to air, may become relatively impermeable to liquids, such as blood, due to the swelling of the moisture reactive granules entrapped within the pores/voids within the polymeric matrix.

[0082] With reference to Fig. 19, another embodiment of the present invention is shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiment shown in Fig. 19 is identical in all respects to that shown in Fig. 17 with the following exception.

[0083] In the embodiment shown in Fig. 19, a portion of the flexible sleeve **150** may be made to be porous to air. A challenge associated with making the flexible porous sleeve **150** shown in Fig. 19 is that many methods of making a material porous may render the material less flexible. For example, porous "soaker" hoses are made by mixing ground rubber with a thermoplastic such as polyethylene which allows the ground rubber to be "sintered" or stuck together by melting the polyethylene. The addition of the polyethylene makes the hose much stiffer than a plain rubber hose. The same may be true when making a fully porous multiple sample sleeve as shown in Fig. 18 – the resulting sleeve may be less flexible than required. As a result, one solution is to restrict the porous portion of the flexible sleeve **150** to the area near but not all the way at the open end of the sleeve as shown in Fig. 19, so that air can vent from the sleeve while still permitting the open end of the sleeve and the closed end of the sleeve to be made of relatively more flexible material which does not vent. This way the open end of the sleeve may be flexible enough to be stretched over the sleeve connector **330** and the closed end of the sleeve may be flexible enough to be pierced by the second rear cannula **141** without breaking apart while reverting to its original shape after being compressed by the vacuum tube after its removal. This ability to maintain the sleeve's compressibility and "memory" function may be important to the proper functioning of the

sleeve.

[0084] With reference to Fig. 19, the flexible sleeve **150** may be made of a first type of flexible sleeve material which does not substantially vent air (i.e., is the air-impermeable portion of the sleeve) such as the material described in U.S. Patent No. 3,877,465 to Miyake, for example, and of a second type of flexible sleeve material that makes up the venting member **160** which is air-permeable and completely or partially blood-impermeable (i.e., the air-permeable blood-impermeable portion of the sleeve) and formed as a venting port or wall portion added to or incorporated or integrated into the sleeve **150**. The venting member **160** may be of any shape or size suitable for permitting air to vent from the interior of the sleeve **150** while completely or substantially preventing the passage of blood. The venting member **160** may be made of some flexible material other than just air, meaning that the venting member **160** is not merely an opening, but rather a second type of material having numerous small air passages as distinguished from the first type of material that makes up the flexible sleeve **150** or a single larger opening or hole in the first type of material.

[0085] In the embodiment of the invention shown in Fig. 19, the venting member **160** may be constructed of a material that is largely air-permeable, but partially, largely, or entirely impermeable to blood, and preferably made of similar or the same material as used to construct the sleeve **151** shown in Figure 18. Preferably, the venting member **160** may be provided as near to the open end of the flexible sleeve **150** as is practically possible, however, in alternative embodiments, the venting member may be placed in alternate locations closer to or near the closed end of the flexible sleeve **150**.

[0086] The porous venting member **160** shown in Fig. 19 could be achieved by forming a part of the sleeve wall by partially hydrating an absorbent such as polyacrylamide gel with water and mixing it with a heat cured injection molding silicone. When subjected to the typical curing temperatures of 120-200° degrees Celsius the water may convert to steam once the sleeve is ejected from the mold. This may create an open cell structure which contains granules of polyacrylamide. These granules may

be processed further during a post cure phase where the granules are further dehydrated with heated dry air. This drying process may create open spaces around each granule which allows air to escape. These same granules absorb water and swell when exposed to blood, thereby sealing the venting portion to prevent leakage. With particular reference to Fig. 19, the resulting porous blood-impermeable air-permeable ring shaped venting member **160** can be inserted into sleeve molds where transparent silicone can be injected adjacent to both edges of the venting port, thus bonding the venting portion with the transparent, more flexible body portion material of the sleeve.

[0087] With reference to Figs. 20-22, three other embodiments of the present invention are shown in which all reference characters refer to like elements shown in the previous drawing figures. The embodiments shown in Figs. 20-22 are identical in all respects to those shown in Figs. 17-19, respectively, with the following exception. With respect to Figs. 20-22, the central well opening **338** is defined by the well bottom wall **123** and the sleeve connector **330**. The second rear cannula (shown in Figs. 17-19) is not provided. When the front cannula **130** is introduced to the vein of a patient air may vent from the rear cannula **140** through the venting members **160** or air-permeable, blood-impermeable flexible sleeve **151** shown in Figs. 20-22. After the air is vented, blood may fill the well passage **336** and the aperture **340**. Blood may be viewed either through the central body **100**, the butterfly connection tube **182** (in embodiments that use a butterfly needle), through a transparent or translucent flexible sleeve **150** and transparent or translucent guide tube **116**, or through the optional viewing window **340**. As noted above, the size of the well **117** may be sufficient to permit blood to fill the aperture **342** without developing sufficient air back-pressure to prevent such filling.

[0088] It is appreciated that the embodiments of the invention shown in Figs. 1-24 may be altered as follows without departing from the intended scope of the invention. The shoulder **119**, the dimples **217** and the radial lines **219** on the bottom of the well **117** could be replaced by a shoulder, raised dimples or raised radial lines on the surface of the venting member **160** closest to the well bottom wall **123**. Accordingly, the

illustrations provided in Figs. 1, 4 and 5 of the shoulder **119**, the dimples **217** and the radial lines **219** are intended to also illustrate such features as they may be provided on a venting member.

[0089] With regard to Figs. 23-24, the butterfly needle **180** may be connected to the Luer-type hub **102** via a butterfly connection tube **182**. The butterfly needle **180** may include a butterfly (*i.e.*, front) cannula **184** and one or more wings **186**. The butterfly cannula **184** may be inserted directly into the body lumen for blood collection. Flash may be observed in the transparent or translucent butterfly connection tube **182**, in which case the central body **100** need not be transparent or translucent (although it could be).

[0090] With continued reference to Figs. 23-24, known butterfly needles may use a butterfly connection tube **182** approximately 12 or more inches in length. This length of tubing is used so as to provide a sufficiently long column of air to permit flash observation when the blood-drawing device **10** is not provided with an air vent. Specifically, when a butterfly connection tube is used without an air vent, the flow of fluid through the butterfly needle may compress the volume of air in the butterfly connection tube **182**, the fluid passage **110**, the rear cannula **140**, and the space between the rear cannula and the flexible sleeve **150**. Because there is no vent provided, as blood flows into the device, the air in the device exerts an increasing level of backpressure on the blood, which may prevent blood flow and flash detection. The inclusion of a butterfly connection tube approximately 12 inches in length or greater increases the relative volume of air in the blood collection device. The increased volume of air in the device may permit flash detection before the air backpressure in the device rises to a level that prevents further blood flow into the device and could frustrate flash detection. Butterfly connection tubes of this length may be coiled in packaging, and retain some coil memory after they are removed from their packaging. Previously coiled butterfly connection tubes may resist being straightened for use and have an inherent bias towards returning to their coiled shape. Accordingly, manipulation of a

butterfly needle attached to a previously coiled butterfly connection tube may be difficult due to the connection tube's tendency to recoil. This action can be the cause of accidental needle sticks for the healthcare worker and the patient. Furthermore, the coil memory of the tubing may make handling generally difficult for lumen insertion, and/or maintenance of the needle in the lumen.

[0091] The butterfly connection tube **182** used in the devices shown in Figs. 23-24 may be less than approximately 12 inches in length, and more preferably, may be only a few inches in length as a result of the inclusion of a venting member **160** in the blood-drawing device **10**. The inclusion of the venting member **160** may obviate the need for a relatively long column of air in the butterfly connection tube that otherwise may be needed to indicate flash. The use of a shortened butterfly connection tube **182** may also obviate the need to coil the tube prior to use, thereby eliminating the issues associated with coil memory in the tube, as well as make it possible to use rigid or semi-rigid connection tubes that may better enable placement of the front cannula into the body lumen.

[0092] Each of the embodiments of the present invention shown in all of the afore-noted figures may also utilize a transparent or translucent flexible sleeve **150** to provide flash detection. An example of a transparent sleeve is disclosed in U.S. Patent No. 3,886,930 to Ryan, which is hereby incorporated by reference. Use of a transparent or translucent sleeve **150** may make it unnecessary for the central body **100** or other elements of the device to be constructed of transparent or translucent material because the flash may be detected through the wall of the sleeve itself and thereby allow for the retrofitting of known blood-drawing devices to provide air venting and flash detection without other modification of the device. Use of a transparent or translucent sleeve **150** may also obviate the need to have discreet front and rear cannulae **130** and **140**. The front and rear cannulae may be constructed from a single integral piece of material because in this embodiment of the invention there may be no need to view flash in the central body **100**.

[0093] Each of the embodiments of the invention described above may also be modified such that the porous member **160** includes or is constructed of any one or more of a number of substances that may permit air venting, and limit and reduce blood seepage, but not completely prevent blood seepage through the particular porous structure. For example, hydrophilic and/or hydrophobic substances such as polyethylene and granular starch, cellulose, polyacrylamide gel, or the like may be used. Such substances are known in the art, and may be used to permit gas (*e.g.*, air) to flow through them, but absorb or block liquid substances. Accordingly, a porous member comprised of these materials may be used to permit the air in a blood drawing device to vent past it until it is contacted by a liquid, such as blood, at which time the blood may be absorbed.

[0094] Similarly, glass powder or fiber may be used to simulate clotting, or a clotting agent, such as dilute Russell Viper Venom, may be used to permit air venting with little or reduced blood seepage. Russell Viper Venom is known in the art as a clotting agent. A porous member **160** impregnated with a clotting agent or simulating clotting agent may be used to permit the air in a blood drawing device to vent until it is contacted by blood, at which time the blood may clot or act as clotted and reduce further blood seepage through the porous member. As a result, use of hydrophilic and/or clotting agents in the previously described porous member may permit improved blood flow into a blood drawing device and flash detection.

[0095] It will be apparent to those skilled in the art that variations and modifications of the present invention can be made without departing from the scope or spirit of the invention. For example, the shape, size, and material selection for the various components of the blood-drawing device may be changed without departing from the intended scope of the invention and appended claims. It is further appreciated that forming one or more elements of the apparatus embodiments of the present invention integrally as opposed to separately is intended to fall within the scope of the invention and appended claims.

WHAT IS CLAIMED IS:

1. A guide tube assembly for connection to a device for drawing fluid from a lumen, comprising:

a guide tube (116) having an open end (118) and a well (117);

a flexible sleeve (150, 151) having an interior space in fluid communication with the well (117) and extending into the guide tube (116);

one or more passages (332, 334, 336, 338) extending through the guide tube (116) which are in fluid communication with the flexible sleeve (150) interior space; and

a venting member (160) connected to the guide tube (116) or incorporated into the flexible sleeve (150, 151), said venting member in fluid communication with the one or more passages (332, 334, 336, 338) and disposed between the flexible sleeve (150, 151) interior space and an ambient.

2. The guide tube assembly of Claim 1, wherein:

the guide tube (116) has an interior opening (127) and a substantially closed end (129);

the well (117) is defined by a well bottom wall (123) and is formed in the substantially closed end (129) of the guide tube (116);

one of the one or more passages is a central well opening (338) extending from the well (117) to the guide tube interior opening (127);

the venting member (160) is connected to the guide tube (116) within the guide tube interior opening (127);

the flexible sleeve (150) is mounted on the venting member (160) and extends into the guide tube interior opening (127), said sleeve defining an interior space; and

one or more well bottom extensions (121) extend into the guide tube interior opening (127) adjacent to the venting member (160).

3. The guide tube of Claim 2 wherein the venting member (160) has a base (300) exposed to the ambient and a barb portion (302) adapted to receive the flexible sleeve (150).

4. The guide tube of Claim 3 wherein the venting member (160) is adhered to the well bottom wall (123).

5. The guide tube of Claim 3 wherein the venting member (160) contacts raised dimples (217) provided on the well bottom wall (123).

6. The guide tube of Claim 3 wherein the venting member (160) contacts a raised shoulder (119) provided on the well bottom wall (123).

7. The guide tube of Claim 3 wherein the venting member (160) contacts raised radial lines (219) provided on the well bottom wall (123).

8. The guide tube of Claim 2 wherein the central well opening (338) is defined by a rear cannula (141) connected to the guide tube (116) and extending into the guide tube interior opening (127).

9. The guide tube of Claim 8 wherein the rear cannula (141) has a stepped diameter (143).

10. The guide tube of Claim 2 further comprising a well bottom wall (123) upper surface (125) adapted to seal against a central body (100) of a blood drawing device (10).

11. The guide tube of Claim 2 wherein the one or more well bottom extensions (121) are adapted to retain the venting member (160) by a frictional fit.

12. The guide tube of Claim 2 wherein the one or more well bottom extensions (121) extend an equal to greater distance into the guide tube interior opening (127) than the venting member (160).

13. The guide tube of Claim 2 further comprising:

a well passage (336) extending from the well (117) to an aperture (342) provided in a side wall of the guide tube (116); and

a viewing window (344) disposed in the aperture (342).

14. The guide tube of Claim 2 wherein the guide tube (116) and the flexible sleeve (150) are transparent or translucent.

15. The guide tube assembly of Claim 1, wherein:

the guide tube (116) has an interior opening (127) and a substantially closed end (129);

the well (117) is defined by a well bottom wall (123) and is formed in the substantially closed end (129) of the guide tube (116);

one of the one or more passages is a central well opening (338) extending from the well (117) to the guide tube interior opening (127);

the venting member (160) is connected to the guide tube (116) within the guide tube interior opening (127), said venting member having a base (300) and a barb portion (302); and

the flexible sleeve (150) is mounted on the venting member (160) and extends into the guide tube interior opening (127), said sleeve defining an interior space and being mounted on said venting member so that the base (300) of the venting member is exposed to an ambient.

16. The guide tube of Claim 15 wherein the venting member (160) is adhered to the well bottom wall (123).

17. The guide tube of Claim 15 wherein the central well opening (338) is defined by a rear cannula (141) connected to the guide tube (116) and extending into the guide tube interior opening (127).

18. The guide tube of Claim 17 wherein the rear cannula (141) has a stepped diameter (143).

19. The guide tube of Claim 15 further comprising a well bottom wall (123) upper surface (125) adapted to seal against a central body (100) of a blood drawing device (10).

20. The guide tube of Claim 15 further comprising:

a well passage (336) extending from the well (117) to an aperture (342) provided in a side wall of the guide tube (116); and

a viewing window (344) disposed in the aperture (342).

21. The guide tube of Claim 15 wherein the guide tube (116) and the flexible sleeve

(150) are transparent or translucent.

22. The guide tube assembly of Claim 1 further comprising:

a sleeve connector (330) extending from a well bottom wall (123) into a guide tube interior opening (127), and wherein

the guide tube (116) has a substantially closed end (129);

the well (117) is defined by the well bottom wall (123) and is formed in the substantially closed end (129) of the guide tube (116);

one of the one or more passages is a central well opening (338) extending from the well (117) to the guide tube interior opening (127) through the sleeve connector (330);

the flexible sleeve (150) is mounted on the sleeve connector (330) and extends into the guide tube interior opening (127), said sleeve defining an interior space; and

the one or more passages (332, 334, 336, 338) connect the sleeve interior space with an aperture (342) provided in a wall of the guide tube (116).

23. The guide tube of Claim 22 wherein the venting member (160) is disposed in the aperture (342).

24. The guide tube of Claim 23 further comprising a viewing window (340) disposed in the aperture (342).

25. The guide tube of Claim 24 wherein the viewing window (340) is disposed within the venting member (160).

26. The guide tube of Claim 24 wherein the viewing window (340) is disposed about the venting member (160).

27. The guide tube of Claim 24 wherein the viewing window (340) is disposed adjacent to the venting member (160).

28. The guide tube of Claim 22 further comprising a viewing window (340) disposed in the aperture (342).

29. The guide tube of Claim 22 further comprising:

a second aperture in the guide tube (116) wall communicating with the one or

more passages (332, 334, 336, 338); and

a viewing window (340) disposed in the second aperture.

30. The guide tube of Claim 22 wherein the central well opening (338) is defined by a rear cannula (141) connected to the guide tube (116) and extending into the guide tube interior opening (127).

31. The guide tube of Claim 30 wherein the rear cannula (141) has a stepped diameter (143).

32. The guide tube of Claim 22 further comprising a well bottom wall (123) upper surface (125) adapted to seal against a central body (100) of a blood drawing device (10).

33. The guide tube of Claim 22 further comprising a sealing membrane (310) disposed in the well (117) along the well bottom wall (123).

34. The guide tube of Claim 22 wherein the one or more passages (332, 334, 336, 338) communicate with the well (117).

35. The guide tube of Claim 22 wherein the venting member (160) is disposed in the well (117) along the well bottom wall (123).

36. The guide tube of Claim 22 wherein the aperture (340) is surrounded by one or more raised features (344) on the wall of the guide tube (116).

37. The guide tube of Claim 22 wherein the venting member (160) is disposed in a tubulation (154) provided in the side wall of the flexible sleeve (150).

38. The guide tube of Claim 37 further comprising a viewing window (340) disposed in the aperture (342).

39. The guide tube of Claim 37 wherein the central well opening (338) is defined by a rear cannula (141) connected to the guide tube (116) and extending into the guide tube interior opening (127).

40. The guide tube of Claim 39 wherein the rear cannula (141) has a stepped diameter (143).

41. The guide tube of Claim 22 wherein the venting member (160) comprises an air-

permeable sleeve (151) or is integrated into a portion of the flexible sleeve (150).

42. The guide tube of Claim 41 further comprising a viewing window (340) disposed in the aperture (342).

43. The guide tube of Claim 41 wherein the central well opening (338) is defined by a rear cannula (141) connected to the guide tube (116) and extending into the guide tube interior opening (127).

44. The guide tube of Claim 43 wherein the rear cannula (141) has a stepped diameter (143).

45. The guide tube of Claim 22 wherein the guide tube (116) and the flexible sleeve (150) are transparent or translucent.

46. The device of Claims 2, 15 and 22 wherein the venting member (160) is permeable to air and impermeable to blood.

47. The device of Claim 1, further comprising:

a first connector (103) of a Luer-adapter connected to the guide tube (116); and

a butterfly needle (180) connected to the first connector of the Luer-adapter by a second connector (102).

48. The device of Claim 1, further comprising:

a first connector (103) of a Luer-adapter integrally formed in an end of the guide tube (116) opposite the guide tube open end (118); and

a butterfly needle (180) connected to the first connector of the Luer-adapter by a second connector (102).

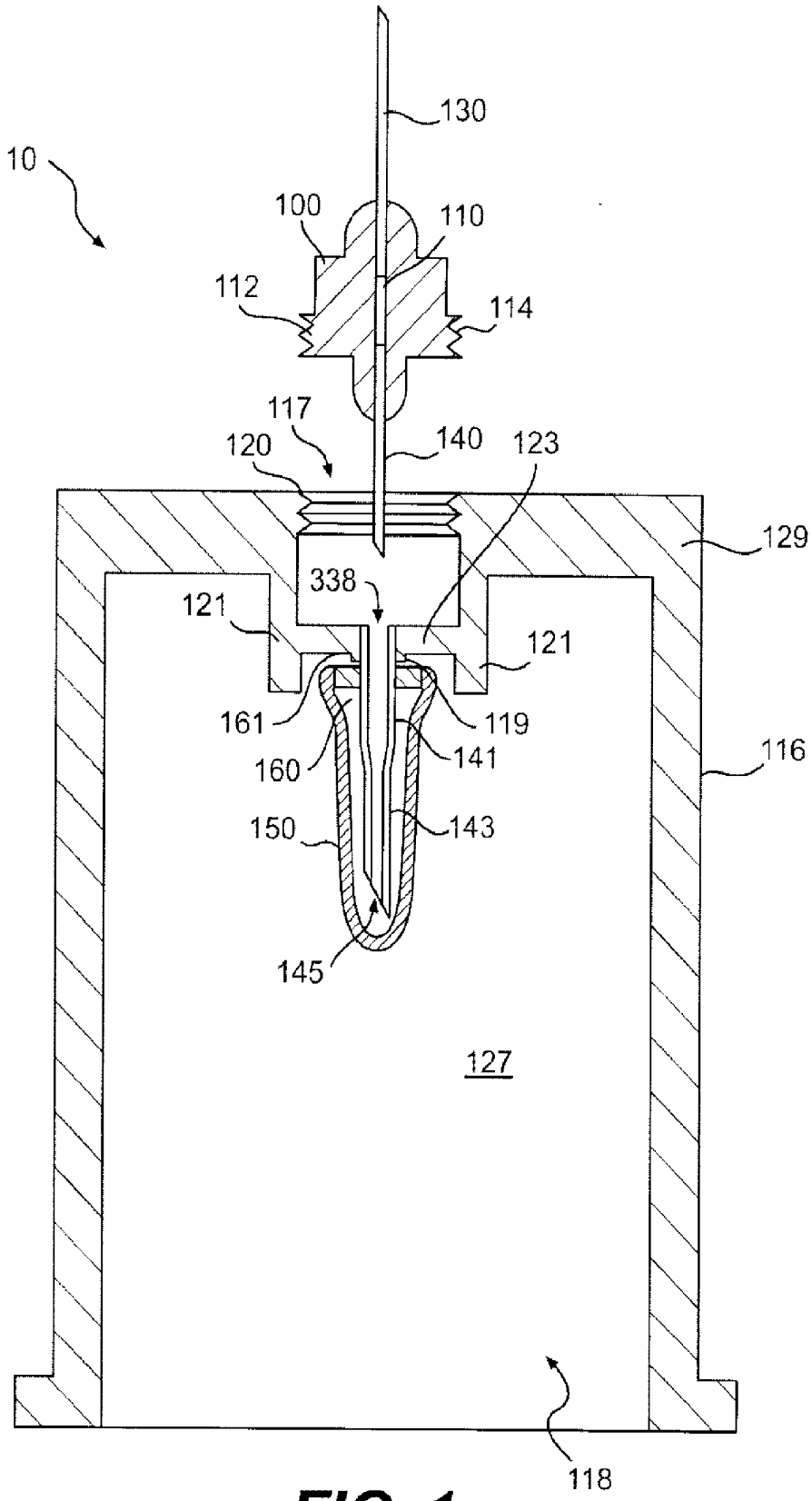

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FIG. 1

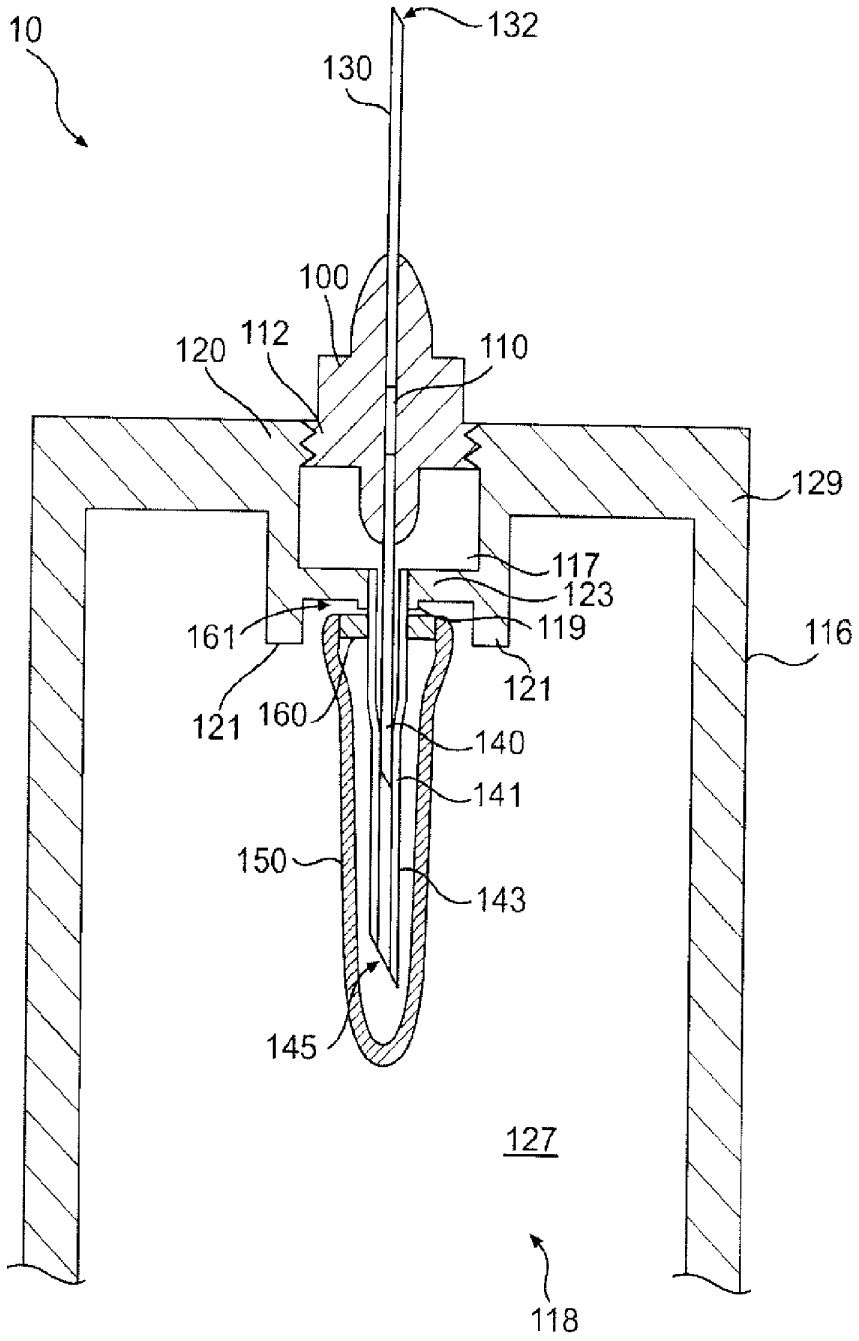

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FIG. 2

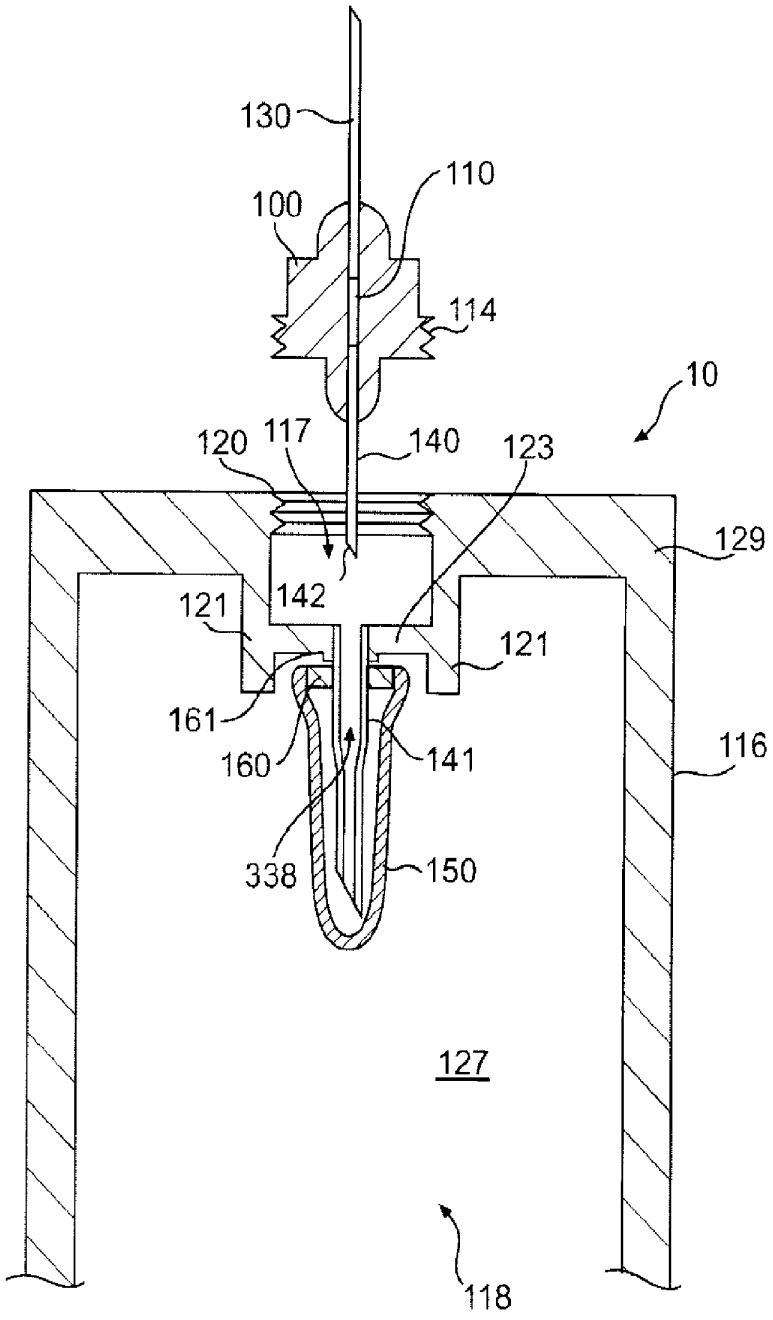


FIG. 3

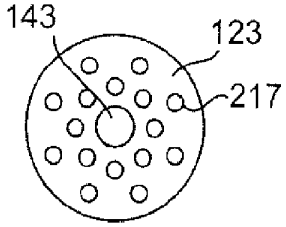


FIG. 4

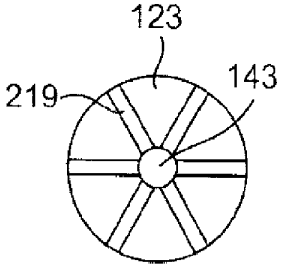


FIG. 5

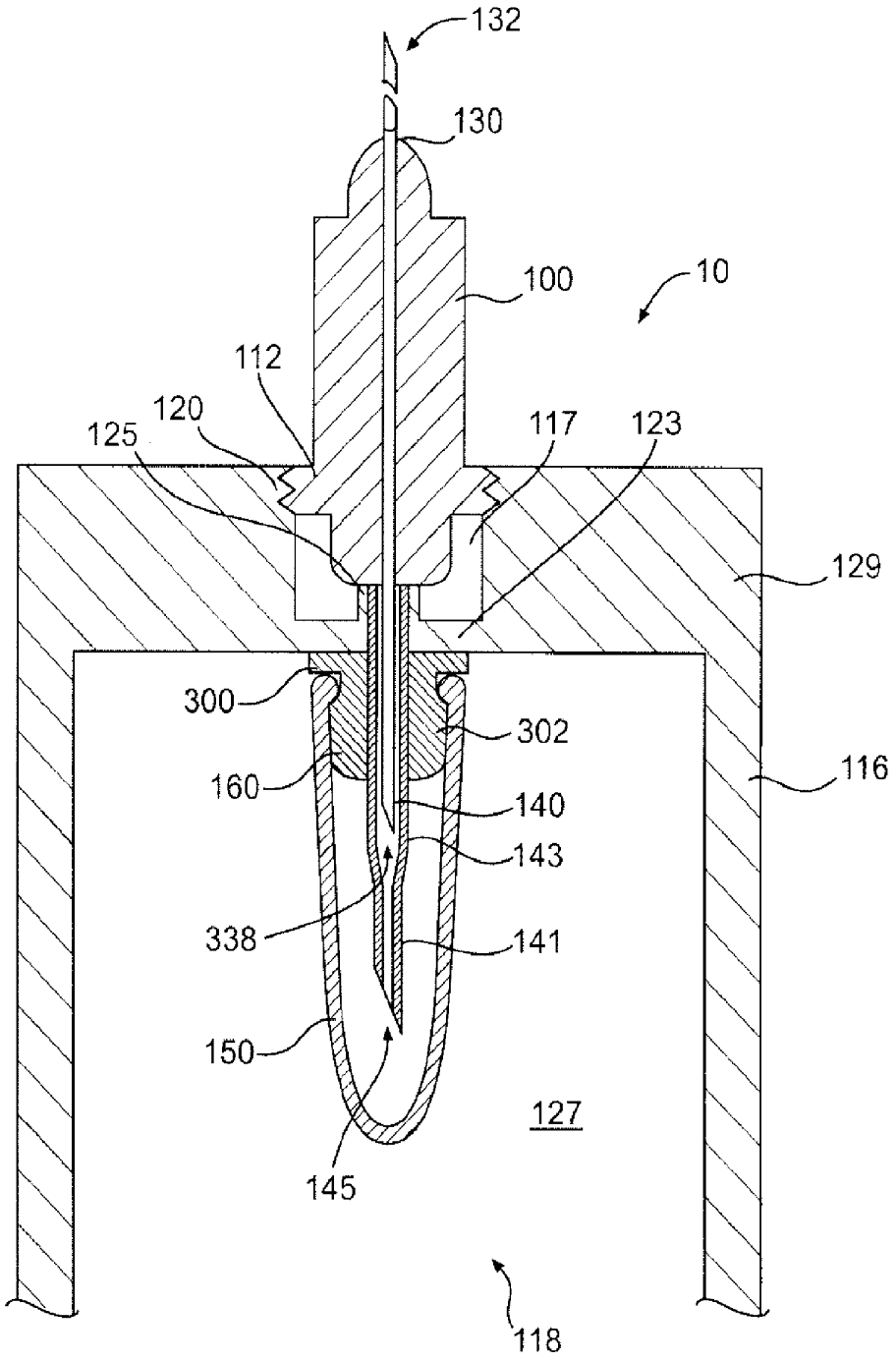

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FIG. 6

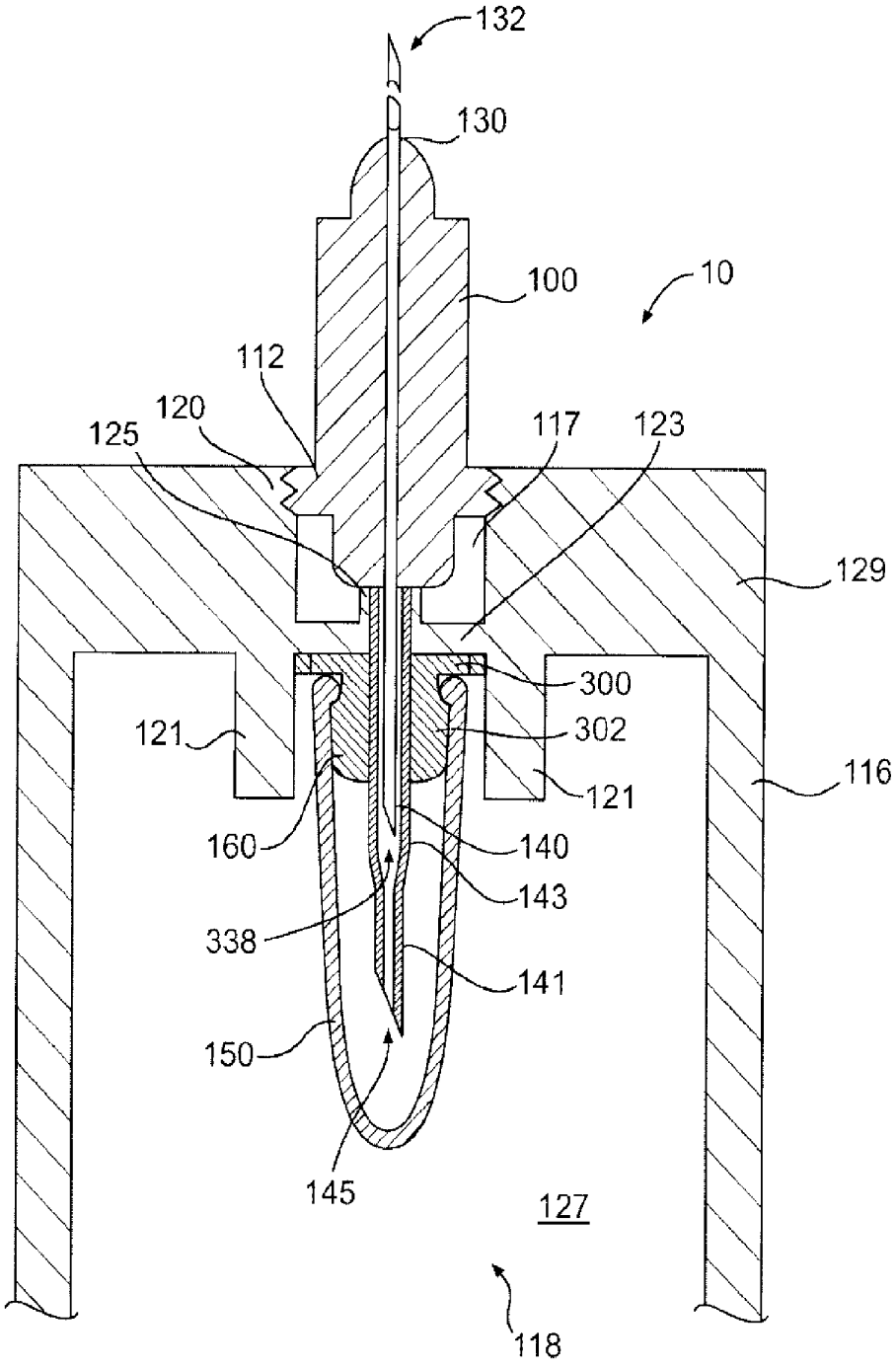

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FIG. 7

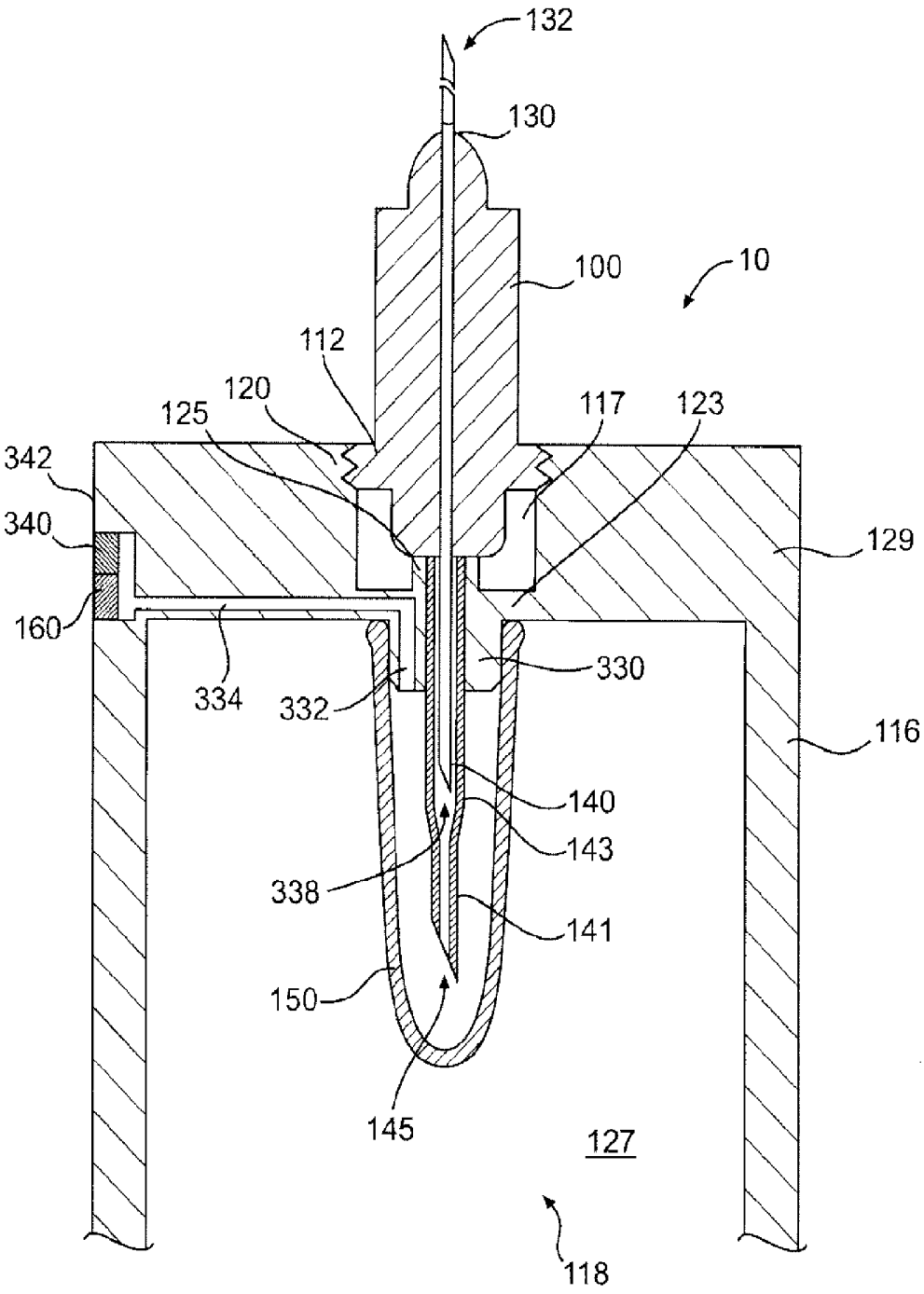

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FIG. 8

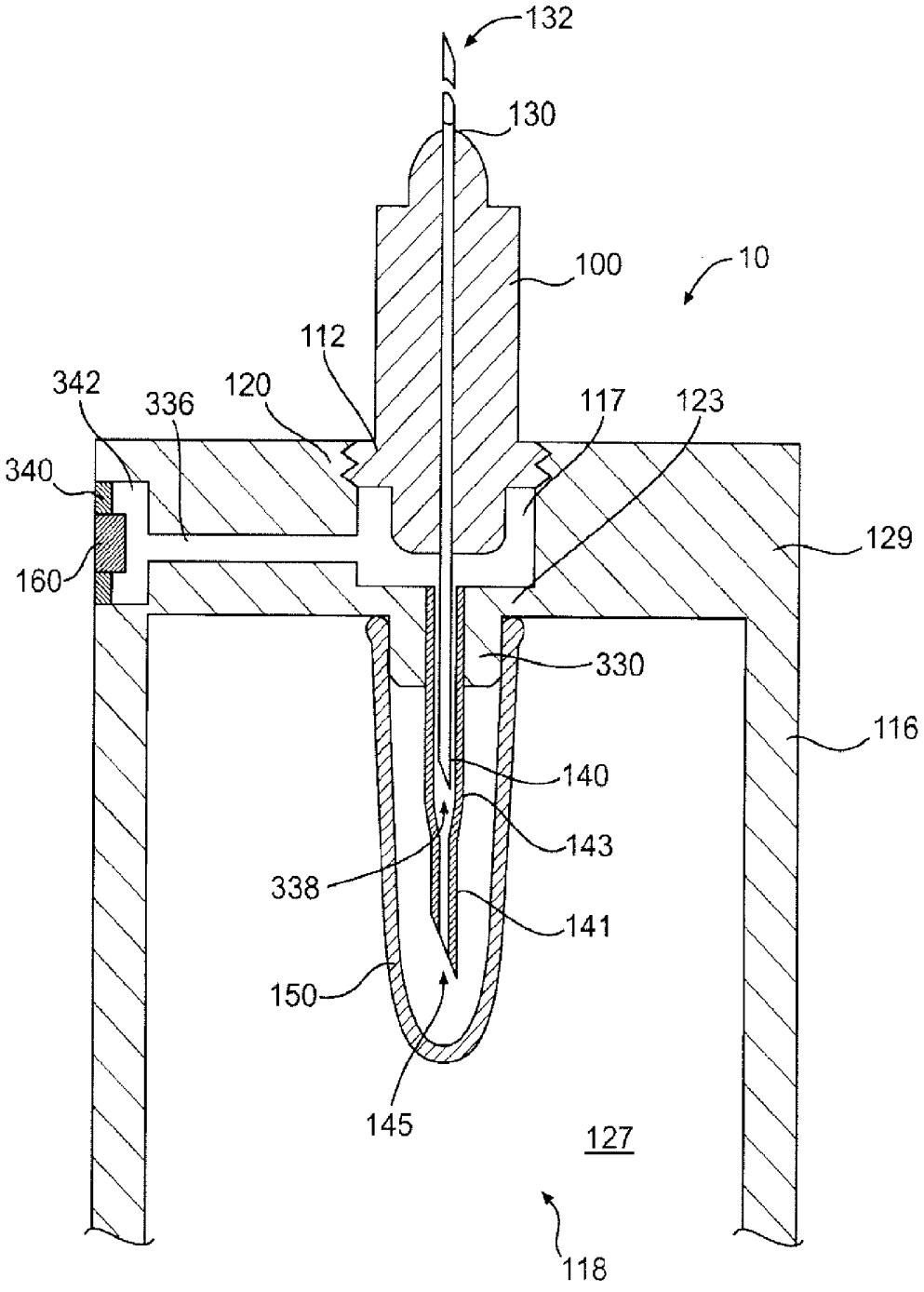

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FIG. 9

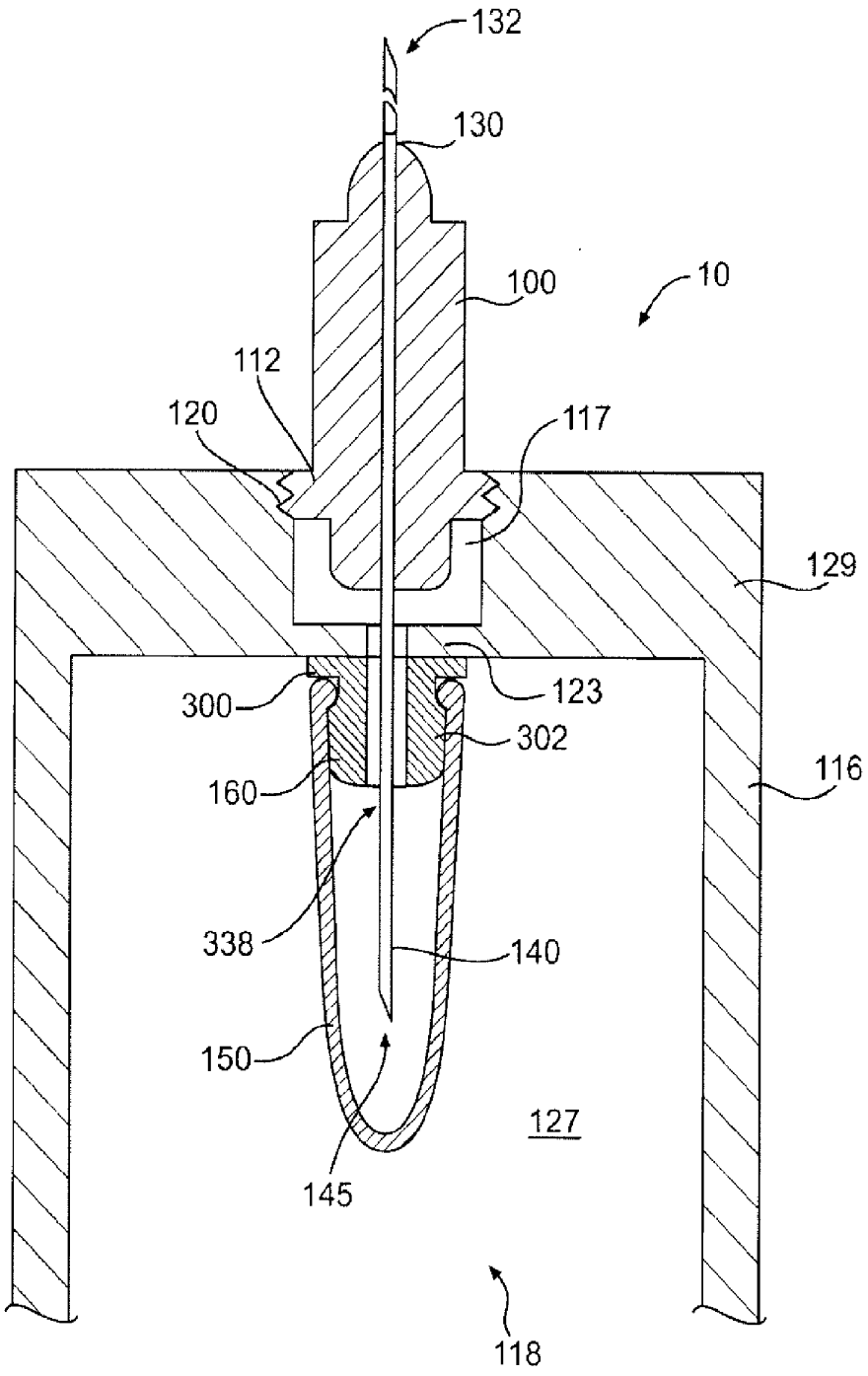

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FIG. 10

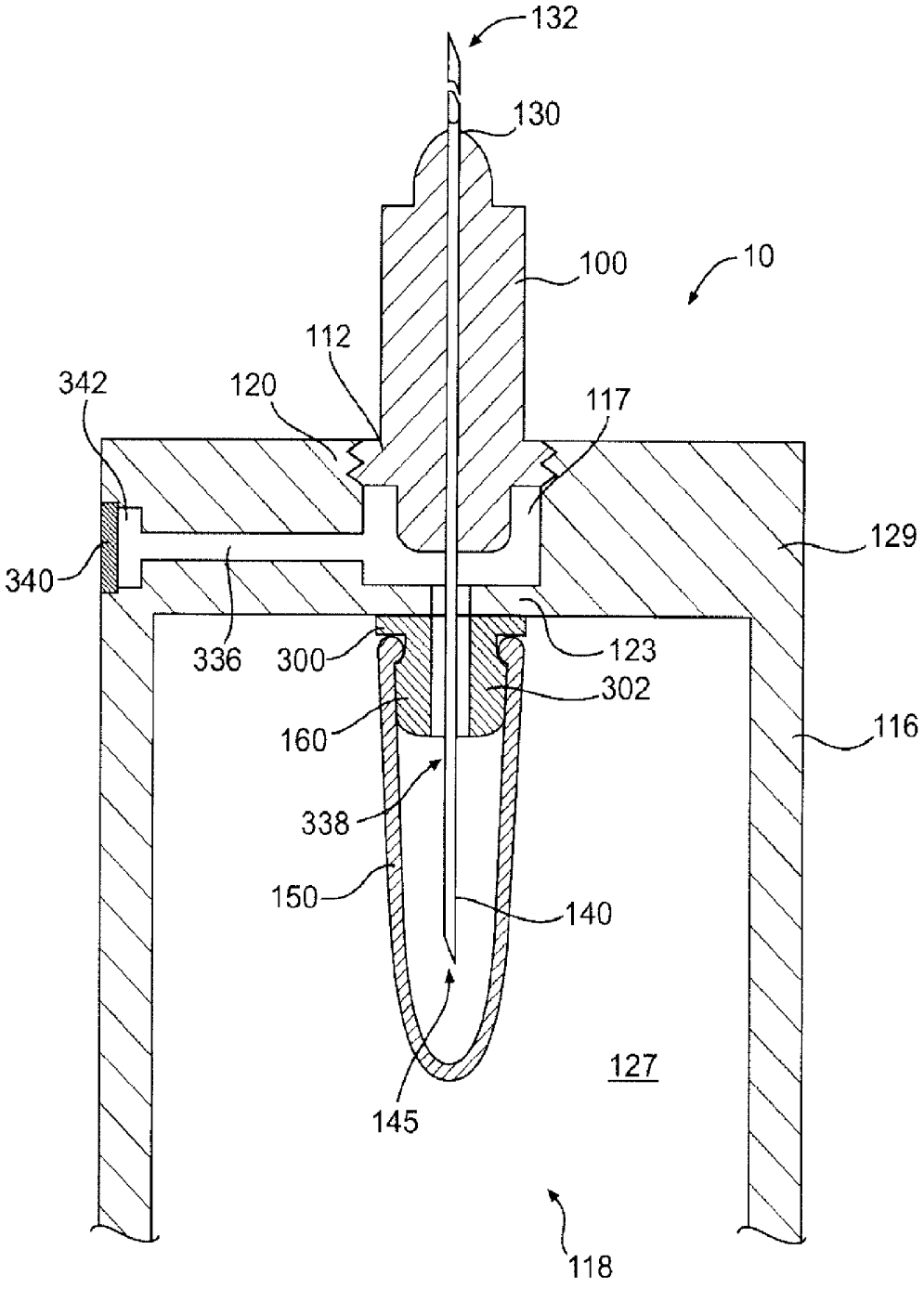

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FIG. 11

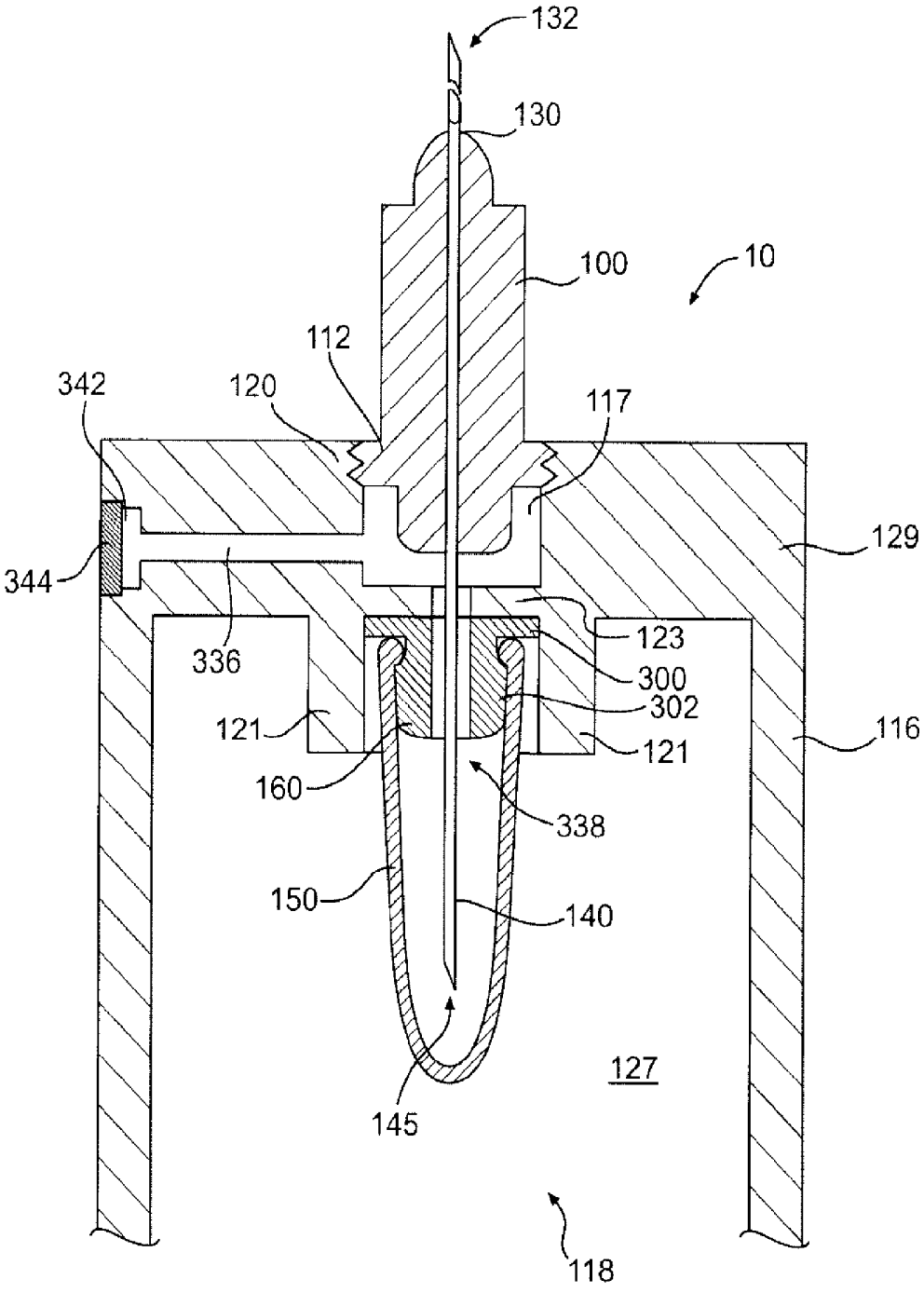

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FIG. 12

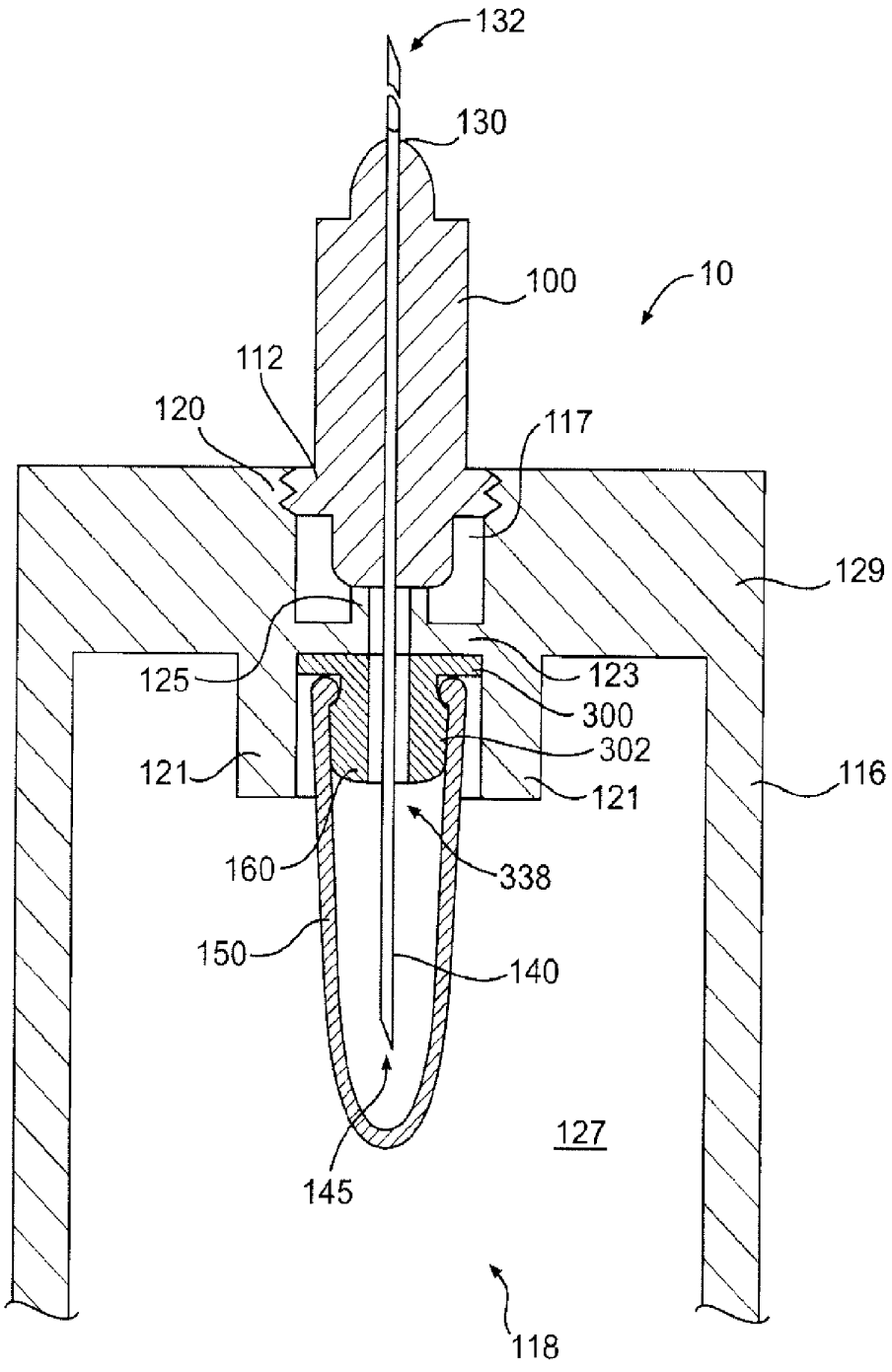

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FIG. 13

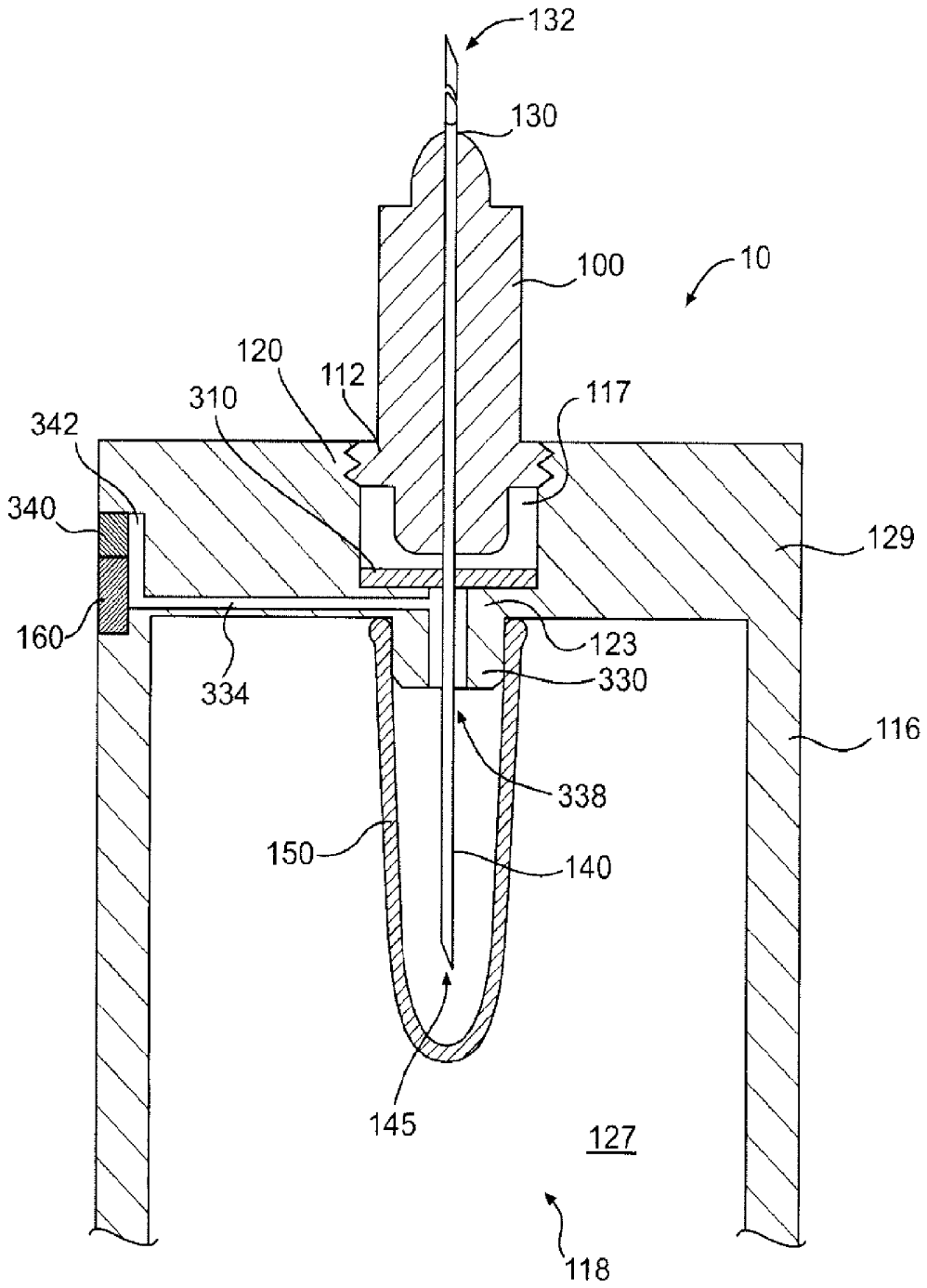

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FIG. 14

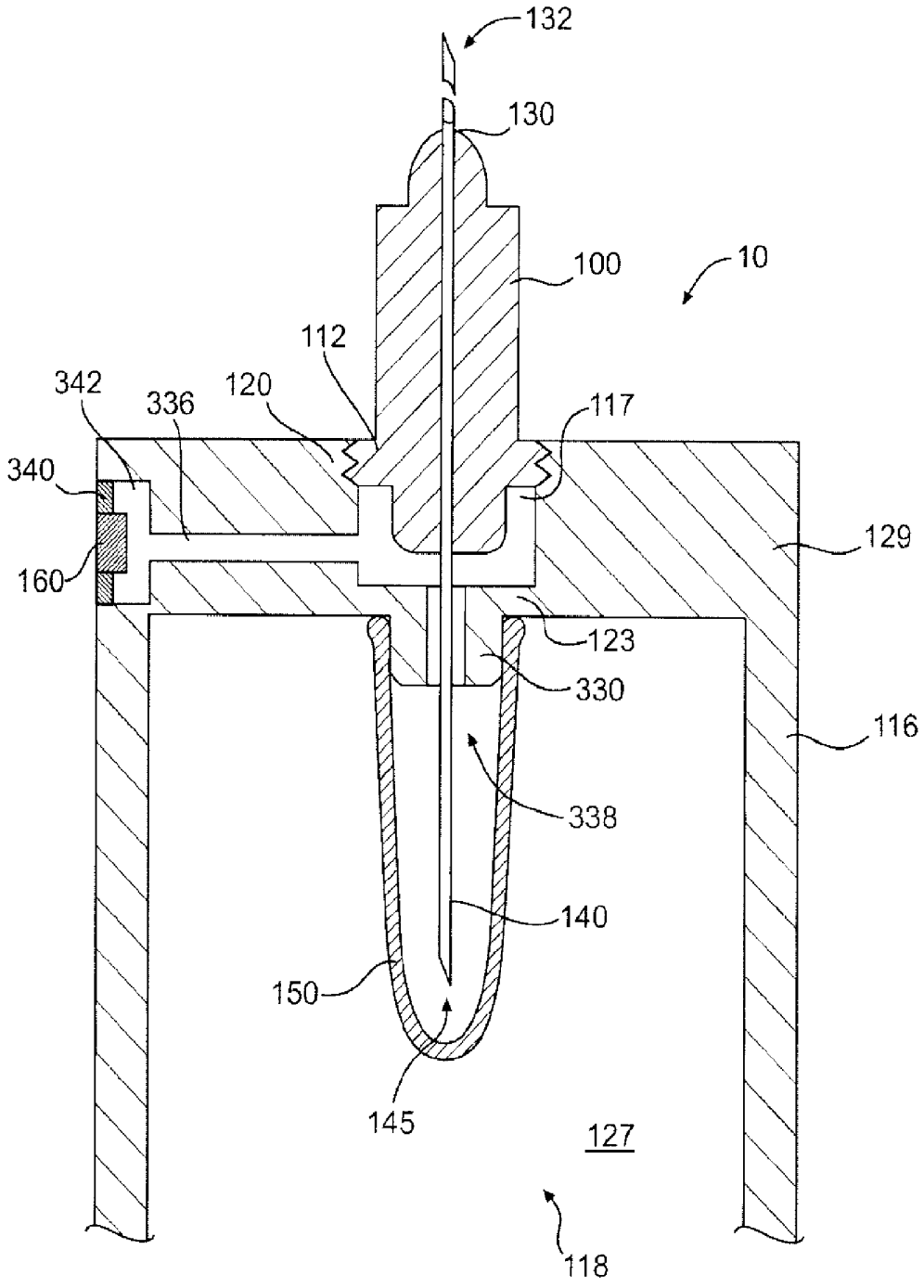

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FIG. 15

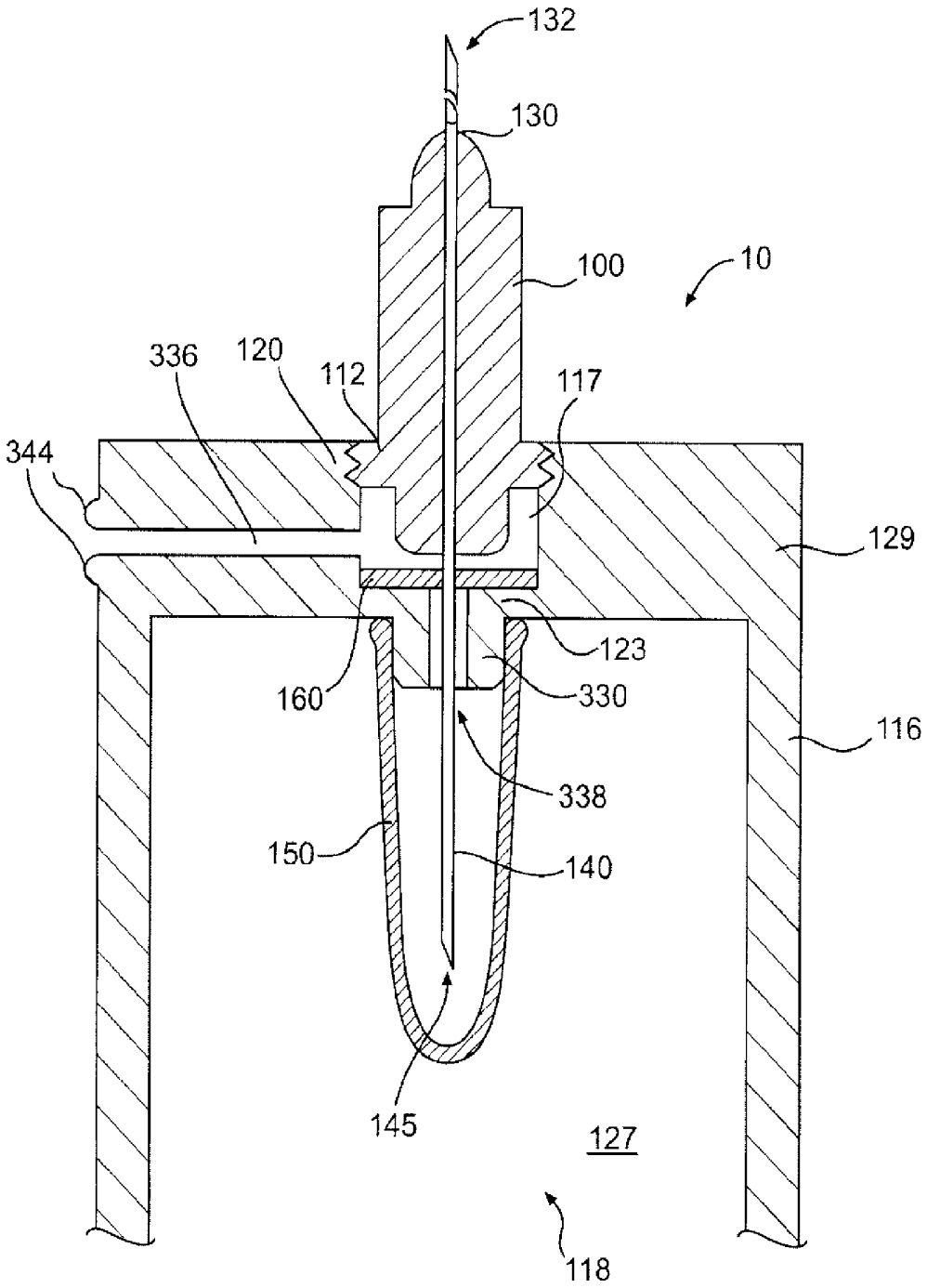

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FIG. 16

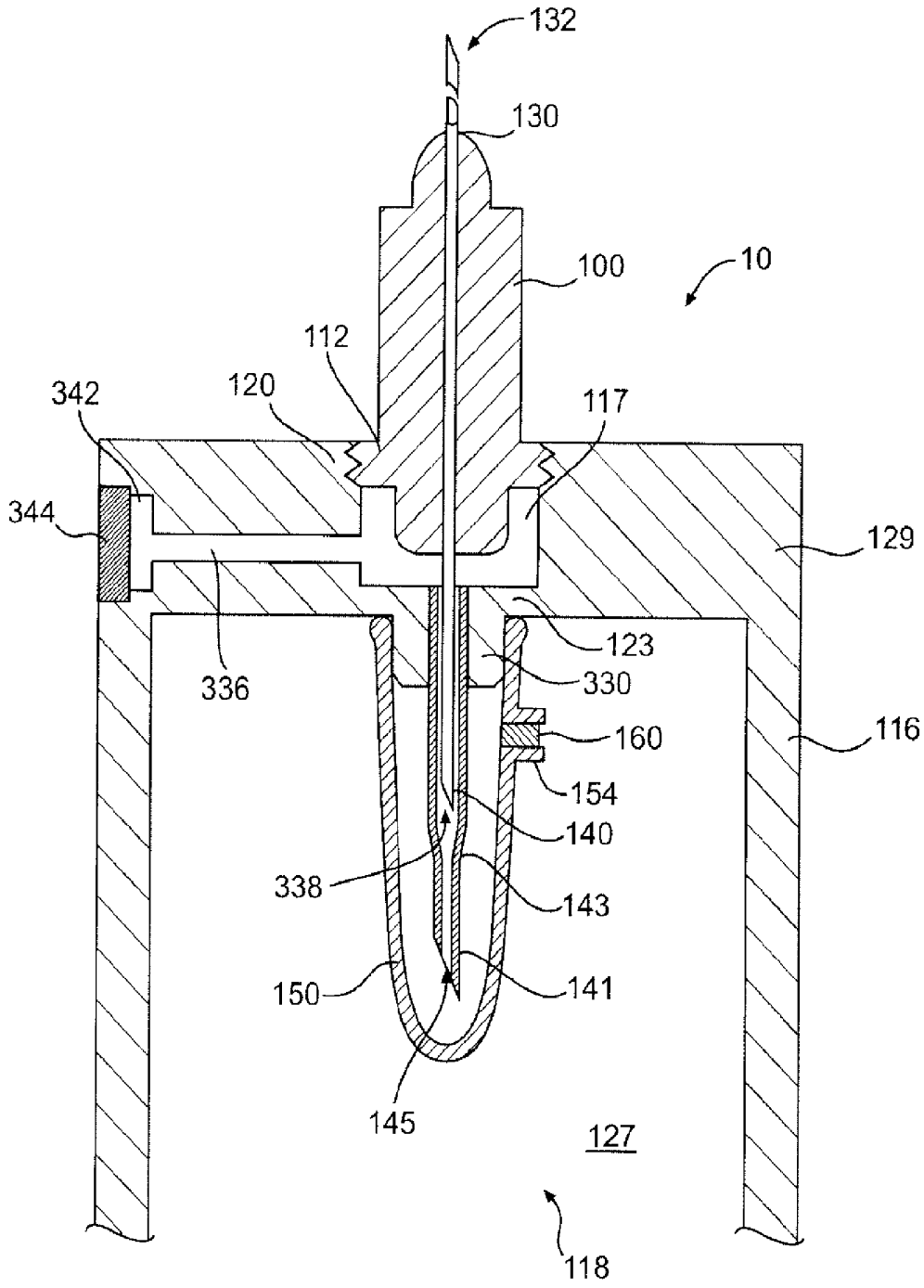

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FIG. 17

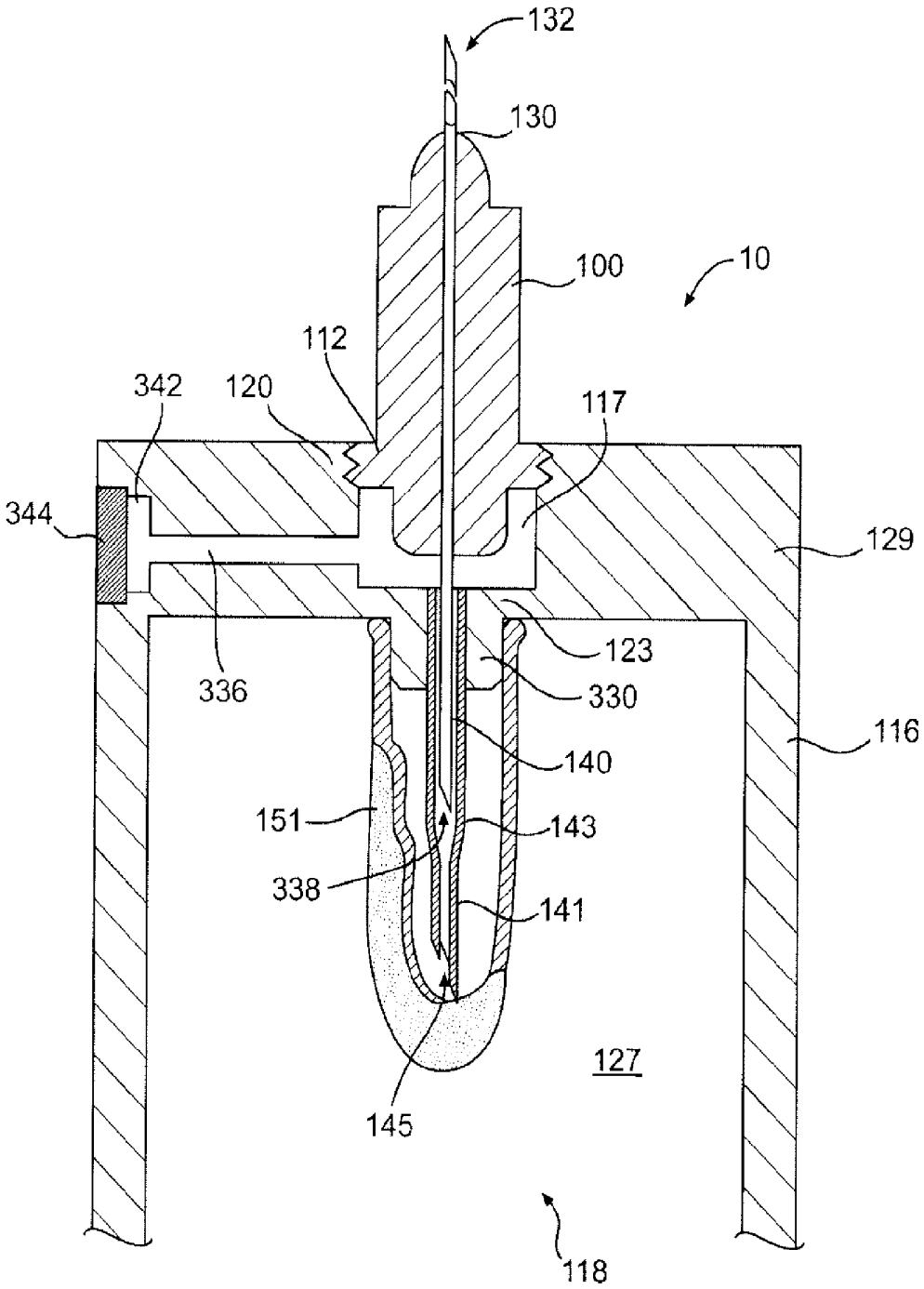

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FIG. 18

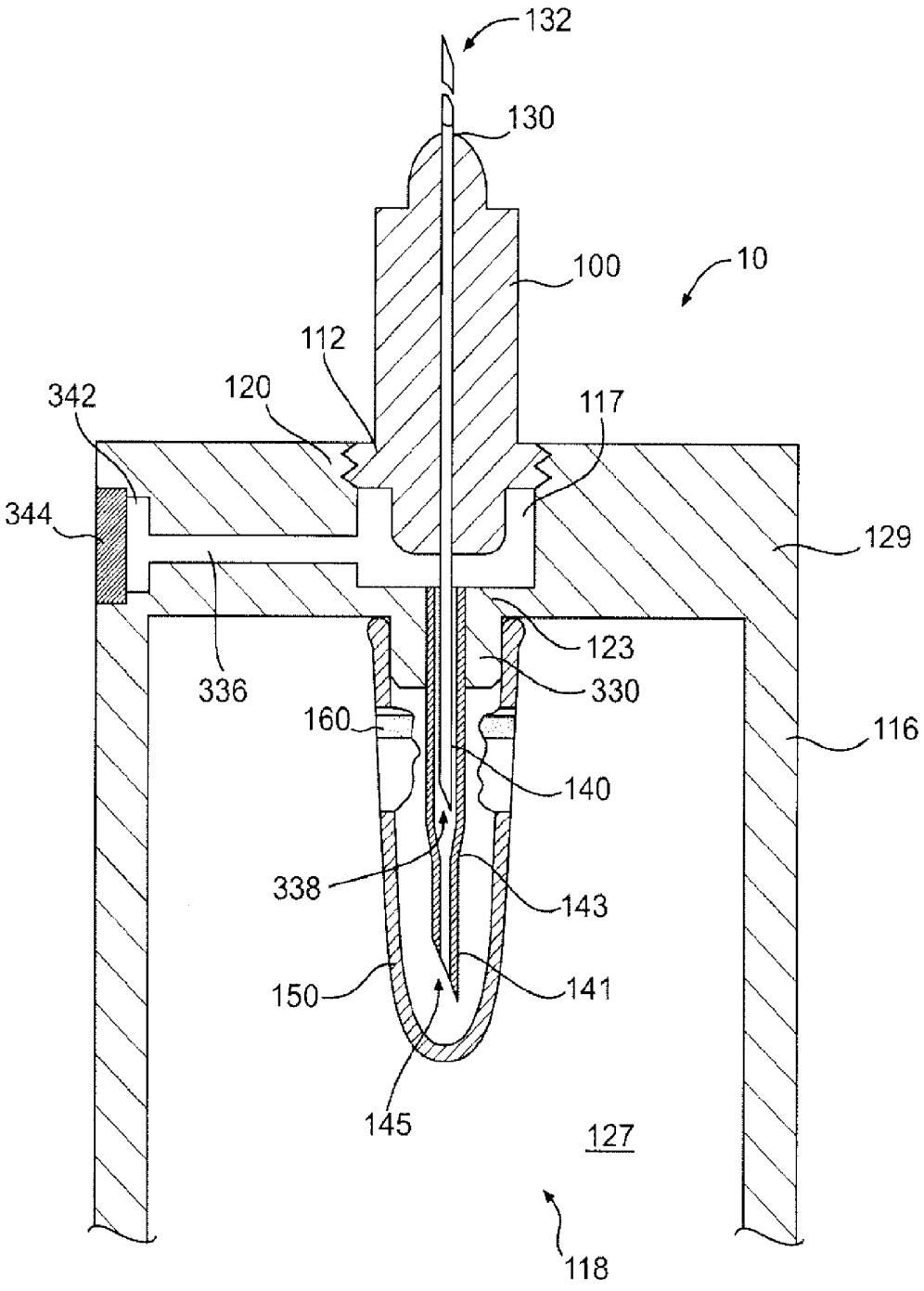

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FIG. 19

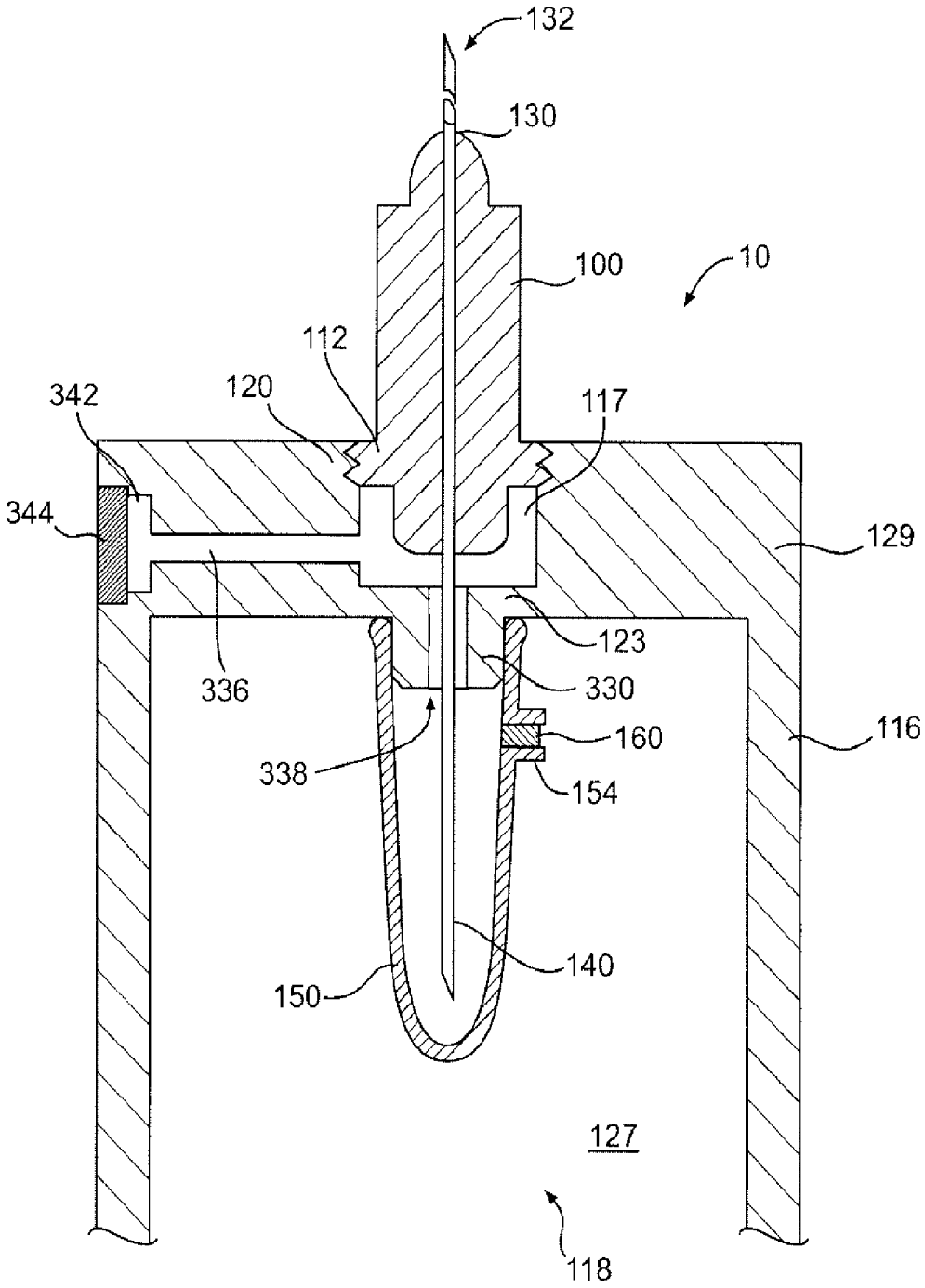

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FIG. 20

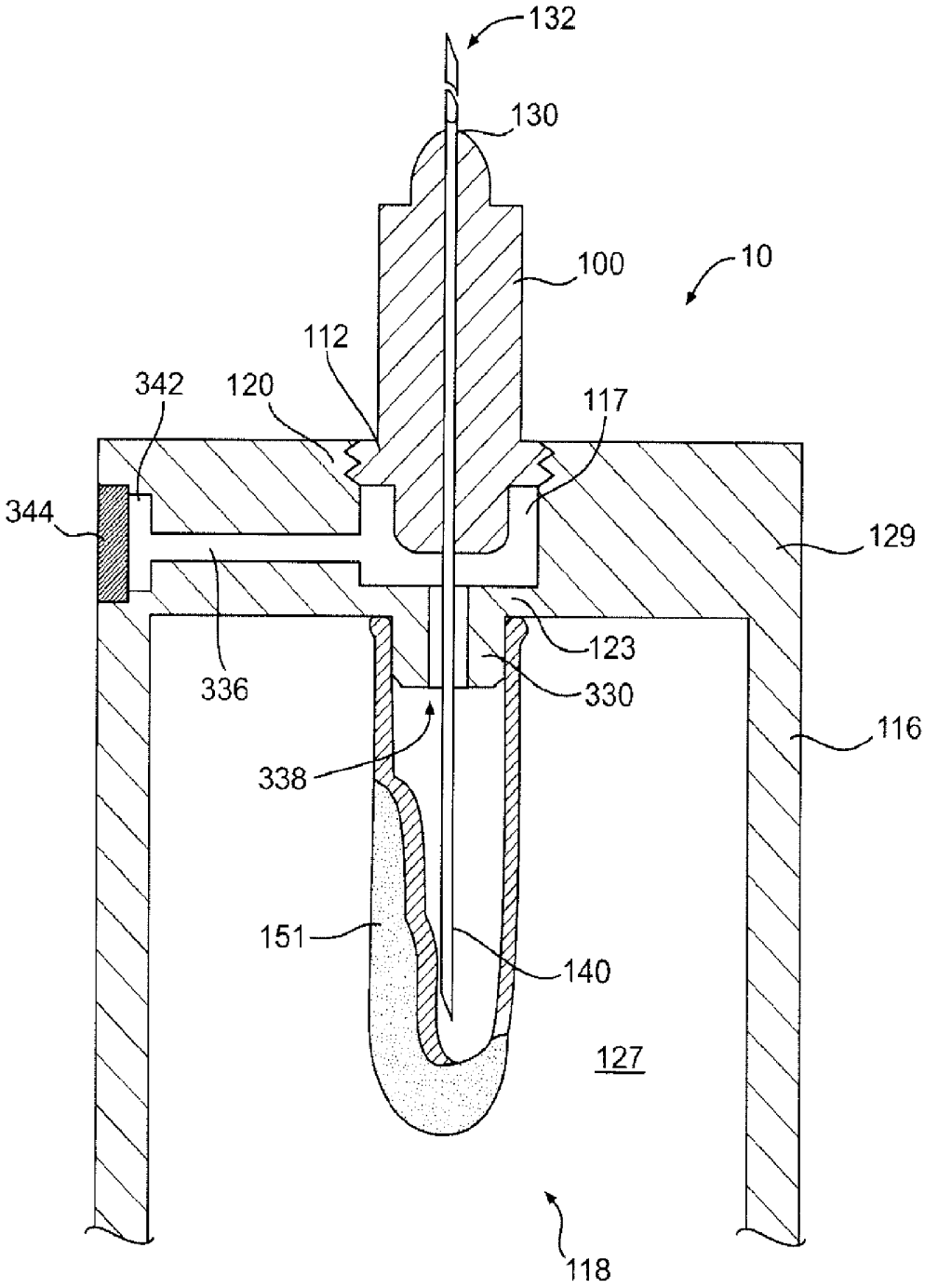

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FIG. 21

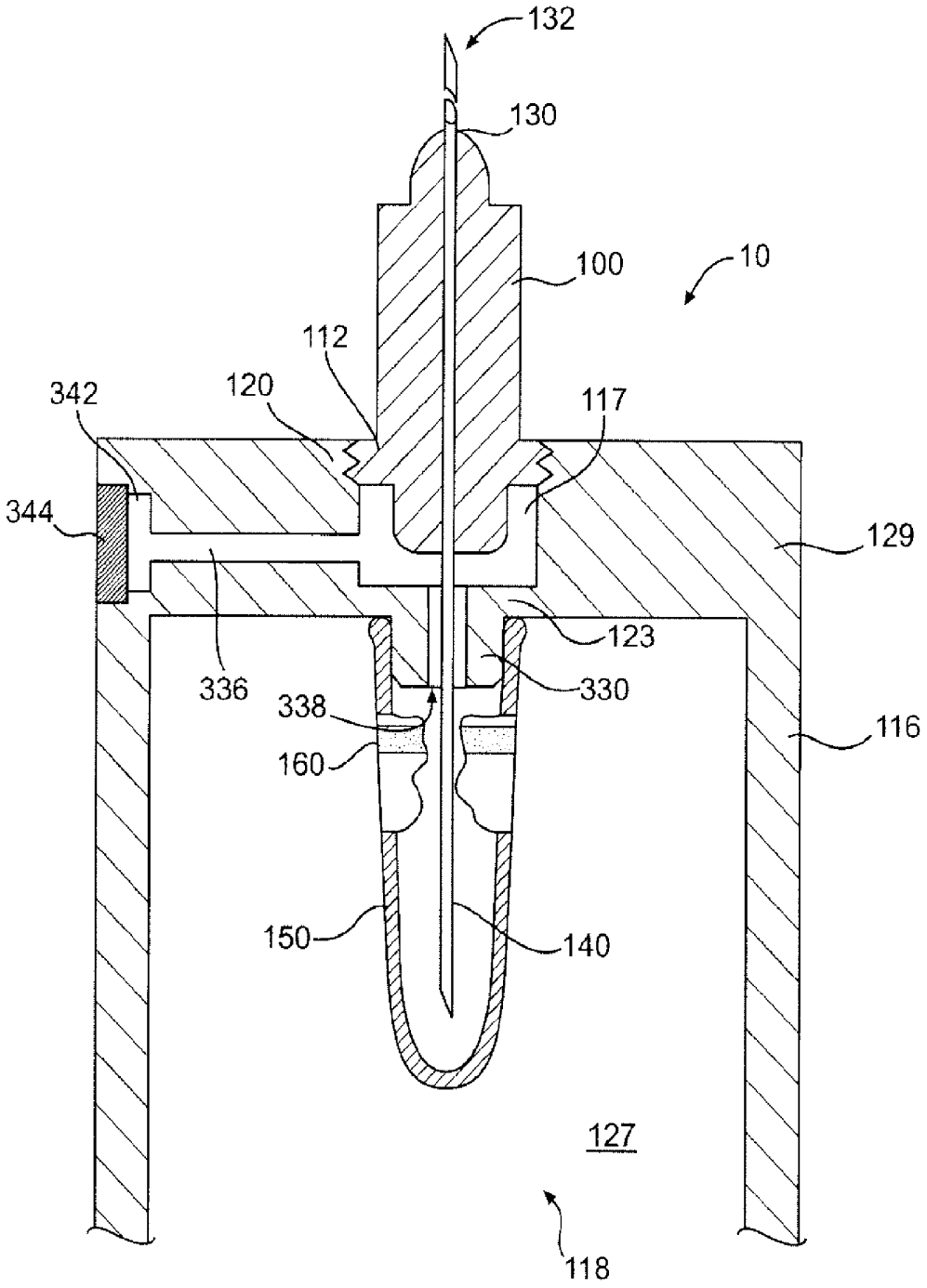

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FIG. 22

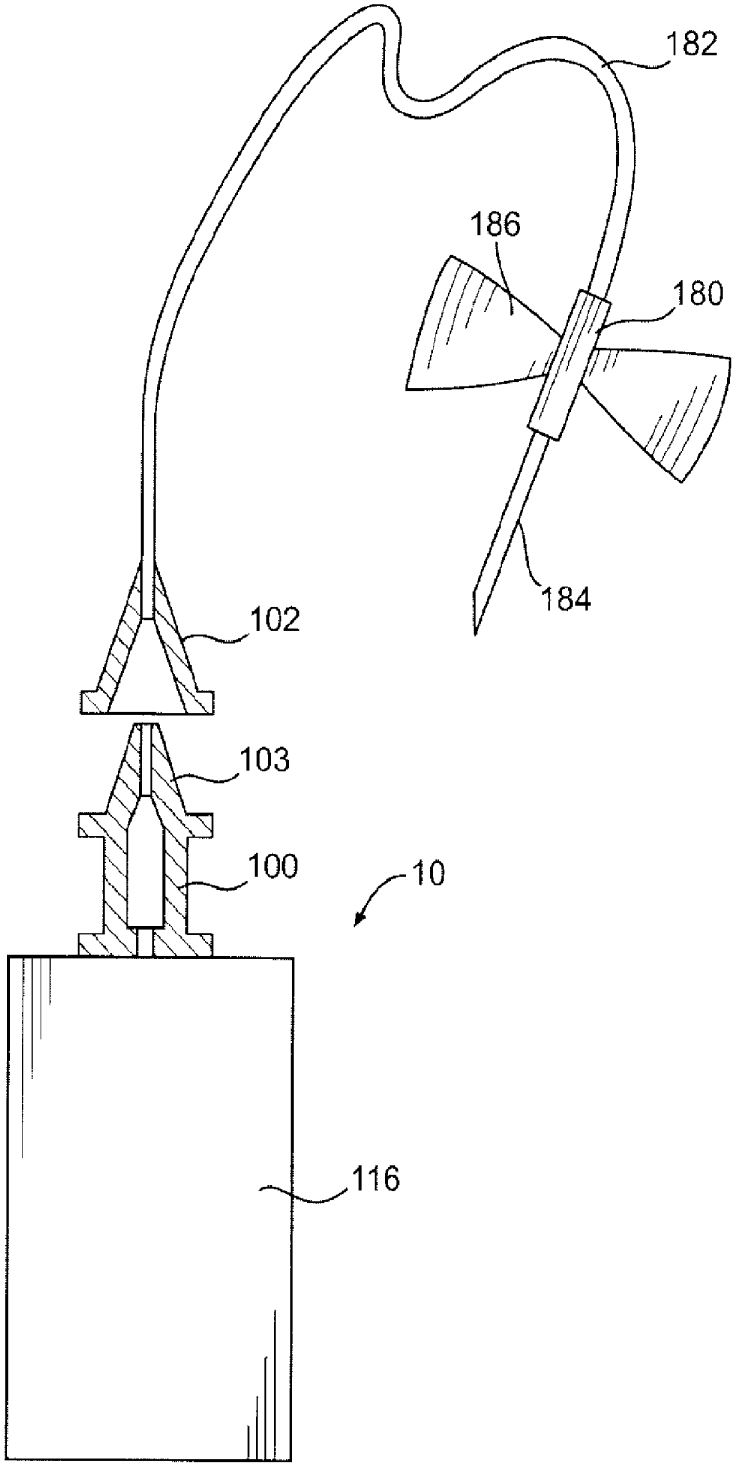


FIG. 23

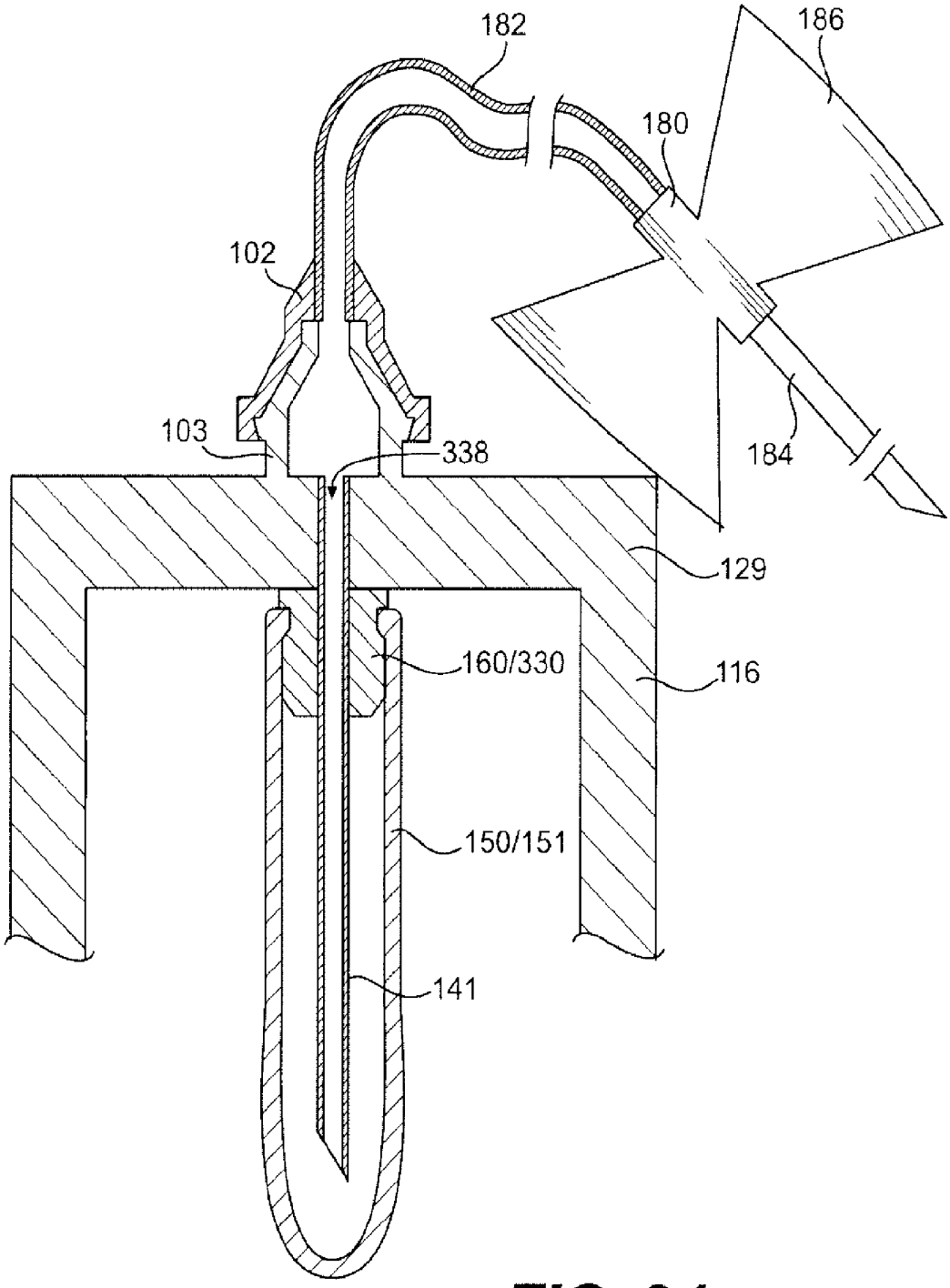


FIG. 24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/040030

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61M 5/36 (2010.01)
USPC - 604/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61M 5/36, 5/178 (2010.01)
USPC - 604/122, 164

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent, Freepatentsonline, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0086085 A1 (BROWN) 10 April 2008 (10.04.2008) entire document	1-48
Y	US 2003/0153874 A1 (TAL) 14 August 2003 (14.08.2003) entire document	1-48
Y	EP0 440 479 B1 (VAN HEUGTEN) 07 August 1991 (07.08.1991) entire document	2-14

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2010	30 AUG 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

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JP 2013-240628

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(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Published patent publication (A)
(11) [Publication number] JP 2013-240628 (P2013-240628A)
(43) [Published date] December 5, 2013 (2013.12.5)
(54) [Title of Invention] Ventilating phlebotomy needle with flashback chamber
(51) [International Patent Classification]
A61B 5/154 (2006.01)
A61B 5/153 (2006.01)
[FI]
A61B 5/14 300E
A61B 5/14 300F
[Request for examination] Yes
[Number of claims] 12
[Application form] OL
[Application in foreign language]
[Total number of pages] 14
(21) [Application number]] Patent application 2013-147592 (P2013-147592)
(22) [Filing date] July 16, 2013 (2013.7.16)

(62) [Indication of division] Division of patent application 2009-544044 (P2009-544044) [Original filing date] December 20, 2007 (2007.12.20) (31) [Priority claim number] 60/877,937 (32) [Priority date] December 29, 2006 (2006.12.29) (33)) [Country claiming priority] United States (US) (71) [Applicant]

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[Name] Covidien Limited Partnership
(74) [Agent]
[Identification Number] 100107489
[Patent Attorney]
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(72) [Inventor]
[Name] Eugene E. Weilbacher
(72) [Inventor]
[Name] Anthony Jay. Satchetti
(72) [Inventor]
[Name] Michael Jay. Noble
[Theme code (reference)]
4C038
[F term (reference)]
4C038TA01
4C038TA03
4C038UJ02

wrap up close

(57) [Summary] (Modified)
[Problem] To provide a cheaper and simpler phlebotomy needle that facilitates visualization of flashbacks.
A central portion (106) of the needle (100) includes a hole or opening (110) that communicates with the flow path defined by the needle (100), and a transparent housing (112) covers the opening (110). Positioned around to facilitate visualization of blood flow through needle 100 .
A material that allows passage of air and provides an indication of blood flow through needle

100 is positioned over opening 110 . The material is in the form of plugs or alternatively in th e form of patches or collars. The phlebotomy needle includes a needle 100, a housing 112 hav ing a passive vent, and an observation area for visualizing blood flow in the housing 112. FIG. [Selection drawing] Fig. 2-1

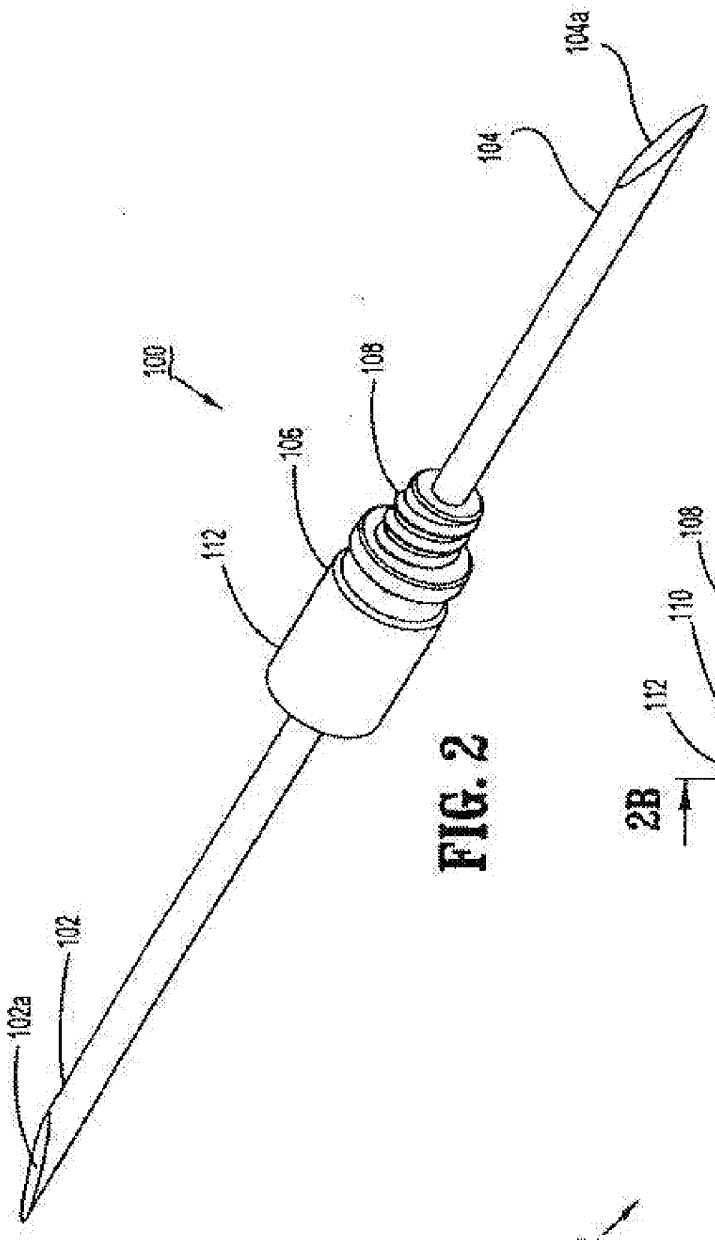


FIG. 2

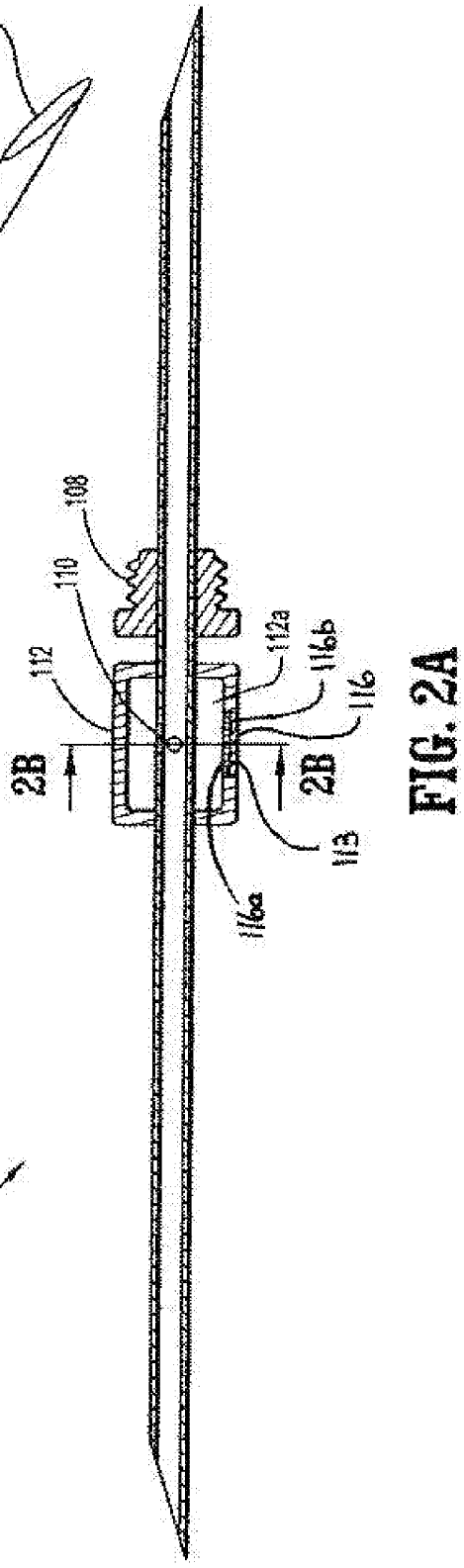


FIG. 2A

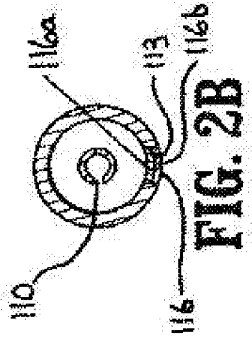


FIG. 2B

The scope of the claims open ----

Claims:

1. A

_phlebotomy needle: a distal needle portion

_having a sharpened distal end configured to pierce tissue; and a distal needle portion configured to pierce a stopper of a blood collection tube. a proximal needle portion having a sharpened proximal end, the distal needle portion and the proximal needle portion defining a fluid channel; a housing supported over the needle

_; a housing, comprising a passive vent, the housing defining a viewing area for viewing blood in the housing; and an elastomeric shield positioned about the proximal needle portion

_, A phlebotomy needle comprising an elastomeric shield and an elastomeric shield wherein the proximal needle portion defines a fluid flow path into the housing.

2. The phlebotomy needle of claim 1

, further comprising a fluted member positioned within said housing, said fluted member defining a plurality of fluid channels.

3.

The phlebotomy needle of claim 2, wherein said fluted member extends distally beyond said elastomeric shield.

4.

The phlebotomy needle of claim 2, wherein the fluid channel of the fluted member is configured to allow the passage of blood.

5.

The phlebotomy needle of claim 2, further comprising a hydrophilic material supported within said housing. 6. The phlebotomy of claim 5, wherein said flow path directs blood from the proximal end of said needle into the fluid channel of said fluted member and into contact with said hydrophilic material

.

needle.

[Claim 7]

6. The phlebotomy needle of claim 5, wherein a portion of said fluted member is surrounded by said hydrophilic material.

8. The method of claim

5, wherein a proximal end of said fluted member is surrounded by said elastomeric shield and a distal end of said fluted member is surrounded by said hydrophilic material. Phlebotomy needle.

9.
The phlebotomy needle of claim 5, wherein the proximal portion of the housing includes an inwardly extending annular rib.
10.
The elastomeric shield has an open distal end including an annular flange, and an annular rib of the housing engages the flange to extend the distal end of the elastomeric shield into the housing. 10. The phlebotomy needle of claim 9, held in the
11.
The phlebotomy needle of claim 10, wherein the elastomeric shield flange is positioned adjacent to the hydrophilic material.
12.
The phlebotomy needle of claim 1, wherein the distal end of said elastomeric shield is received in said housing and the proximal end of said elastomeric shield extends proximally from said housing.

detailed description open ----

Description: BACKGROUND 1.
Technical Field The present disclosure relates to medical needles having structures that facilitate visualization of flashback. More particularly, the present disclosure provides vented phlebotomy needles that include structures that facilitate visualization of flashback.

Regarding. 2. Background of Related Art
Medical devices for drawing blood from a patient are well known. These devices include standard needle-syringes, butterfly needle sets, and phlebotomy needles. A butterfly needle set typically includes a hollow needle having a sharpened distal end and a proximal end secured to a needle hub. A proximal portion of the needle hub is connected to flexible tubing. The needle hub defines a fluid conduit in communication with the tubing and includes a pair of flexible, radially extending wings that facilitate grasping of the butterfly needle set by a medical practitioner. Generally, the flexible tubing is formed of a transparent material that allows medical personnel to visualize blood flow, or flashback, through the tubing proximate to the needle hub. Flashback visualization allows medical personnel to confirm that the needle has been correctly inserted into the patient. [0003] Some clinicians utilize a hypodermic needle-syringe with a clear needle hub to take blood samples. During insertion, these clinicians usually observe flashb

acks in the needle hub. Phlebotomy needles generally do not include structures for visualizin g flashback. The lack of a flashback visualization feature on the phlebotomy needle is not a m ajor drawback for more experienced HCWs, but for HCWs with little experience of drawing blo od with a phlebotomy needle, the needle may be a problem. Not having any means of confirm ing proper positioning in the patient can increase the time required to draw blood and can incr ease patient discomfort. [0005]

In an attempt to overcome the above disadvantages, US Pat. No. 6,200,300 to Norris et al. discloses a phlebotomy needle, which is attachable to a blood collection tube, comprises an ou ter needle, an inner needle, and a valve (bulb). The valve is transparent, allowing medical pe rsonnel to visualize the blood when the outer needle is correctly positioned within the patien t's vein. The valve also includes a button that can be depressed by a medical practitioner to v ent air from within the needle. Air in the needle prevents blood from flowing through the need le and must be vented.
[0006]
[
0006] US Pat.
No. 5,450,856 . SUMMARY OF THE INVENTION [0007] The Norris phlebotomy needle is a H owever, a cheaper and simpler phlebotomy needle that facilitates flashback visualization is de sired. SUMMARY OF THE INVENTION The present disclosure relates to a phlebotomy needle having a sharpened distal end configured to penetrate tissue.

a proximal needle portion having a sharpened proximal end configured to penetrate a blood c ollection tube stopper; and a central needle portion defining an opening. The distal needle por tion, the proximal needle portion and the central needle portion define a fluid channel in com munication with the opening. A material is positioned adjacent to the opening. The material is

of a type that allows air to exit the fluid channel through the openings while preventing the pa ssage of blood. In one embodiment, the material provides a visual indication of blood flow, or flashback, adjacent the opening.

[0009]

In one embodiment, the material comprises a hydrophobic material. In alternative embodim ents, the material comprises a hydrophilic capillary action material. In yet another embodime nt, the material includes hydrophobic plugs. Alternatively, the material may define a collar pos itioned around the opening.

[0010]

In one embodiment, the opening is circular. Alternatively, the openings are envisioned to be of various configurations, such as rectangular or slot-shaped.

[0011]

In one embodiment, a transparent housing is positioned around the opening to facilitate visu alization of the flashback. A housing may also be positioned to contain the material and may i nclude a vent for venting air from the needle.

[0012]

In one embodiment, the phlebotomy needle includes engagement structure configured to en gage the needle holder.

In one

embodiment, a check valve is provided to prevent air from entering the fluid channel throug h the opening. In yet another embodiment, the phlebotomy needle includes a needle holder. For example, the present invention provides the following items.

(Item 1)

A phlebotomy needle,

a distal needle portion having a sharpened distal end configured to penetrate tissue and a sh arpened

proximal end configured to pierce a stopper of a blood collection tube. and a central needle p ortion

defining an opening, wherein the distal needle portion, the proximal needle portion and the c entral needle portion are in fluid communication with the opening a central needle portion defi ning a channel;

A material positioned adjacent to the opening of a type that allows air to exit the fluid chann el through the opening while preventing the passage of blood to reduce blood flow.

A phlebotomy needle comprising a material that further enables visual indication .

(Item 2)

The phlebotomy needle of item 1, wherein the material comprises a hydrophobic material.

3.

The phlebotomy needle of claim 1, wherein said material comprises a hydrophilic capillary ac tion material.

4.

The phlebotomy needle of claim 1, wherein said material comprises an inner layer of hydrophilic material facing towards said opening and an outer layer of hydrophobic material.

(Item 5)

The phlebotomy needle according to item 1, wherein the opening is circular.

6.

The phlebotomy needle of claim 1, wherein the opening defines an elongated slot.

7.

The phlebotomy needle of claim 1, further comprising a transparent housing positioned around the opening. Clause 8.

The phlebotomy needle of clause 1, further comprising an engagement structure supported by the phlebotomy needle, the

engagement structure configured to engage a needle holder.

9.

The phlebotomy needle of claim 1, wherein the material defines a collar covering the opening and positioned about the needle.

10.

The phlebotomy needle of claim 9, further comprising a transparent housing positioned around the collar material.

11.

The phlebotomy needle of claim 1, further comprising a check valve for preventing air from entering the fluid channel through the opening.

12.

The phlebotomy needle of claim 1, further comprising a needle holder.

13.

The phlebotomy needle of claim 1, wherein the material provides a visual indication of blood flow through the opening.

(Item 14)

A phlebotomy needle, a

distal needle portion having a sharpened distal end configured to penetrate tissue and a

sharpened proximal end configured to pierce a stopper of a blood collection tube. and a central needle portion

defining an opening, wherein the distal needle portion, the proximal needle portion and the central needle portion are in fluid communication with the opening A central needle portion defining a channel and

a hydrophobic material positioned adjacent the opening to permit air to exit the fluid channel through the opening while allowing blood to exit the fluid channel. A hydrophobic material of a type that prevents passage and further permits visual indication of blood flow, a

transparent housing positioned around the opening, and

an engagement supported by the phlebotomy needle. A

phlebotomy needle comprising: a structure, and an engagement structure configured to eng age the needle holder .

(Item 15)

The phlebotomy needle of item 14, further comprising the needle holder.

(Item 16)

A phlebotomy needle,

a distal needle portion having a sharp distal tip configured to penetrate tissue;

a proximal needle portion having a sharpened proximal end configured to penetrate a blood collection tube stopper; and a central needle portion

defining an opening, the distal needle portion, the proximal The needle portion and the centr al needle portion define a fluid channel in communication with the opening, a hydrophilic

capillary action material positioned adjacent the central needle portion and the opening, whe rein air flows into the a hydrophilic capillary active material of a type that allows exiting the fl uid channel through the opening while preventing the passage of blood, further permitting a v isual indication of blood flow; and the opening

. and an engagement structure supported by the phlebotomy needle

, the engagement structure configured to engage a needle holder

.

(Item 17)

The phlebotomy needle of item 16, further comprising the needle holder.

(Item 18)

A phlebotomy needle, the phlebotomy needle

penetrating a distal needle portion having a sharpened distal end configured to penetrate tis sue and a stopper of a blood collection tube. a proximal needle portion having a pointed proxi mal end configured to define a fluid channel

; a housing that includes a passive vent and

defines an observation area for visualizing blood in the housing

.

(Item 19)

19, further comprising an elastomeric shield positioned about the proximal needle portion, th e elastomeric shield and the proximal needle portion defining a fluid flow path into the housin g; Phlebotomy needle as described.

(Item 20)

20. The phlebotomy needle of any one of items 18 and 19, further comprising a fluted memb er positioned within the housing, the fluted member defining a plurality of fluid channels.

(Item 21)

The phlebotomy needle according to any one of items 18 to 20, further including a hydrophili c material supported within the housing.

22.

The phlebotomy needle of any one of items 18-21, wherein the needle has a central portion defining an opening into the housing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

An embodiment of the presently disclosed vented phlebotomy needle with a flashback chamber is disclosed herein with reference to the drawings.

1 is a perspective view, with parts separated, of a "prior art" phlebotomy needle with a needle holder, a protective needle cover and a blood collection tube shown in phantom; FIG.

1A is a side cross-sectional view of an assembled "prior art" phlebotomy needle, needle holder, and blood collection tube shown in phantom, with the distal portion of the phlebotomy needle positioned within a vein; It is

2-1 is a side perspective view of one embodiment of the presently disclosed phlebotomy needle; FIG . 2A is a cross-sectional view of the phlebotomy needle shown in FIG. 2; FIG . 2B is a cross-sectional view along section line 2B-2B of FIG. 2A.

2-2C is a side cross-sectional view of another embodiment of a phlebotomy needle of the present disclosure; FIG.

3 is a side cross-sectional view of an alternate embodiment of the phlebotomy needle of the present disclosure; FIG . FIG. 3A is a cross-sectional view taken along section line 3A--3A of FIG.

FIG. 4 is a side perspective cutaway view of another embodiment of the phlebotomy needle of the present disclosure; FIG . FIG. 4A is a cross-sectional view along section line 4A--4A of FIG.

FIG. 5 is a side perspective cutaway view of another embodiment of the phlebotomy needle of the present disclosure; FIG.

6 is a side cross-sectional view of another embodiment of the phlebotomy needle of the present disclosure; FIG.

7 is a cross-sectional view along section line 7-7 of FIG. 6; FIG. DETAILED DESCRIPTION OF EMBODIMENTS

Embodiments of vented phlebotomy needles of the present disclosure with flashback chambers will now be described in detail with reference to the drawings

, In the drawings, like reference numbers indicate identical or corresponding elements in each of the several drawings. FIG . 1 shows a known phlebotomy needle 10, needle holder 12, and needle covers 14 and 16. As shown in FIG. A blood collection tube 17 is shown in phantom. Phlebotomy needle 10 includes a distal needle portion 20 , a proximal needle portion 22 and an intermediate needle hub 23 with an engaging portion 24 . Engaging portion 24 is provided to facilitate connecting phlebotomy needle 10 to needle holder 12 . In one embodiment, the engaging portion includes a male fitting 24 a configured to engage a female fitting or engaging member 26 , which engages the distal end of needle holder 12 . provided to Alternatively, oth

er engagement structures may be used, including screws, snap-type connectors, and the like. An elastomeric shield 28 is positioned over the proximal needle portion 22 to seal the proxima l needle portion 22, as described in further detail below . [0017]

Needle holder 12 includes a substantially cylindrical body 30 having a distal end including en gagement member 26 and a proximal end including a pair of flange members 32 . Flange me mber 32 facilitates grasping and insertion of blood collection tube 17 by medical personnel. Cy lindrical body 30 defines cavity 34 (FIG. 1A) for receiving blood collection tube 17 . Blood coll ection tube, usually
17 is sealed by a penetrable stopper 17a to define a low pressure cavity 17b (FIG. 1A). The di stal end of holder 12 defines an opening 36 through engagement member 26 , opening 36 siz ed to receive proximal needle portion 22 . In use, needle 10 is secured to the distal end of n eedle holder 12 via engagement portion 24 and engagement member 26, as shown in FIG. 1A .
When needle 10 is secured to needle holder 12 , proximal needle portion 22 is positioned with in cavity 34 of body 30 of needle holder 12 and elastomeric shield 28 is positioned over proxi mal needle portion 22 . be. A blood collection tube 17 (shown in phantom) containing a penet rable stopper 17a is then positioned within cavity 34 . When blood collection tube 17 is inserte d into cavity 34 , proximal needle portion 22 engages stopper 17 a and penetrates shield 28 . Shield 28 is compressed downward (FIG. 1A) so that proximal needle portion 22 penetrates st opper 40 and enters cavity 17b of blood collection tube 17 . Once the distal needle portion 20 is properly positioned in the patient's vein 38 and the blood collection tube 17 is positioned wi thin the cavity 34, blood is typically flowed through the needle 10 and into the blood collection tube 17. The blood collection tube 17 is maintained under vacuum. When the blood collection tube 17 is removed from the needle holder 12 , the resilient elastomeric shield 28 returns to it s original configuration, covering and sealing the proximal needle portion 22 .
[0019]
FIGS. 2 and 2A illustrate one embodiment of the phlebotomy needle of the present disclosur e with a flashback chamber, generally indicated as 100. FIG. Needle 100 includes distal end 1 02 , proximal end 104 and central portion 106 . Distal end 102 has a pointed end 102a config ured to penetrate patient tissue, and proximal end 104 is configured to pierce stopper 17a of blood collection tube 17 (see FIG. 1A). It has a sharp edge 104a. Central portion 106 includes an engagement member 108, as discussed above, which is configured to engage a needle hol der (FIG. 1). Central portion 106 also includes an opening or hole 110 and a translucent or tra

nsparent housing 112 positioned around central portion 106 of the portion defining opening 1 10 . Although opening 110 is shown as circular, other configurations are envisioned, such as r ectangular, square, oval, elongated slot 39 (FIG. 5), and the like. A transparent housing 112 d efines a blood reservoir 112a. Vent openings 113 are preferably formed in transparent housin g 112 . Vent opening 113 facilitates venting needle 100 and allows blood flow through needle 100 . As discussed below, the vent opening 113 of the housing 112 may be covered with a ma terial that allows passage of air but not liquid, such as blood, for example. Referring to FIGS. 2A and 2B, vent opening 113 may be covered with filter 116

.

Filter 116 preferably includes an inner layer 116a of hydrophilic material and an outer layer 1 16b of hydrophobic material. Preferably, at least one of layers 116a and 116b has a pore size of less than 0.45 microns. Such a pore size allows air to pass through but prevents bacteria fr om entering the housing 112 .

[0021]

Referring to FIG. 2C, in an alternative embodiment, filter 116 may be replaced by a hydroph obic check valve, such as flap valve 150, for example. As shown, flap valve 150 is configured t o flex outward from housing 112 to expose vent opening 113 and vent housing 112 when bloo d begins to flow into housing 112 . be.

A hydrophobic sheet 152 is positioned over opening 113 to prevent blood from exiting vent op ening 113 when the check valve is open . Prior to blood beginning to flow into housing 112 , fl ap valve 150 seals opening 113 to prevent material from entering housing 112 . Alternatively, flap valve 150 may be formed from a hydrophilic material if the pore size of the hydrophilic m aterial is sized to block the passage of blood components. When the distal end 102 of needle 100 is properly positioned within the patient's vein, ie,

blood

The transparent housing 112 allows the medical practitioner to visualize blood flow through th e needle 100 as air flows through the needle 100 and air is vented and blood enters the reser voir 112a through the opening 110. make it possible. This allows the medical practitioner to c onfirm that the distal end 102 of the needle 100 has been properly positioned within the patie nt's vein for drawing blood. This provides a significant benefit to medical practitioners attempt ing to draw blood from patients, especially those who have limited experience with drawing bl ood from patients with phlebotomy needles.

[0023]

FIG. 3 illustrates an alternative embodiment of the vented phlebotomy needle of the present disclosure with a flashback chamber generally indicated as 200. As shown in FIG. Needle 200 i s substantially similar to needle 100, except as described below. Needle 200 includes distal en d 202 , proximal end 204 and central portion 206 . Distal end 202 has a sharpened end 202a configured to pierce patient tissue, and proximal end 204 has a sharpened end 202a configure

d to pierce a stopper of a blood collection tube (see FIG. 1A). It has a tapered end 204a. Cent ral portion 206 includes an opening or hole 210 and an engagement member 212a. Material 2 14 is positioned over hole 210 . Material 214 may be a hydrophilic material that wicks blood in to the material so that blood flow through needle 200 can be readily discerned by medical per sonnel. To facilitate venting of needle 200, material 214 may be a hydrophilic material that is permeable to air but impermeable to liquids, such as blood. In one embodiment, the hydrophil ic material can be of the type that changes color when in contact with blood. The material ma y be in the form of collar 250 (Fig. 3) or plug 252 (Fig. 4). Additionally, the material may be p ositioned within a transparent housing or hub 212, or alternatively positioned adjacent openin g 210 without any housing. In an alternative embodiment, the material is a hydrophobic mate rial that is air permeable but blood impermeable. It is noted that ventilation openings 226 ma y be provided in housing 212 to facilitate ventilation of the housing. A vent can be in the form of an opening in housing 212 that allows air to flow out of housing 212 as blood enters.

[0024]

In an alternative embodiment, further illustrated in FIGS. 3 and 3A, material 214 may be for med of an expandable material that allows air to pass through vent openings 226 before cont acting the expandable material with blood. enable Material 214 may expand upon contact with blood, closing vent opening 226 . Although only hydrophilic and hydrophobic materials have been disclosed herein, other materials that facilitate the passage of air while preventing the p assage of blood and provide an indication of blood flow are disclosed in the present disclosure .

phlebotomy needles. The material may have other configurations not disclosed herein. For exa mple, the material may define a pad that covers the opening.

FIGS.

6 and 7 illustrate another embodiment of the phlebotomy needle of the present disclosure wi th a flashback chamber, generally indicated as device 398. FIG. Phlebotomy needle 398 includ es needle 400 and stepped housing 408 . Needle 400 includes distal end 402 , proximal end 4 04 and central portion 406 . Distal end 402 has a pointed end 402a configured to penetrate ti ssue of a patient, and proximal end 404 is adapted to pierce a stopper (not shown) of a blood collection tube (not shown). It has a configured pointed end 404a.

The

stepped housing 408 has a distal portion 408a and a larger diameter proximal portion 408b. A stepped housing 408 is supported at the central portion 406 . Distal portion 408a defines a t hroughbore 412 sized to receive central portion 406 of the needle. Distal portion 408a is seale d and secured to needle 400 using adhesive 410, for example. Alternatively, other known tech niques such as crimping, clamping, screws, welding, etc. may be used to secure needle 400 to housing 408 . Proximal portion 408b is a transparent or translucent material.

formed to facilitate visualization within proximal portion 408 b of housing 408 . Proximal porti on 408 b also defines a through hole 414 that communicates with through hole 412 but has a

larger diameter than through hole 412 . Proximal portion 408 b defines an annular recess 416 between portion 408 b and proximal end 404 of needle 400 . Recess 416 is sized to receive hy drophilic material 418 and inner fluted member 420 . An inner fluted member 420 is positione d around proximal end 404 of needle 400 and defines a plurality of channels 422 in communic ation with hydrophilic material 418 . A ventilation opening 409 is provided through housing 40 8 .

[0028]

An elastomeric shield 428 is positioned over the proximal end 404 of the needle 400 . As dis cussed above, elastomeric shield 428 may be resilient, sealing proximal end 404 of needle 40 0 when proximal end 404 of needle 400 is not connected to a blood collection tube (not show n). function to Elastomeric shield 428 includes a closed proximal end 428a and an open distal end 428b. Open distal end 428 b includes an annular flange 430 positioned adjacent material 418 within recess 416 of housing 408 . A proximal portion 408b of the housing 408 includes a n inwardly extending annular rib 432 that engages a flange 430 of an elastomeric shield 428 a nd a distal end 428b of the shield 428. within recess 416 of housing 408 . A channel 436 is de fined between elastomeric shield 428 and proximal end 404 of needle 400 , as indicated by ar row 434 . Channel 436 directs blood from proximal end 404 of needle 400 into fluted channel 422 of fluted member 420 and into contact with hydrophilic material 418 . In use, when blood contacts material 418 , material 418 provides a visual indication of blood flow that is visible th rough proximal portion 408 b of housing 408 .

[0029]

defined with filter 116 (FIGS. 2A-2B), defined with filter 252 (FIGS. 4-4A), or defined with fil ter 39 (FIG. 5), or defined with check valve 150 (FIG. 5). FIG. 2C) Vent opening 113, as well as openings 226 (FIGS. 3-3A) and opening 409 (FIG. 6) can all be described as passive vent o penings, which are positioned within the needle cannula. Allows gases with pressures greater than atmospheric pressure to automatically leak into the atmosphere. These passive ventilatio n openings do not require any action by the user of the device according to the invention.

[0030]

It is understood that various modifications may be made to the embodiments disclosed herei n. Therefore, the above should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the sc ope and spirit of the claims appended hereto.

drawing open —

[Fig. 1-1]

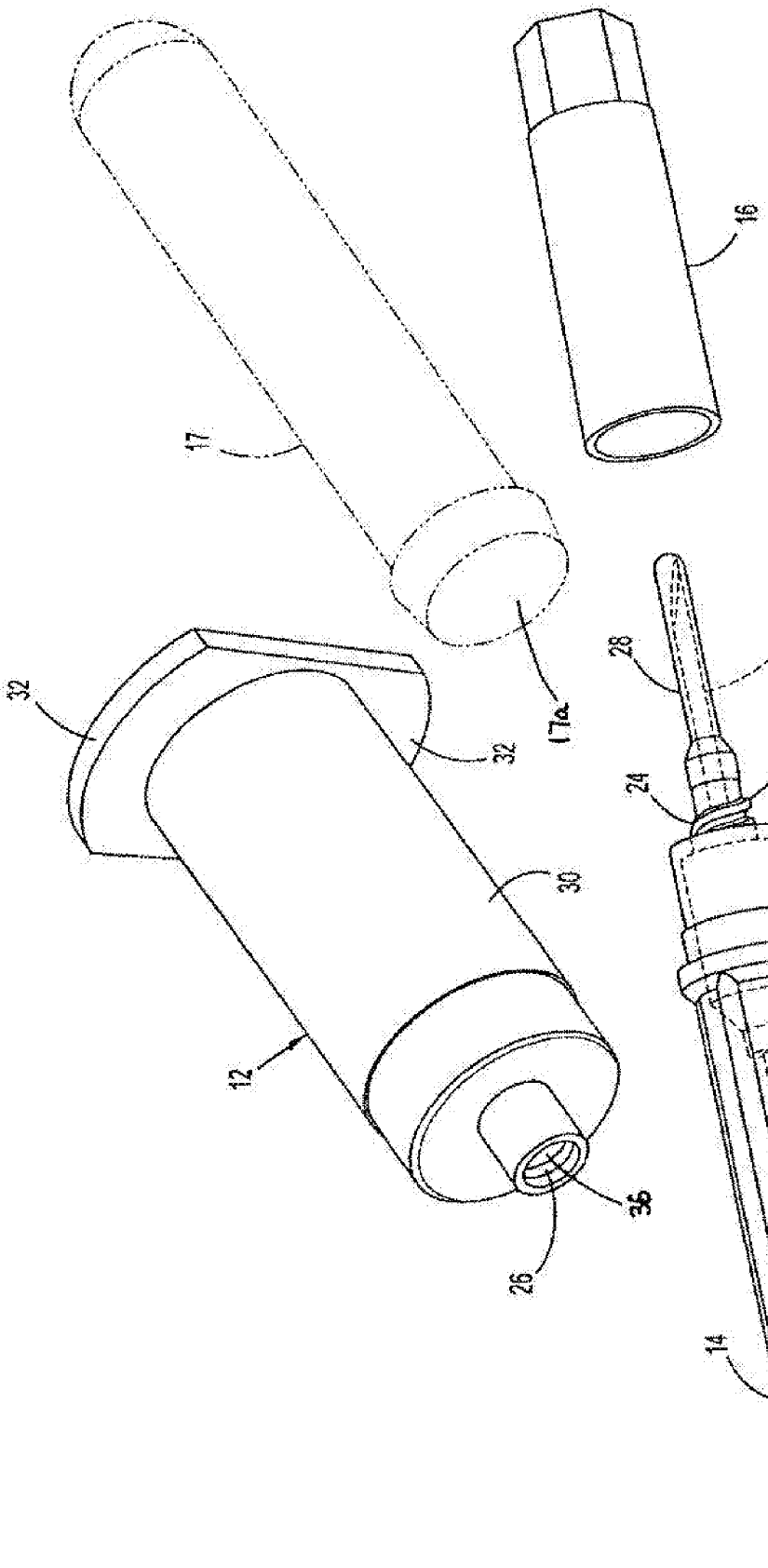


FIG. 1

[Figure 1-2]

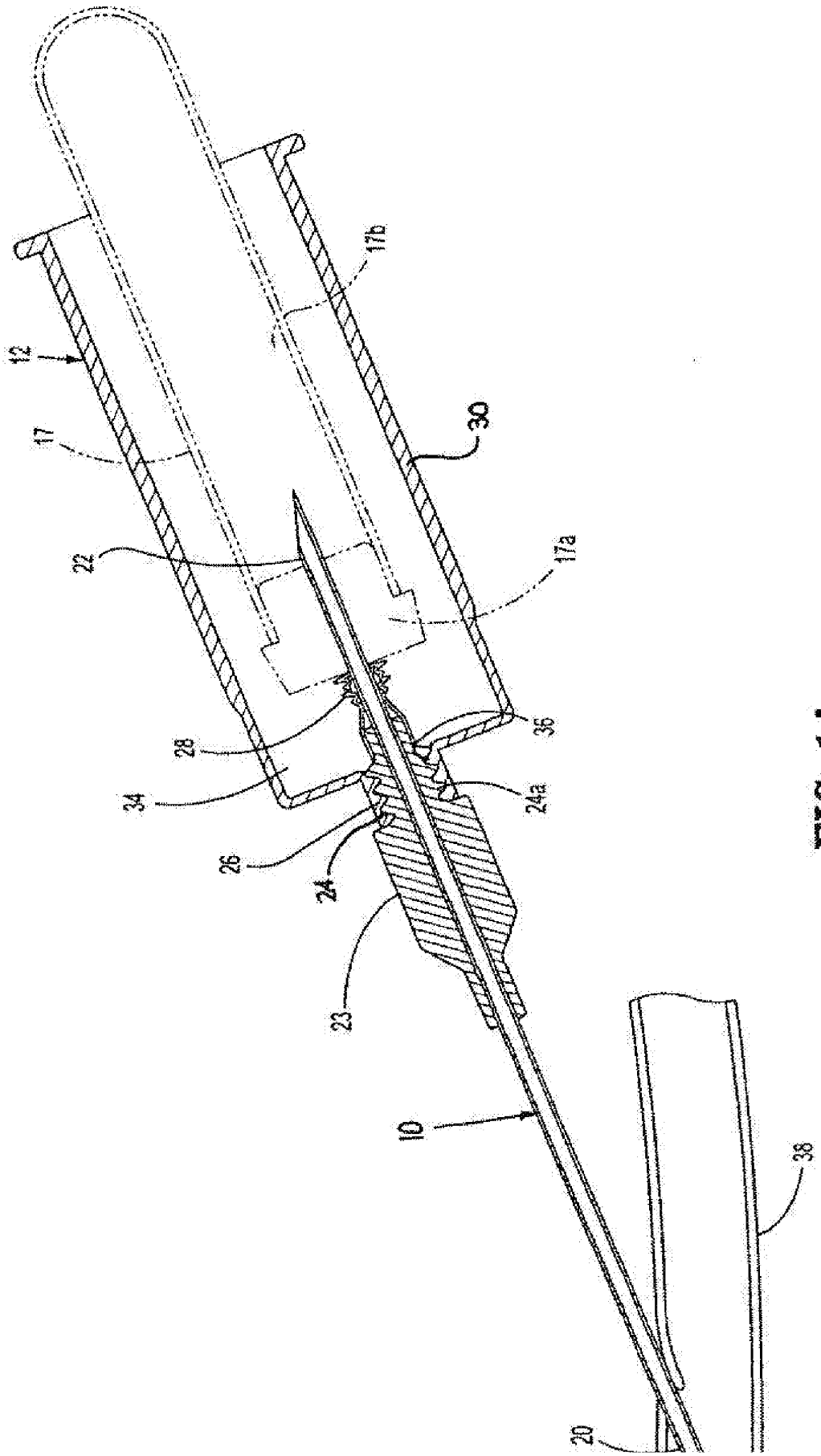
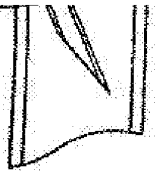


FIG. 1A

[Figure 2-1]



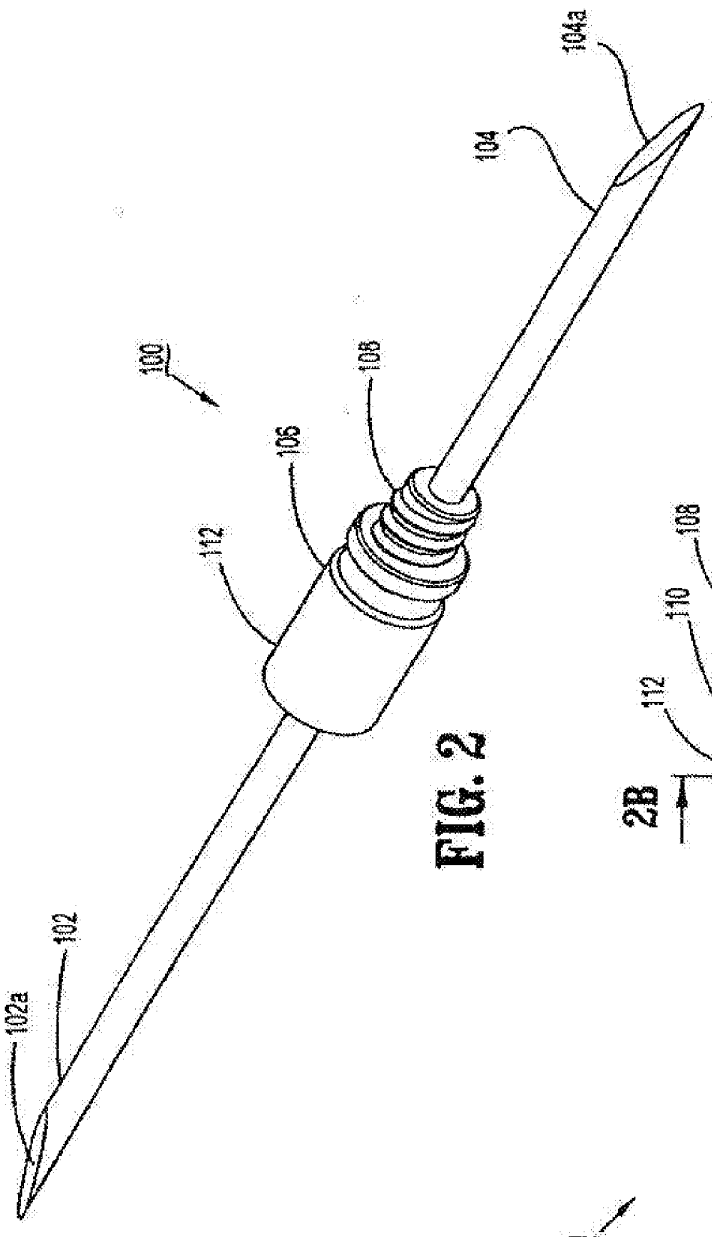


FIG. 2

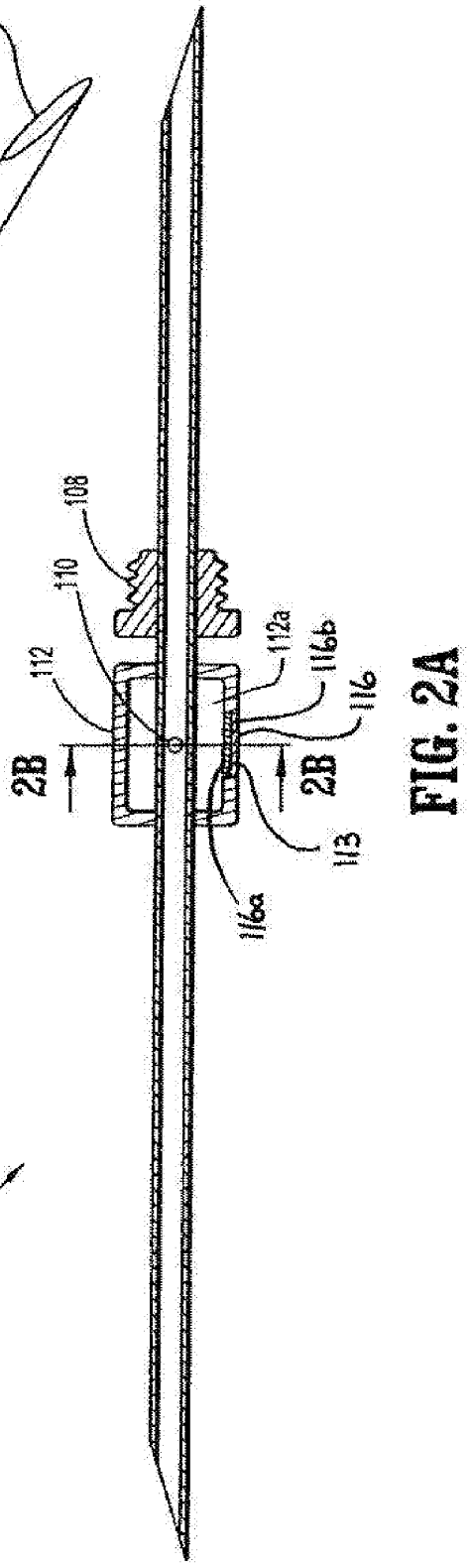


FIG. 2A

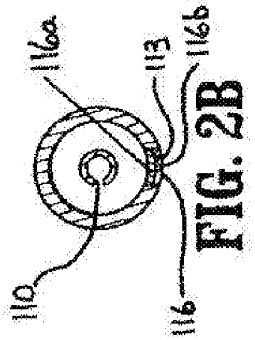


FIG. 2B

[Figure 2-2]

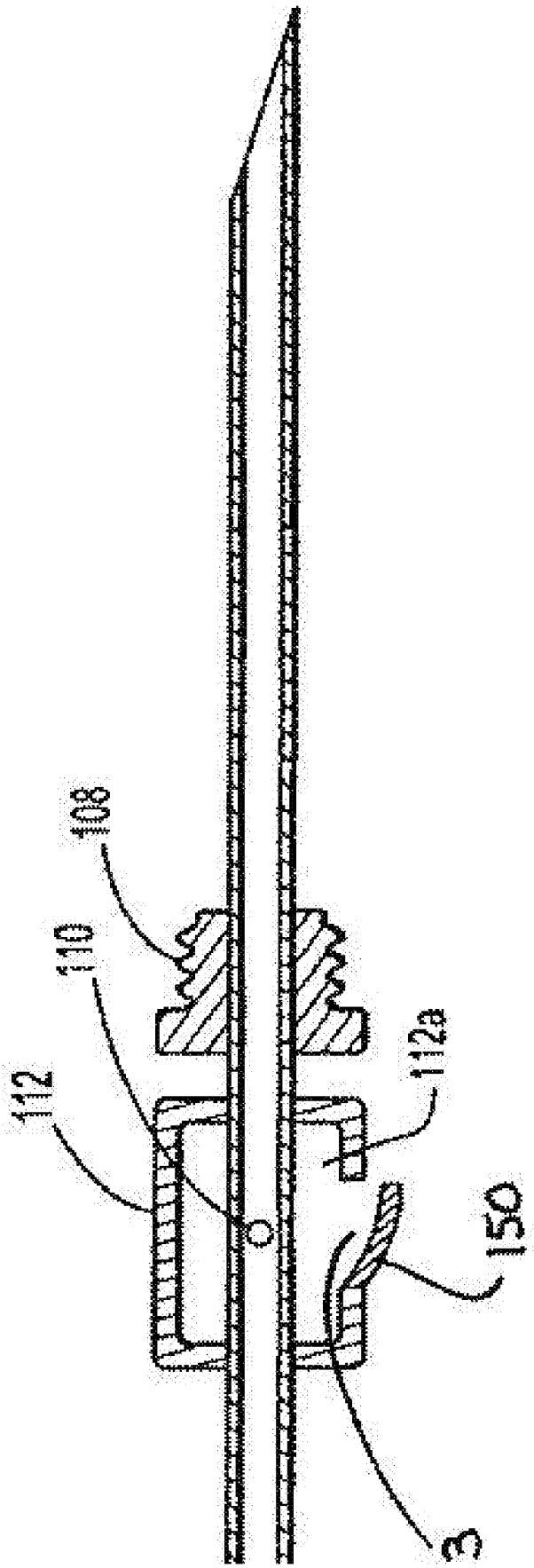
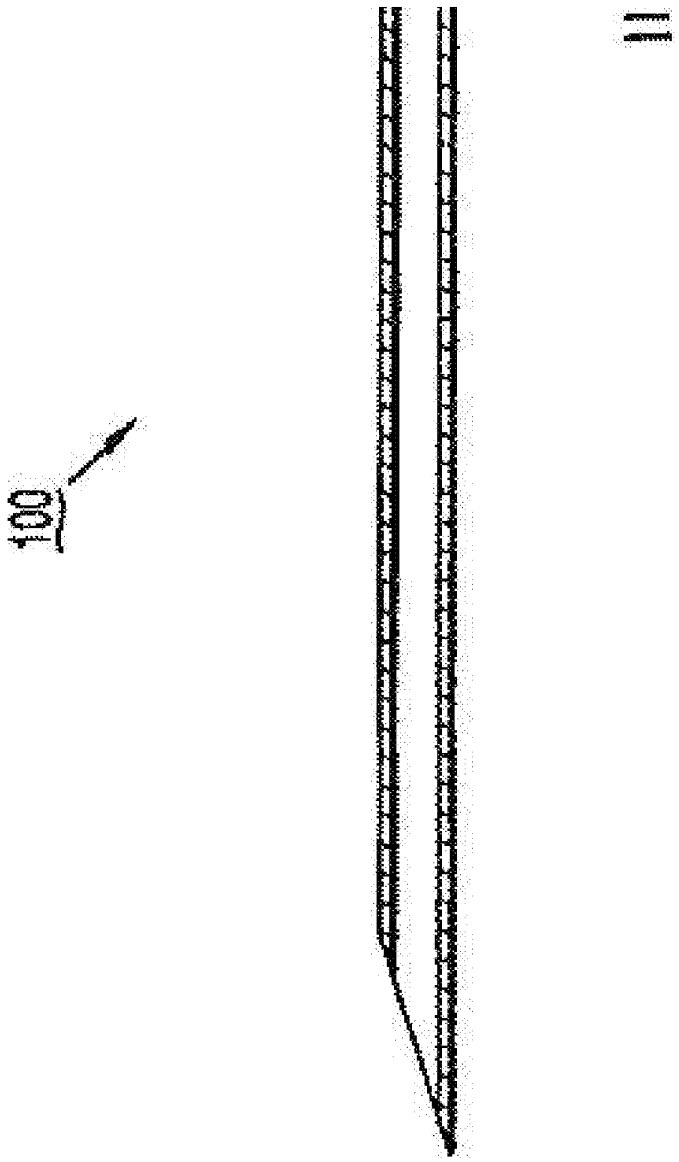


FIG. 2C

[Figure 3]



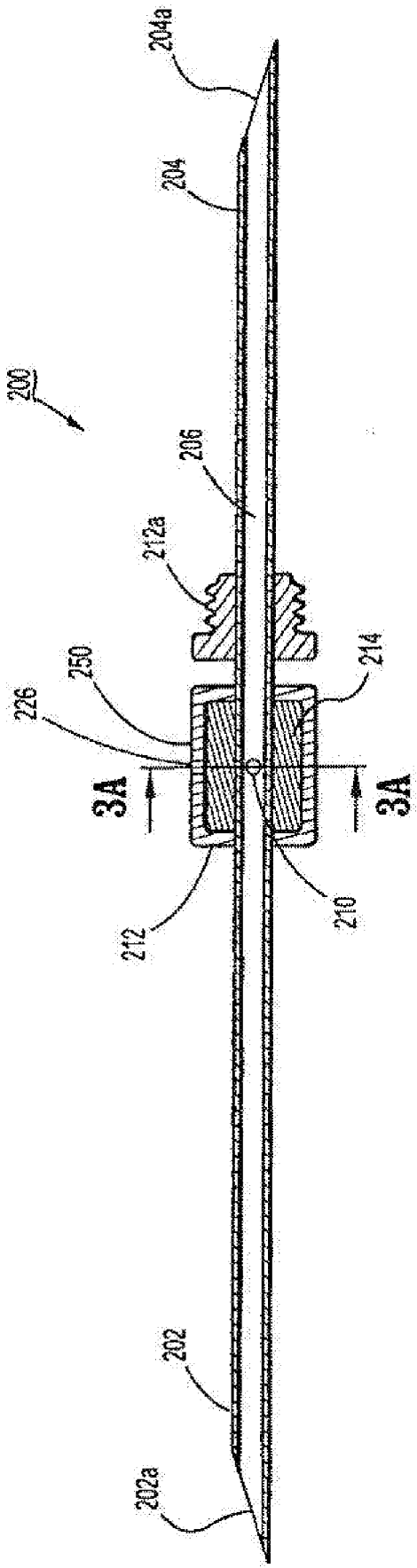

200
204a
204
206
212a
214
250
226
3A
3A
212
210
202
202a

FIG. 3

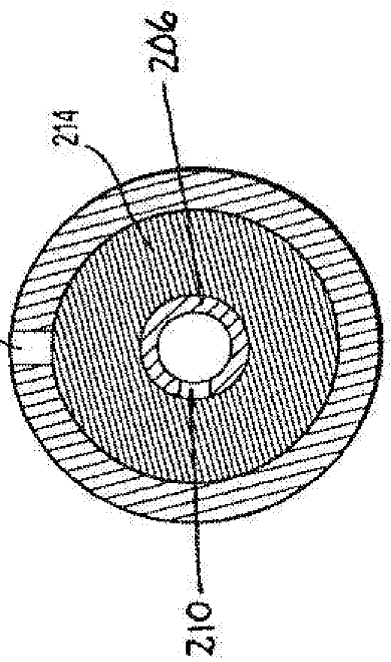

206
214
226
210

FIG. 3A

[Figure 4]

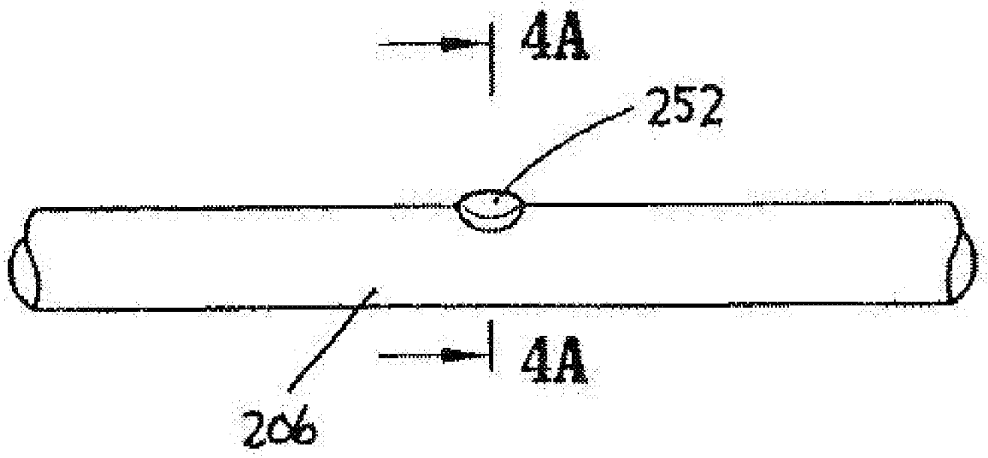


FIG. 4

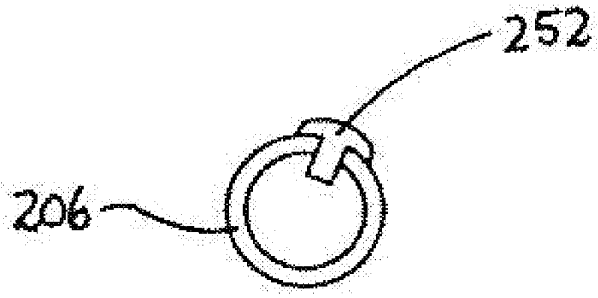


FIG. 4A

[Figure 5]

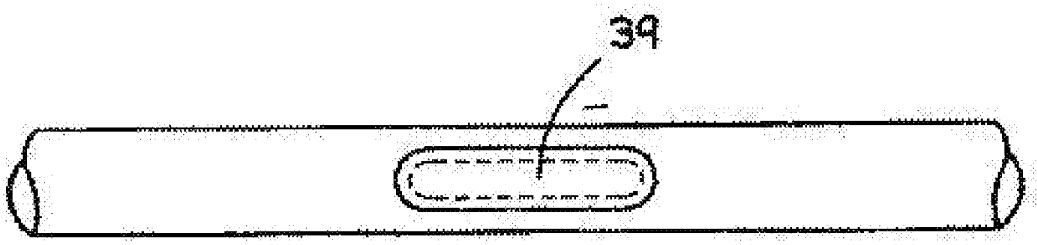


FIG. 5

[Fig. 6]

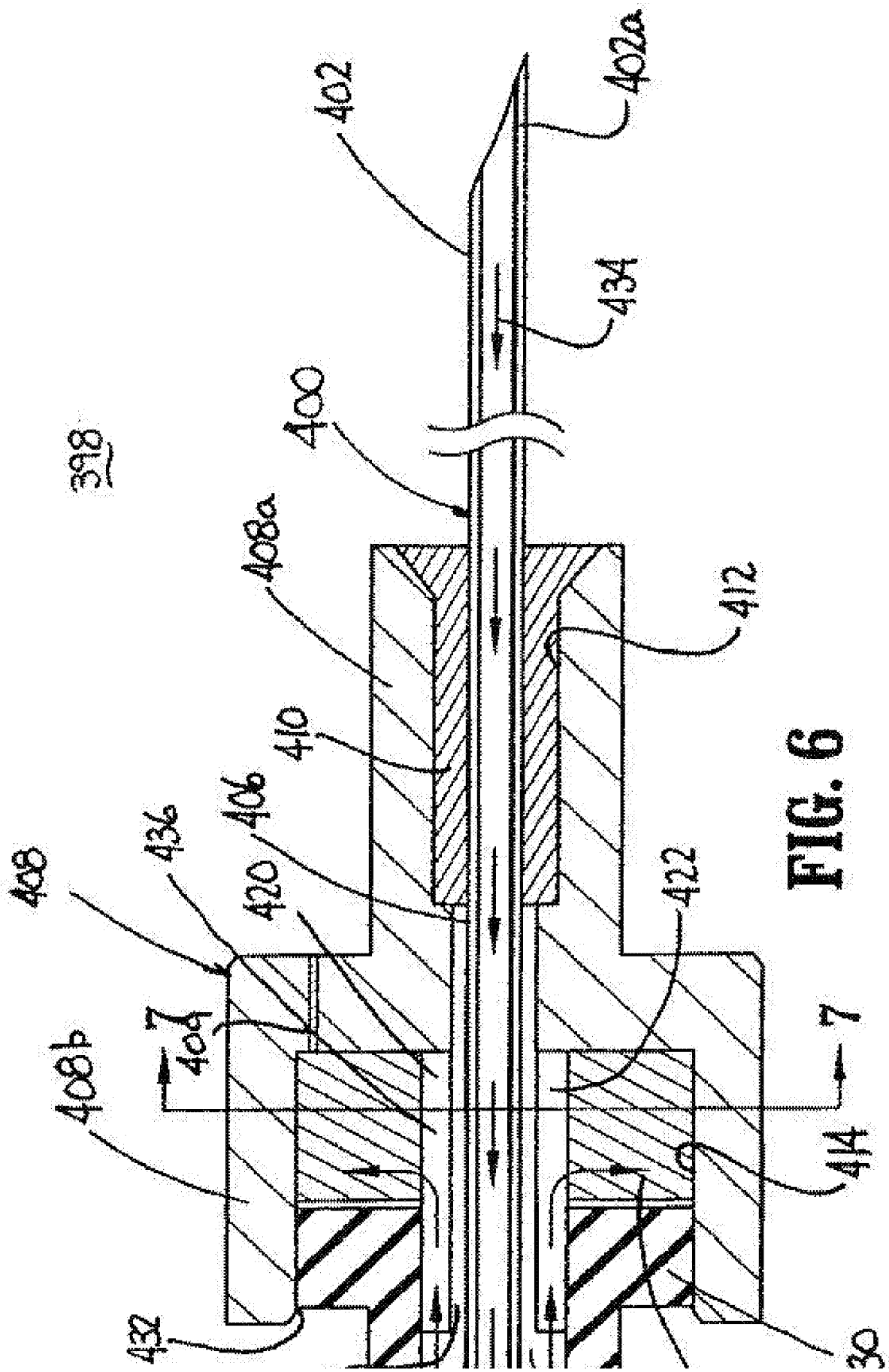

402
402a
434
400
398
408a
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436
408
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422
7
404
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408b
414
432
30

FIG. 6

[Fig. 7]

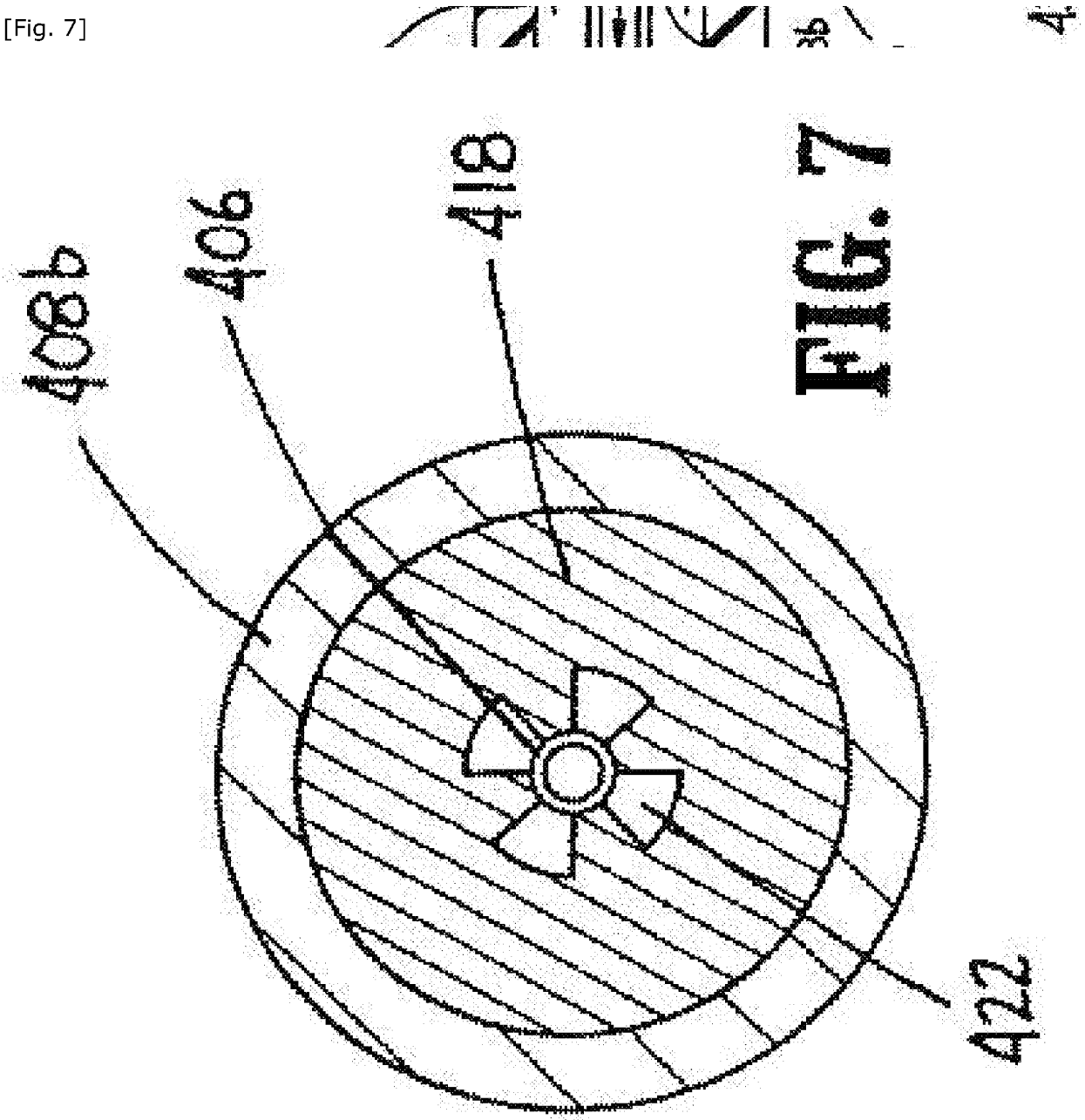


FIG. 7

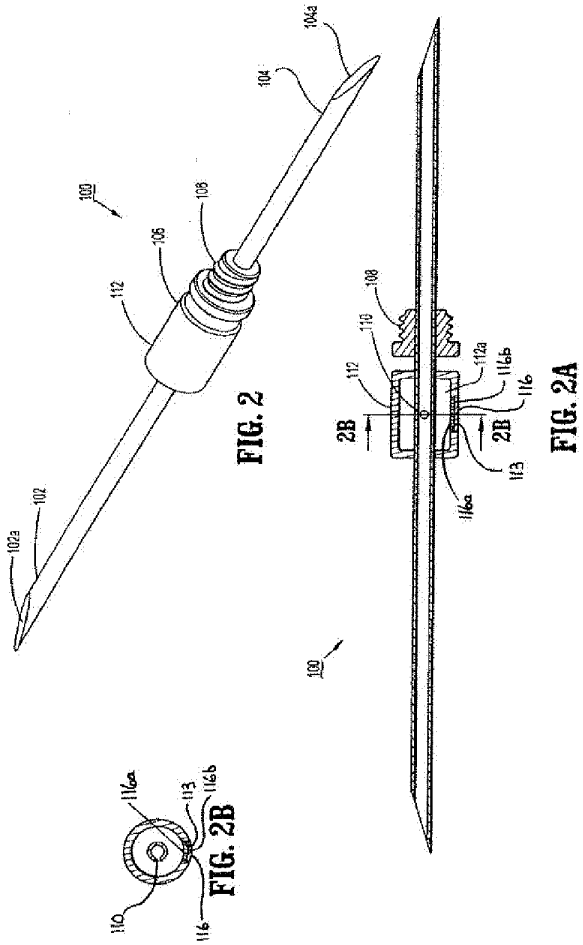
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Representative drawing | 1-1 | 1-2 | 2-1 | 2-2 | 3 | Four | Five | 6 | 7

Magnify and Rotate



Representative drawing

1 / 1 display

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VENTED PHLEBOTOMY NEEDLE WITH FLASHBACK CHAMBER

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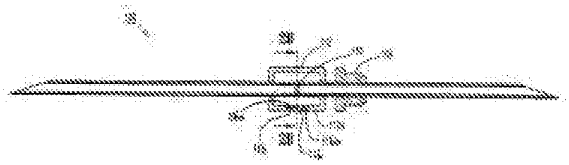
Classification: **- international:** ***A61B5/153; A61B5/154***
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150389 (EP, US); A61B5/150473 (EP, US); A61B5/150572 (EP, US); A61B5/150732 (EP, US); A61B5/1545 (EP, US)**

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Abstract of JP2013240628 (A)



PROBLEM TO BE SOLVED: To provide a less expensive, less complex phlebotomy needle which facilitates visualization of flashback.SOLUTION: A central portion 106 of a needle 100 includes a hole or opening 110 which communicates with a flow channel defined by the needle 100 and a transparent housing 112 is positioned about the opening 110 to facilitate visualization of blood flow through the needle 100. A material which allows passage of air and provides an indication of blood flow through the needle 100 is positioned over the opening 110. The material is in the form of a plug or, alternately, in the form of a patch or collar. The phlebotomy needle includes the needle 100 and the housing 112 having a passive vent and a viewing region for visualizing blood flow in the housing 112.

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A61B	5/153	(2006.01)	A61B	5/14	300F	

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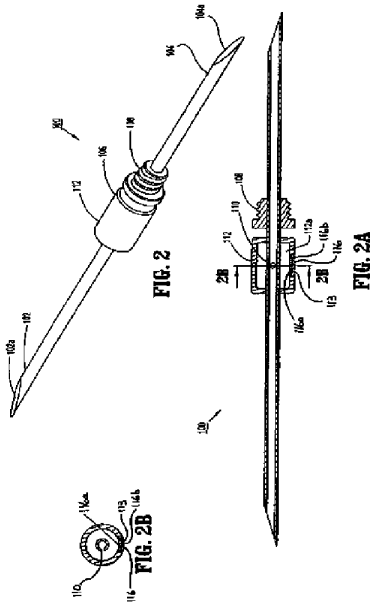
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最終頁に続く

(54)【発明の名称】フラッシュバックチャンバを備えた通気型瀉血針

(57)【要約】　（修正有）
【課題】フラッシュバックの可視化を容易にするより安価な、より簡単な瀉血針の提供。
【解決手段】針１００の中央部分１０６は穴または開口部１１０を含み、該穴または開口部１１０は、針１００によって画定された流路と連通し、透明の筐体１１２が、開口部１１０の周りに位置決めされ、針１００を通る血流の可視化を容易にする。空気の通過を可能にし、針１００を通る血流の表示を提供する材料が、開口部１１０を覆い位置決めされる。材料は、プラグの形であるか、または代替として、パッチまたはカラーの形である。瀉血針は、針１００と、受動通気孔を有する筐体１１２と、筐体１１２の血流を可視化するための観察領域とを含む。
【選択図】図２－１



【特許請求の範囲】
【請求項１】
瀉血針であって：
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分とを有し、該遠位の針部分と該近位の針部分が流体チャンネルを画定する、針；
該針上に支持される筐体であって、受動通気孔を含み、該筐体が該筐体中に血液を観察するための観察領域を画定する、筐体；および
該近位の針部分の周りに位置決めされるエラストマーのシールドであって、該エラストマーのシールドおよび該近位の針部分が該筐体中への流体の流路を画定する、エラストマーのシールド、を備える、瀉血針。
【請求項２】
前記筐体内に位置決めされる縦溝のある部材をさらに含み、該縦溝のある部材が複数の流体チャンネルを画定する、請求項１に記載の瀉血針。
【請求項３】
前記縦溝のある部材が、前記エラストマーのシールドを超えて遠位方向に延びる、請求項２に記載の瀉血針。
【請求項４】
前記縦溝のある部材の流体チャンネルが血液の通過を可能にするように構成されている、請求項２に記載の瀉血針。
【請求項５】
前記筐体内に支持される親水性材料をさらに含む、請求項２に記載の瀉血針。
【請求項６】
前記流路が、血液を、前記針の近位端から前記縦溝のある部材の流体チャンネル中に、および前記親水性材料との接触に向ける、請求項５に記載の瀉血針。
【請求項７】
前記縦溝のある部材の一部分が、前記親水性材料によって取り囲まれる、請求項５に記載の瀉血針。
【請求項８】
前記縦溝のある部材の近位端が前記エラストマーのシールドによって取り囲まれ、そして該縦溝のある部材の遠位端が前記親水性材料によって取り囲まれる、請求項５に記載の瀉血針。
【請求項９】
前記筐体の近位部分が、内方に延びる環状のリブを含む、請求項５に記載の瀉血針。
【請求項１０】
前記エラストマーのシールドが環状のフランジを含む開いた遠位端を有し、前記筐体の環状のリブが該フランジを係合し、該エラストマーのシールドの遠位端を該筐体内に保持する、請求項９に記載の瀉血針。
【請求項１１】
前記エラストマーのシールドのフランジが、前記親水性材料に隣接して位置決めされる、請求項１０に記載の瀉血針。
【請求項１２】
前記エラストマーシールドの遠位端が前記筐体中に受容され、そして該エラストマーシールドの近位端が該筐体から近位方向に延びる、請求項１に記載の瀉血針。
【発明の詳細な説明】
【技術分野】
【０００１】
（１．技術分野）
本開示は、フラッシュバックの可視化を容易にする構造を有する医療用針に関する。より詳細には、本開示は、フラッシュバックの可視化を容易にする構造を含む通気型瀉血針

に関する。
【背景技術】
【０００２】
（２．関連技術の背景）
患者から血液を抜き取る医療用デバイスは周知である。これらのデバイスは、標準的な針－注射器、蝶型針セット、および瀉血針を含む。通常、蝶型針セットは、尖った遠位端および針ハブに固定された近位端を有する中空の針を含む。針ハブの近位部分は、可撓性の配管に接続されている。針ハブは、配管と連通する流体導管を画定し、一対の可撓性の、半径方向に延びるウィングを含み、該ウィングは、医療従事者による蝶型針セットの把持を容易にする。一般に、可撓性の配管は、医療従事者が、針ハブに直近の配管を通る血流、すなわちフラッシュバックを可視化することを可能にする透明の材料で形成される。フラッシュバックの可視化は、針が患者の中に正しく挿入されたことを、医療従事者が確認することを可能にする。
【０００３】
一部の臨床医は、血液サンプルを採取するために、透明の針ハブを備えた皮下針－注射器を利用する。挿入の間、これらの臨床医たちは通常、針ハブの中のフラッシュバックを観察する。
【０００４】
一般に、瀉血針は、フラッシュバックを可視化するための構造を含んでいない。瀉血針にフラッシュバックを可視化するための構造がないことは、より経験のある医療従事者にとっては大きな欠点ではないが、瀉血針によって血液を抜き取る経験をほとんど有しない医療従事者にとっては、針が正しく患者の中に位置決めされたことを確認するいかなる手段もないことは、血液を抜き取るために必要な時間を増加させ得、患者の不快を増加させ得る。
【０００５】
上記の不利を克服する試みとして、Ｎｏｒｒｉｓらへの特許文献１は、瀉血針を開示し、該瀉血針は、採血管に取り付け可能であり、外側針、内側針、およびそれらの間にバルブ（ｂｕｌｂ）を含む。バルブは、透明であり、外側針が正しく患者の静脈内に位置決めされたとき、医療従事者が血液を可視化することを可能にする。バルブは、針内から空気を通気するために医療従事者によって押し下げられ得るボタンも含む。針内の空気は、血液が針を通って流れることを妨げ、通気されなければならない。
【先行技術文献】
【特許文献】
【０００６】
【特許文献１】米国特許第５，４５０，８５６号明細書
【発明の概要】
【発明が解決しようとする課題】
【０００７】
Ｎｏｒｒｉｓの瀉血針は、フラッシュバックの可視化を容易にするが、フラッシュバックの可視化を容易にするより安価な、より簡単な瀉血針が望まれる。
【課題を解決するための手段】
【０００８】
本開示は瀉血針に関し、該瀉血針は、組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、および開口部を画定する中央の針部分とを含む。遠位の針部分、近位の針部分および中央の針部分は、開口部と連通する流体チャンネルを画定する。材料が、開口部に隣接して位置決めされる。材料は、空気が開口部を通って流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものである。一実施形態において、材料は、開口部に隣接する血流、すなわちフラッシュバックの可視表示を提供する。
【０００９】

一実施形態において、材料は疎水性材料を含む。代替の実施形態において、材料は親水性毛管作用材料を含む。さらに別の実施形態において、材料は疎水性のプラグを含む。あるいは、材料は開口部の周りに位置決めされたカラー部を画定し得る。

【００１０】

一実施形態において、開口部は円形である。あるいは、開口部は様々な構成、例えば長方形またはスロット形状であることが想定されている。

【００１１】

一実施形態において、透明の筐体が開口部の周りに位置決めされ、フラッシュバックの可視化を容易にする。筐体はまた、材料を包含するように位置決めされ得、針から空気を通気するための通気孔を含み得る。

【００１２】

一実施形態において、瀉血針は、針ホルダーと係合するように構成された係合構造を含む。

【００１３】

一実施形態において、空気が開口部を通って流体チャンネルの中に入ることを阻止するために、逆止弁が提供される。さらに別の実施形態において、瀉血針は、針ホルダーを含む。

例えば、本発明は以下の項目を提供する。

（項目１）

瀉血針であって、

組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、

採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、

開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、

該開口部に隣接して位置決めされた材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、材料と

を備えている、瀉血針。

（項目２）

上記材料は疎水性材料を含む、項目１に記載の瀉血針。

（項目３）

上記材料は親水性毛管作用材料を含む、項目１に記載の瀉血針。

（項目４）

上記材料は、上記開口部の方に向かう親水性材料の内側層と、疎水性材料の外側層とを含む、項目１に記載の瀉血針。

（項目５）

上記開口部は円形である、項目１に記載の瀉血針。

（項目６）

上記開口部は細長いスロットを画定する、項目１に記載の瀉血針。

（項目７）

上記開口部の周りに位置決めされた透明の筐体をさらに含む、項目１に記載の瀉血針。

（項目８）

上記瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造をさらに含む、項目１に記載の瀉血針。

（項目９）

上記材料は、上記開口部を覆い上記針の周りに位置決めされたカラー部を画定する、項目１に記載の瀉血針。

（項目１０）

上記カラー部の材料の周りに位置決めされた透明の筐体をさらに含む、項目９に記載の瀉血針。

（項目１１）
空気が、上記開口部を通って上記流体チャンネルの中に入ることを阻止するための逆止弁をさらに含む、項目１に記載の瀉血針。
（項目１２）
針ホルダーをさらに含む、項目１に記載の瀉血針。
（項目１３）
上記材料は、上記開口部を通る血流の可視表示を提供する、項目１に記載の瀉血針。
（項目１４）
瀉血針であって、
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、
採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、
開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、
該開口部に隣接して位置決めされた疎水性材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、疎水性材料と、
該開口部の周りに位置決めされた透明の筐体と、
該瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造と
を備えている、瀉血針。
（項目１５）
上記針ホルダーをさらに含む、項目１４に記載の瀉血針。
（項目１６）
瀉血針であって、
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、
採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、
開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、
該開口部に隣接して位置決めされた親水性毛管作用材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、親水性毛管作用材料と、
該開口部の周りに位置決めされた透明の筐体と、
該瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造と
を備えている、瀉血針。
（項目１７）
上記針ホルダーをさらに含む、項目１６に記載の瀉血針。
（項目１８）
瀉血針であって、該瀉血針は、
針であって、組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分とを含み、該遠位の針部分および該近位の針部分は、流体チャンネルを画定する、針と、
該針で支持された筐体であって、受動通気孔を含み、該筐体の血液を可視化するための観察領域を画定する、筐体と
を備えている、瀉血針。
（項目１９）
上記近位の針部分の周りに位置決めされたエラストマーのシールドをさらに含み、該エラストマーのシールドおよび該近位の針部分が、上記筐体の中への流体の流路を画定する、項目１８に記載の瀉血針。
（項目２０）

上記筐体内に位置決めされた縦溝のある部材をさらに含み、該縦溝のある部材は、複数の流体チャンネルを画定する、項目１８および項目１９のうちのいずれか一項に記載の瀉血針。

（項目２１）

上記筐体内に支持された親水性材料をさらに含む、項目１８～項目２０のうちのいずれか一項に記載の瀉血針。

（項目２２）

上記針は、上記筐体の中への開口部を画定する中央部分を有する、項目１８～項目２１のうちのいずれか一項に記載の瀉血針。

【図面の簡単な説明】

【００１４】

フラッシュバックチャンバを備えた本開示の通気型瀉血針の実施形態が、図面を参照して本明細書に開示される。

【図１－１】図１は、針ホルダー、保護針カバーおよび幻影で示された採血管を備えた「従来技術」の瀉血針の斜視図であり、部品は分離されている。

【図１－２】図１Ａは、組み立てられた「従来技術」の瀉血針、針ホルダー、および幻影で示された採血管の側面断面図であり、瀉血針の遠位部分は静脈内に位置決めされている。

【図２－１】図２は、本開示の瀉血針の一実施形態の側面斜視図である。図２Ａは、図２で示された瀉血針の断面図である。図２Ｂは、図２Ａの切断線２Ｂ－２Ｂに沿った断面図である。

【図２－２】図２Ｃは、本開示の瀉血針の別の実施形態の側面断面図である。

【図３】図３は、本開示の瀉血針の代替の実施形態の側面断面図である。図３Ａは、図３の切断線３Ａ－３Ａに沿った断面図である。

【図４】図４は、本開示の瀉血針の別の実施形態の側面斜視切取り図である。図４Ａは、図４の切断線４Ａ－４Ａに沿った断面図である。

【図５】図５は、本開示の瀉血針の別の実施形態の側面斜視切取り図である。

【図６】図６は、本開示の瀉血針の別の実施形態の側面断面図である。

【図７】図７は、図６の切断線７－７に沿った断面図である。

【発明を実施するための形態】

【００１５】

（実施形態の詳細な記述）

フラッシュバックチャンバを備えた本開示の通気型瀉血針の実施形態がここで、図面を参照して詳細に記述され、該図面においては、同様の参照番号は、幾つかの図面の各々において同一のまたは対応する要素を示す。

【００１６】

図１は、公知の瀉血針１０、針ホルダー１２、ならびに針カバー１４および１６を示す。採血管１７が幻影で示されている。瀉血針１０は、遠位の針部分２０と、近位の針部分２２と、係合部分２４を備えた中間の針ハブ２３とを含む。係合部分２４は、瀉血針１０を針ホルダー１２に接続することを容易にするように提供される。一実施形態において、係合部分は、雄継手２４ａを含み、雄継手２４ａは、雌継手または係合部材２６と係合するように構成され、係合部材２６は、針ホルダー１２の遠位端に提供される。あるいは、ねじ、スナップ型コネクタ、その他を含む他の係合構造が使用され得る。下にさらに詳細に記述されるように、エラストマーのシールド２８が近位の針部分２２を覆い位置決めされ、近位の針部分２２をシールする。

【００１７】

針ホルダー１２は、実質的に円筒状の本体３０を含み、実質的に円筒状の本体３０は、係合部材２６を含む遠位端および一対のフランジ部材３２を含む近位端を有する。フランジ部材３２は、医療従事者による採血管１７の把持および挿入を容易にする。円筒状の本体３０は、採血管１７を受け入れるための空洞３４（図１Ａ）を画定する。通常、採血管

１７は、貫通可能ストッパ１７ａによってシールされ、低圧の空洞１７ｂ（図１Ａ）を画定する。ホルダー１２の遠位端は、係合部材２６を通る開口部３６を画定し、開口部３６は、近位の針部分２２を受け入れる大きさとされる。

【００１８】

図１Ａに示されるように、使用に際して、針１０は、係合部分２４および係合部材２６を介して針ホルダー１２の遠位端に固定される。針１０が針ホルダー１２に固定されると、近位の針部分２２は、針ホルダー１２の本体３０の空洞３４内に位置決めされ、エラストマーのシールド２８は、近位の針部分２２を覆い位置決めされる。次に、貫通可能ストッパ１７ａを含む採血管１７（幻影で示される）が、空洞３４内に位置決めされる。採血管１７が空洞３４の中に挿入されると、近位の針部分２２が、ストッパ１７ａと係合し、シールド２８を貫通する。近位の針部分２２が、ストッパ４０を貫通し、採血管１７の空洞１７ｂに入るように、シールド２８は下向きに圧縮（図１Ａ）される。遠位の針部分２０が患者の静脈３８に正しく位置決めされ、採血管１７が空洞３４内に位置決めされると、血液が、針１０を通って採血管１７の中に流入するように、通常、採血管１７は、真空に維持される。採血管１７が針ホルダー１２から取り外されると、弾力的なエラストマーのシールド２８は、その元の構成に戻り、近位の針部分２２を被覆し、近位の針部分２２をシールする。

【００１９】

図２および図２Ａは、概して１００として示されるフラッシュバックチャンバを備えた本開示の瀉血針の一実施形態を示す。針１００は、遠位端１０２と、近位端１０４と、中央部分１０６とを含む。遠位端１０２は、患者の組織を貫通するように構成された尖った端１０２ａを有し、近位端１０４は、採血管１７（図１Ａを参照）のストッパ１７ａを貫通するように構成された尖った端１０４ａを有する。中央部分１０６は、上に論議されたように、係合部材１０８を含み、係合部材１０８は針ホルダー（図１）と係合するように構成される。中央部分１０６はまた、開口部または穴１１０と、開口部１１０を画定する部分の中央部分１０６の周りに位置決めされた半透明または透明の筐体１１２とを含む。開口部１１０は円形として示されているが、他の構成、例えば長方形、正方形、楕円形、細長いスロット３９（図５）、その他が想定されている。透明の筐体１１２は、血液レザバ１１２ａを画定する。通気開口部１１３は好ましくは、透明の筐体１１２に形成される。通気開口部１１３が針１００の通気を容易にし、針１００を通る血流を可能にする。下に論議されるように、筐体１１２の通気開口部１１３は、空気の通過は許すが、例えば血液のような液体の通過は許さない材料によって被覆され得る。

【００２０】

図２Ａおよび図２Ｂを参照して、通気開口部１１３は、フィルタ１１６で被覆され得る。フィルタ１１６は好ましくは、親水性材料の内側層１１６ａと、疎水性材料の外側層１１６ｂとを含む。好ましくは、層１１６ａおよび層１１６ｂのうちの少なくとも１つは、０．４５ミクロンを下回る孔サイズを有する。かかる孔サイズは、空気の通過は可能にするが、バクテリアが筐体１１２の中に入ることを防止する。

【００２１】

図２Ｃを参照して、代替の実施形態において、フィルタ１１６は、例えばフラップ弁１５０のような疎水性逆止弁によって置き換えられ得る。図示のように、フラップ弁１５０は、筐体１１２の中に血液が流入し始めると、筐体１１２から外向きに曲がり、通気開口部１１３を露出させ、筐体１１２を通気するように構成される。逆止弁が開いたとき、血液が通気開口部１１３から出ることを防止するために、疎水性シート１５２が開口部１１３を覆い位置決めされる。血液が筐体１１２の中に流入し始めるのに先立って、フラップ弁１５０は開口部１１３をシールし、物質が筐体１１２の中に入ることを防止する。あるいは、フラップ弁１５０は、親水性材料の孔サイズが血液成分の通過を遮るサイズである場合は、該親水性材料から形成され得る。

【００２２】

針１００の遠位端１０２が患者の静脈内に正しく位置決めされたとき、すなわち、血液

が針１００を通って流れ、空気が通気されて、血液が開口部１１０を通ってレザバ１１２ａの中に入るとき、透明の筐体１１２は、医療実施者が針１００を通る血流を可視化することを可能にする。これによって、医療実施者は、針１００の遠位端１０２が、血液を抜き取るために患者の静脈内に正しく位置決めされたことを確認することができる。これは、患者から血液を抜き取ろうと試みる医療実施者に対して、特に瀉血針によって患者から血液を抜き取ることについて限られた経験しか有しないような実施者に対して大きな利益を提供する。

【００２３】

図３は、概して２００として示されるフラッシュバックチャンバを備えた本開示の通気型瀉血針の代替の実施形態を示す。針２００は、下に記述されるとおりを除いて、針１００と実質的に同様である。針２００は、遠位端２０２と、近位端２０４と、中央部分２０６とを含む。遠位端２０２は、患者の組織を貫通するように構成された尖った端２０２ａを有し、近位端２０４は、採血管（図１Ａを参照）のストッパを貫通するように構成された尖った端２０４ａを有する。中央部分２０６は、開口部または穴２１０と係合部材２１２ａとを含む。材料２１４は、穴２１０を覆い位置決めされている。医療従事者が針２００を通る血流を容易に識別し得るように、材料２１４は、材料の中に血液を毛管作用で吸い込む親水性の材料であり得る。針２００の通気を容易にするために、材料２１４は、空気に対しては透過性があるが、例えば血液のように液体に対しては透過性がない親水性材料であり得る。一実施形態において、親水性材料は、血液と接触したとき、色が変わるタイプのものであり得る。材料は、カラー２５０（図３）またはプラグ２５２（図４）の形であり得る。さらに、材料は、透明の筐体もしくはハブ２１２内に位置決めされ得るか、または代替的に、いかなる筐体もなく開口部２１０に隣接して位置決めされ得る。代替の実施形態において、材料は、空気は通すが血液は通さない疎水性の材料である。通気開口部２２６は筐体２１２に提供され得、筐体の通気を容易にし得ることに留意される。通気孔は、筐体２１２における開口部の形であり得、該開口部は、血液が入ると筐体２１２から空気が流れ出ることを可能にする。

【００２４】

図３および図３Ａでさらに示される代替の実施形態において、材料２１４は、膨張可能な材料で形成され得、該膨張可能な材料が血液と接触する前に、空気が通気開口部２２６を通ることを可能にする。材料２１４は、血液と接触すると膨張し得、通気開口部２２６を閉じ得る。

【００２５】

本明細書において、親水性材料および疎水性材料のみが開示されたが、血液の通過を防止しながら空気の通過を容易にし、血流の表示を提供する他の材料が、本開示の瀉血針に対して使用され得る。材料は、本明細書に開示されていない他の構成を有し得る。例えば、材料は、開口部を被覆するパッドを画定し得る。

【００２６】

図６および図７は、概してデバイス３９８として示されるフラッシュバックチャンバを備えた本開示の瀉血針の別の実施形態を示す。瀉血針３９８は、針４００と段付き筐体４０８とを含む。針４００は、遠位端４０２と、近位端４０４と、中央部分４０６とを含む。遠位端４０２は、患者の組織を貫通するように構成された尖った端４０２ａを有し、近位端４０４は、採血管（図示されず）のストッパ（図示されず）を貫通するように構成された尖った端４０４ａを有する。

【００２７】

段付き筐体４０８は、遠位部分４０８ａおよびより大きな直径の近位部分４０８ｂを有する。段付き筐体４０８は、中央部分４０６で支持されている。遠位部分４０８ａは、針の中央部分４０６を受け入れる大きさとされた通し穴４１２を画定する。遠位部分４０８ａは、例えば接着剤４１０を使用して、針４００にシールされ、固定される。あるいは、他の公知の技術、例えばクリンプ加工、クランプ、ねじ、溶接その他が使用され得、針４００を筐体４０８に固定し得る。近位部分４０８ｂは、透明の材料または半透明の材料で

形成され、筐体４０８の近位部分４０８ｂ内の可視化を容易にする。近位部分４０８ｂはまた、通し穴４１４を画定し、通し穴４１４は通し穴４１２と連通するが、通し穴４１２よりも直径が大きい。近位部分４０８ｂは、部分４０８ｂと針４００の近位端４０４との間に環状のリセス４１６を画定する。リセス４１６は、親水性材料４１８および内側の縦溝のある部材４２０を受け入れるような大きさとされる。内側の縦溝のある部材４２０が、針４００の近位端４０４の周りに位置決めされ、親水性材料４１８と連通する複数のチャンネル４２２を画定する。通気開口部４０９は、筐体４０８を通して提供される。

【００２８】

エラストマーのシールド４２８は、針４００の近位端４０４を覆い位置決めされる。上に論議されたように、エラストマーのシールド４２８は弾力的であり得、針４００の近位端４０４が採血管（図示されず）に接続されていないとき、針４００の近位端４０４をシールするように機能する。エラストマーのシールド４２８は、閉じた近位端４２８ａと開いた遠位端４２８ｂとを含む。開いた遠位端４２８ｂは環状のフランジ４３０を含み、環状のフランジ４３０は、筐体４０８のリセス４１６内で材料４１８に隣接して位置決めされる。筐体４０８の近位部分４０８ｂは、内向きに延びる環状のリブ４３２を含み、内向きに延びる環状のリブ４３２は、エラストマーのシールド４２８のフランジ４３０と係合し、シールド４２８の遠位端４２８ｂを筐体４０８のリセス４１６内に保持するように位置決めされる。矢印４３４によって示されるように、流路４３６は、エラストマーのシールド４２８と針４００の近位端４０４との間に画定される。流路４３６は、針４００の近位端４０４から縦溝のある部材４２０の縦溝のあるチャンネル４２２の中に血液を導き、親水性材料４１８と接触させる。使用に際して、血液が材料４１８と接触すると、材料４１８は、筐体４０８の近位部分４０８ｂを通して目視可能となる血流の可視表示を提供する。

【００２９】

フィルタ１１６と共に画定された（図２Ａ～図２Ｂ）、フィルタ２５２と共に画定された（図４～図４Ａ）、もしくはフィルタ３９と共に画定された（図５）、または逆止弁１５０と共に画定された（図２Ｃ）通気開口部１１３、ならびに開口部２２６（図３～図３Ａ）および開口部４０９（図６）はすべて、受動通気開口部として記述され得、該受動通気開口部は、針カニューレ内において大気圧よりも大きな圧力の気体が大気中に自動的に漏れることを可能にする。これらの受動通気開口部は、本発明によるデバイスのユーザによるいかなる行動も必要としない。

【００３０】

本明細書に開示された実施形態には、様々な変更がなされ得ることは理解される。したがって、上述は、限定するものとして解釈されるべきではなく、好ましい実施形態の単なる例示として解釈されるべきである。当業者は、本明細書に添付された請求項の範囲および精神内で他の変更に想到する。

【図１－１】

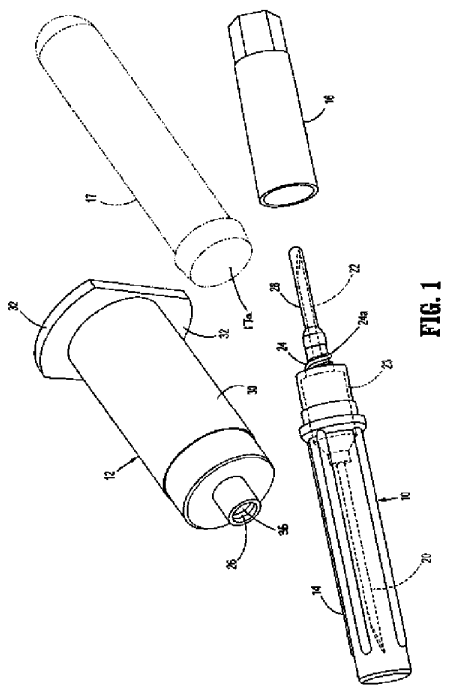


FIG. 1

【図１－２】

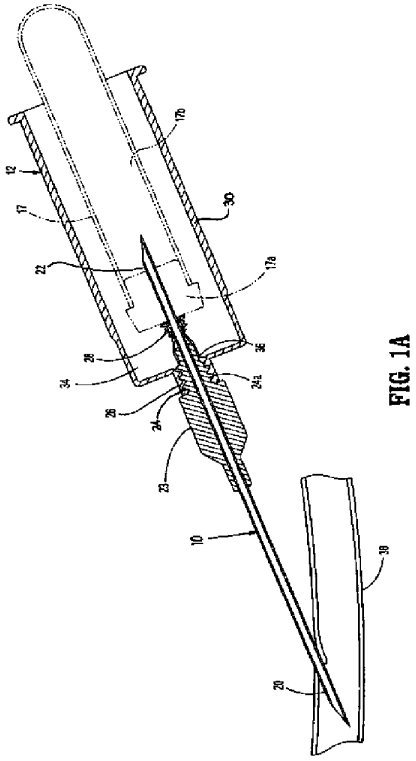


FIG. 1A

【図２－１】

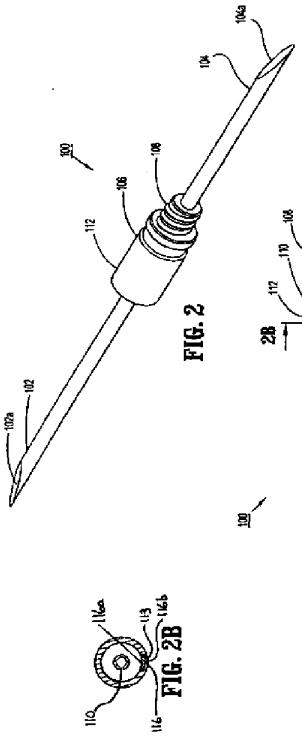


FIG. 2

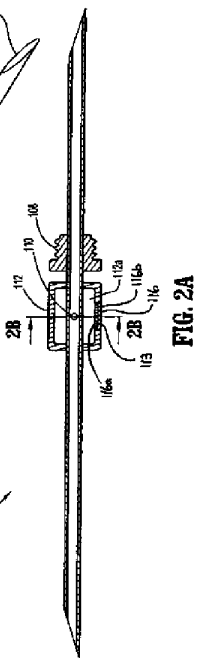


FIG. 2A

FIG. 2B

【図２－２】

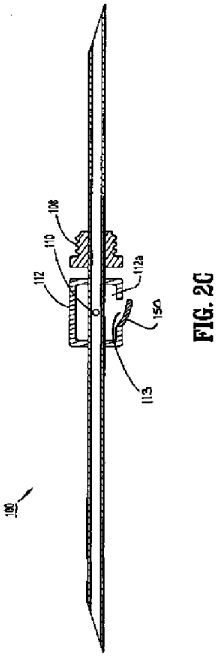


FIG. 2C

【図３】

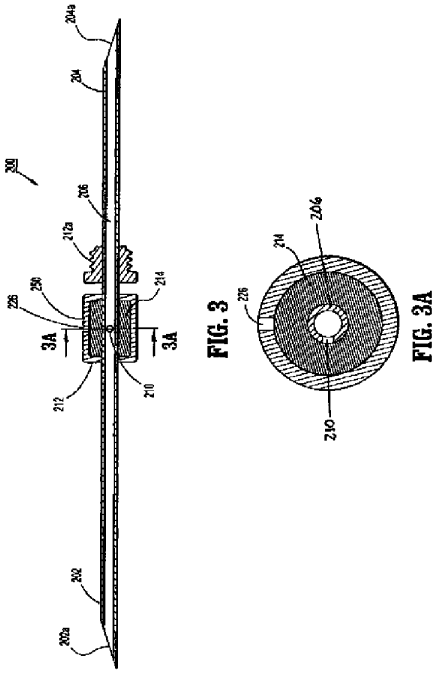


FIG. 3

FIG. 3A

【図４】

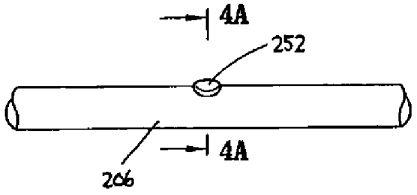


FIG. 4

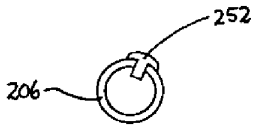


FIG. 4A

【図５】

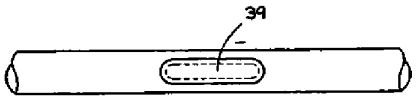


FIG. 5

【図６】

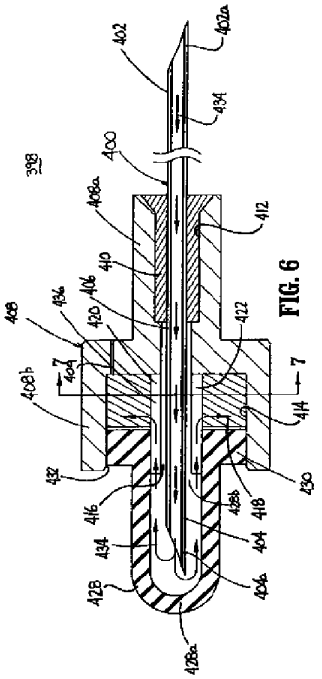


FIG. 6

【図７】

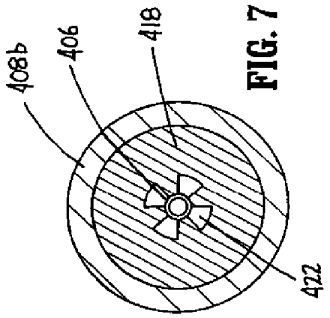


FIG. 7

フロントページの続き

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Fターム(参考) 4C038 TA01 TA03 UJ02

【外国語明細書】
2013240628000001.pdf

Abstract of DE 29913417 (A1)

Device for taking blood from a blood vessel5 (B), with a housing (1), with a hollow needle (10) that can be inserted through the blood vessel wall into the interior of the blood vessel (B), and with means for sucking the blood through the interior of the hollow needle, characterized, that the hollow needle (10) moves between a retracted position, in which the hollow needle (10) remains at least substantially within the outer contours of the housing, and an extended position, in which the end (19) of the hollow needle (10) protrudes from the housing by a length, is displaceably arranged, and dar means are provided with which the hollow needle (10) can be displaced from its retracted position into its extended position.

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DESCRIPTION DE29913417U1

[0001]

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[0002]

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28 Device for taking blood from a blood vessel

[0005]

32 The invention relates to a device for removing blood from a blood vessel of the type corresponding to the preamble of claim 1.

[0006]

37 Such devices always comprise a hollow needle that is beveled at one end for penetrating the

skin, the tissue lying between the skin and the vessel and the vessel wall, and which is usually equipped with a coupling at its other end, which is used to attach a container with a volume for receiving the blood taken .

[0007]

44 To generate the suction required for taking blood, it is known to design the containers as a piston/cylinder arrangement, after the hollow needle has been inserted into the blood vessel and the container has been coupled, the piston is actuated manually to increase the volume of the vessel.

[0008]

51 D-40239 DÜSSELDORF ;1\1uLVAnYs1iU*£.2 jTELEFON*49 \1Vl / 9*(J 145 -ö TljLEi1AX 49 / 211 / 96 145 - 20

[0009]

56 D-45133 ESSEN F^QM^JiSTI^SSE#*A .

57 J^LEFflN^V 201 \ 84 2}Q - j FAX 4$y 201 / 84 230 - 20

[0010]

61 POSTBANK COLOGNE (BLZ 370 100 50) 115 211 - 504

[0011]

65 The disadvantage of this device is that the patient can only prick the hollow needle into the blood vessel with considerable skill and practice if the person performing the puncture is almost painless for the patient.

68 Furthermore, when the plunger is actuated manually, the needle cannot usually be kept completely still, which means that the needle in the puncture area stretches or even injures the skin, the underlying tissue and the vessel wall, which regularly causes pain to the patient.

[0012]

74 For the latter reason, it is also known to pre-evacuate the vessels having the volume for receiving the blood taken and to seal them in their area to be connected to the coupling of the hollow needle with a closure or

77 Equip valve assembly, which is opened when coupled to the hollow needle, so that the blood to be removed is sucked into the volume of the container without requiring additional manual operation of the device.

[0013]

83 This measure prevents the risk of "wobbly pain" caused by the manual operation of the piston, but the disadvantage is that the insertion of the hollow needle, the subsequent coupling of the pre-evacuated vessel and the frequently necessary replacement of a full container with an empty one In turn, absorption of the blood removed leads to undesired movements of the needle which are painful for the patient.

[0014]

91 It is therefore the object of the invention to provide a device which allows blood to be taken from a blood vessel in a manner that is less painful for the patient.

[0015]

96 This object is solved by the invention presented in claim 1.

[0016]

100 Because in the device according to the invention the hollow needle can be moved between a retracted position, in which the hollow needle remains at least essentially within the outer contours of the housing of the device, and an extended position, in which the end of the hollow needle to be inserted into the blood vessel is pushed out of the housing by one certain length protrudes, is displaceably arranged, and that means are provided with which the hollow needle can be displaced from its retracted to its extended position, it is no longer necessary for the insertion of the needle that both the guide and the displacement during the insertion process of the needle must be accomplished by the person taking the blood sample.

108 Rather, the housing only needs to be positioned at the point on the body where the blood is to be taken and the means for extending the needle then activated.

110 The risk of "wobbling" during insertion of the hollow needle is therefore considerably reduced.

111 Since the means for moving the hollow needle can also be designed in such a way that it can be moved from its retracted to its extended position at high speed and the puncture process therefore only lasts a very short time, the pain associated with taking blood is reduced again.

114 Another advantage is that the high penetration speed of the needle reduces the pressure required in the blood vessel to prevent the vessel walls from collapsing when the needle is inserted, which is usually achieved by applying a pressure cuff, thereby reducing the risk of extravascular bruising.

[0017]

121 The means by which the hollow needle can be moved from its retracted position to its extended

position

[0018]

126 sen preferably have an arrangement which exerts an elastic force acting on the hollow needle in the direction of the retracted to the extended position.

128 In order to carry out the puncture, the hollow needle is then first moved into its retracted position, held in this position by suitable means, for example a locking device, and after the device has been brought to the suitable point on the body, by releasing the means, for example the locking moved to its extended position, with the tip of the hollow needle penetrating the blood vessel.

[0019]

136 In terms of its design, the arrangement for generating the elastic force can have a compression spring.

[0020]

141 However, it is also possible to generate the elastic force with the help of a compressed air reservoir or in a completely different way.

[0021]

146 The pain associated with taking blood from the patient can be further reduced if the housing of the device includes at least one internal volume for receiving the blood taken from the patient.

148 As a result of this measure, a coupling of a vessel for receiving blood taken after the puncture has been made is superfluous, so that "shaking pains" are prevented.

[0022]

153 If existing, commercially available containers are to continue to be used, an embodiment of the device according to the invention is recommended in which the housing includes an adapter arrangement for connecting at least one commercially available container for receiving the blood taken.

157 With this configuration, depending on the requirements, either several containers can be connected to the adapter at the same time,

[0023]

162 or - if this is not desired or possible - several containers can be connected one after the other.

[0024]

166 The means for sucking the blood through the interior of the hollow needle preferably include a negative pressure in the at least one interior volume compared to the outside environment.

168 This negative pressure can be generated, for example, by the inner volume being pre-evacuated and the interior of the hollow needle communicating with the inner volume in its extended position, in other words: only when the hollow needle is in the extended position is its interior connected to the pre-evacuated inner volume.

[0025]

175 However, it is also possible to provide means that only generate the negative pressure when the hollow needle is moved from its retracted to its extended position, to provide a manually or automatically actuated piston/cylinder device, or to bring about the negative pressure in any other way.

[0026]

182 Irrespective of the manner in which the negative pressure for sucking the blood is brought about, there are considerable advantages for the application if the device is designed in such a way that the negative pressure is applied to the hollow needle when it penetrates the blood vessel.

186 This measure effectively prevents painful extravascular bruising (hematoma) as a result of taking blood, which is regularly the case when blood can escape past the hollow needle from the blood vessel into the adjacent tissue during blood taking.

189 Because the suction in this preferred embodiment of the invention already exists when the hollow needle penetrates the blood vessel, blood that would otherwise have gotten into the tissue is also sucked out, even if the opening of the hollow needle is not completely drawn into the blood vessel

[0027]

196 Vessel has penetrated or partially exited the opposite vessel wall.

197 As a further consequence, in this embodiment the "penetration depth" of the tip of the hollow needle for carrying out the blood withdrawal method does not have to be specified as precisely as hitherto, which also makes it easier for the user to take the blood.

[0028]

203 For handling the device according to the invention, it is particularly advantageous to provide the side part of the housing from which the hollow needle protrudes in its extended position with at least one contact surface via which the device is supported on the body surface of a patient

during use.

207 To carry out the removal process, the device then only needs to be placed on a suitable part of the body and the displacement process of the hollow needle started.

[0029]

212 Tests have shown that the blood sampling process can be carried out particularly reliably and with little pain if the at least one contact surface is designed in such a way that when the device is supported on the body surface of the patient, the hollow needle forms an angle of between 5° and 30° with respect to the body surface in the support area - depending on the thickness of the tissue located between the vessel wall through which the hollow needle is intended to penetrate and the support surface.

[0030]

221 The device according to the invention can be used particularly variably when the at least one contact surface is designed in such a way that the angle that the hollow needle forms with the body surface during the removal process can be adjusted.

[0031]

227 In order to prevent the blood vessel intended for the removal process from being pushed away to the side when the device is put on, a particularly preferred

[0032]

232 Embodiment of the device according to the invention, a recess is provided in the at least one contact surface, into which the blood vessel can at least partially bulge and is thus positioned by the lateral boundary surfaces of the recess.

[0033]

238 If blood from a patient is used to carry out various diagnostic or

239 Therapy method required, so it is advantageous to provide a plurality of internal volumes separated from one another or an adapter arrangement for connecting a plurality of containers for receiving blood taken.

[0034]

245 The inner volumes or the containers can then optionally communicate with one another in series or also in parallel.

[0035]

250 In the drawing, exemplary embodiments of the invention are shown schematically.

251 Show it:

[0036]

255 1 shows a detail and diagrammatic view of a first exemplary embodiment of a device according to the invention in a longitudinal section, with the hollow needle being in its retracted position;

[0037]

260 FIG. 2 shows the same embodiment in the same view as in FIG. 1, but with the hollow needle being in its extended position; FIG.

[0038]

265 Fig .. 3 - in part - the same embodiment as in Fig. 1 in a partially cut

[0039]

269 NEN top view (view A in Fig. 1);

[0040]

273 FIG. 4 shows another embodiment of a device according to the invention in a view corresponding to FIG. 3; FIG.

[0041]

278 5--schematically and in detail--an exemplary embodiment corresponding to FIGS. 1 to 3 of a device according to the invention during a removal process, in a view in the direction of the blood vessel used for blood removal;

[0042]

284 6 - schematically - different positions of the beveled end of the hollow needle relative to the position of the blood vessel;

[0043]

289 7 shows an embodiment of a device according to the invention, which comprises a plurality of

volumes communicating with one another in series for receiving blood that has been taken (schematic);

[0044]

295 8 shows an embodiment of a device according to the invention in a view corresponding to FIG

[0045]

299 9 shows an embodiment of a device according to the invention in a view corresponding to FIGS. 7 and 8, which has an adapter plate for connecting two external containers for receiving blood that has been taken.

[0046]

305 The embodiment of a device according to the invention, denoted as 100 as a whole in FIGS. 1 to 3 and shown only partially and schematically in these figures, comprises a housing 1, which in its interior has two internal volumes 3, 4 fluidically connected to one another via a channel 2 for receiving blood.

309 The housing 1 has at its Fig. 1 downward-facing end face 5 on a housing extension 6 whose

[0047]

313 end 7 shown below in FIG. 1 is open.

[0048]

317 The interior 8 of the housing extension 6 serves to accommodate a hollow needle arrangement designated as a whole by 9, which essentially consists of the actual hollow needle 10 directed towards the open end 7 and a hollow needle carrier 11 serving to slidably mount the hollow needle arrangement 9 in the interior 8 of the housing extension 6 , which cooperates with the inner lateral surface 12 of the housing extension 6 at least approximately in a sealing manner.

[0049]

325 With its end face 13 facing away from the hollow needle 10 , the hollow needle carrier 11 is supported on a rigid contact surface 15 of the housing 1 via a pretensioned spiral spring 14 .

[0050]

330 A locking device 16 is used to lock the hollow needle arrangement 9 against the compressive force of the coil spring 14 in the retracted position.

[0051]

335 The hollow needle arrangement 9 has an inner channel 18 which extends from the tip 19 of the hollow needle 10 to a lateral opening 20 in the hollow needle carrier 11 .

[0052]

340 Furthermore, in the side wall of the housing extension 6 shown on the right in FIG.

[0053]

344 To move the hollow needle 10 from its retracted position shown in Fig. 1 to its extended position shown in Fig. 2, the locking device 16 is moved in such a way that the contact surface 17

[0054]

350 is released.

351 Due to the force exerted by the spiral spring 14 on the hollow needle arrangement 9, the latter snaps downwards according to FIG.

353 In this position, the inner channel 18 communicates with the channel 21 via the opening 22 so that the inner volumes 3 and 4 communicate with the inner channel 18 of the hollow needle and blood can flow through the channels 18, 21 and 2 into the inner volumes 3, 4.

[0055]

359 As can also be seen from FIG.

[0056]

363 As illustrated in FIG. 6, blood can only be taken if the hollow needle 10 penetrates just deep enough into the patient's tissue that its tip does not stop before penetrating the wall of the blood vessel B (see

366 6a)), nor does the area of the hollow needle 10 which is bevelled towards the tip 19 project completely through the blood vessel B (cf.

368 Fig. 6e)).

[0057]

372 In order to be able to adapt the "penetration depth" of the tip 19 of the hollow needle 10 required for blood sampling to the individual requirements, a cuff 24 is provided on the housing

extension 6, which is displaceably mounted in the direction of arrow P, with which the effective length of the housing extension 6 and thus the penetration depth the tip 19 of the hollow needle 10 can be changed.

377 The cuff 24 and the housing extension 6 can be equipped with latching means, not shown in the drawing, with which the cuff 24 can be locked in three different basic positions in which the penetration depth is at Kin-

[0058]

383 dern, normal-weight adults or overweight adults usual conditions is adapted.

[0059]

387 Extravascular bruising is also effectively prevented in end positions of the hollow needle 10 in which the tip 19 has not fully penetrated the blood vessel B (Fig. 6b)) or has partially penetrated the opposite wall of the blood vessel B (Fig. 6d)), since the negative pressure for sucking out the blood is already applied to the hollow needle as soon as it has entered the vessel.

[0060]

395 In principle, it is possible for the hollow needle 10 to pierce the blood vessel B essentially perpendicularly to its course.

397 However, such a procedure presupposes that the "penetration depth" must be predetermined almost exactly.

399 In order to avoid this, it is advisable to take the sample at an angle α between the hollow needle 10 and the blood vessel B, which is in the range between 5° and 30°.

401 For this purpose, the exemplary embodiment of the invention shown in FIGS. 1 and 2 has contact surfaces 25, through which the desired angle α is specified.

403 In the exemplary embodiments shown in the drawing, the angle α is fixed.

404 However, it is also within the scope of the invention to design the contact surfaces so variably that the angle α can be changed depending on the intended use of the device.

[0061]

409 As already described and shown again in detail in FIG. 1, a spiral spring 14 can be used to generate the force that drives the hollow needle arrangement from its retracted into its extended position.

412 However, as shown schematically in FIG. 4, it is also possible to provide a compressed air reservoir 26 between the end face 13 and the contact surface 15 or other means suitable for effecting an elastic force for propulsion.

[0062]

418 In order to prevent the vessel from which blood is to be taken from migrating laterally when the device 100 is placed on and the removal process thereby being frustrated, in a preferred embodiment of the invention a recess 27 is provided in the contact surfaces, into which the blood vessel B after the device 100 has been placed on the skin, it is at least partially pressed in and the blood vessel B is thus fixed laterally in the position required for taking blood (see Fig.

424 5).

[0063]

428 As illustrated in FIGS. 7 to 9, devices 100 according to the invention can be equipped in different ways with volumes for taking up blood that has been taken.

430 Thus, several volumes 28, 29, 30--three in FIG.

[0064]

434 It is also possible, as shown in FIG. 8, to provide inner volumes 31, 32, 33 which are arranged parallel to one another and are correspondingly filled approximately at the same time as one another.

[0065]

440 To generate the negative pressure required for filling, the volumes 28 to 33 can be pre-evacuated, or the negative pressure required in them can take place in any other way, for example by connecting the volumes to a piston/cylinder unit, an external pump, etc.

443 In order to avoid extravascular bruising, it is only essential that the negative pressure has already been generated when the tip 19 of the hollow needle 10 penetrates into the vessel.

[0066]

448 In the exemplary embodiment illustrated in FIG.

[0067]

452 Units 36/37 are formed in such a way that the pistons 36 can be displaced into the cylinder 37 by manually operable piston rods 38 .

454 An adapter arrangement 39 is used to attach the piston/cylinder unit 36/37 to this device, which is designated as a whole by 200, from which the housing extension 206 in turn extends downward according to FIG.

457 The hollow needle arrangement 209 and the channels 202 correspond in their technical design

and function to the hollow needle arrangement 9 and the channels 2 as they are described with reference to FIGS. 1 to 3 and therefore do not require any special discussion at this point.

[0068]

463 9 takes place in a manner already described with reference to FIGS. 1 to 3, by pulling out the piston rods 38 into the position shown in FIG of the cylinder 37 against the action of the negative pressure generated prior to the needle propelling and penetrating the blood vessel.

[0069]

469 14

[0070]

473 REFERENCE LIST

[0071]

477 1

478 Housing

479 34

480 volume

2

484 channel

485 35

486 volume

3

490 internal volume

491 36

492 Pistons

4

496 internal volume

497 37

498 cylinder

5

502 face

503 38

504 piston rods

6

508 Housing contζ

509 39

510 adapter assembly

7

514 End

515 40

516 locking protrusions

8

520 interior

521 100

522 contraption

9

526 hollow needle assembly

527 206

528 Housing contζ

10

532 hollow needle

533 209

534 hollow needle assembly

11

538 hollow needle carrier

539 202

540 channels

12

544 inner surface

13

548 face

549 H

550 skin

14

554 spiral spring

555 B

556 blood vessel

15

560 contact surface

561 A

562 Opinion

16

566 locking device

567 P

568 Arrow

17

572 plant area

18

576 inner canal

19

580 Top

20

584 opening

21
588 channel

22
592 End

23
596 attack

24
600 cuff

25
604 contact surface

26
608 compressed air reservoir

27
612 recess

28
616 volume

29
620 volume

30
624 volume

31

628 volume

32

632 volume

33

636 volume

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CLAIMS DE29913417U1

1.

13 Device for taking blood from a blood vessel (B), with a housing (1), with a hollow needle (10) that can be inserted through the blood vessel wall into the interior of the blood vessel (B), and with means for sucking the blood through the interior of the hollow needle, characterized in that the hollow needle (10) moves between a retracted position, in which the hollow needle (10) remains at least substantially within the outer contours of the housing, and an extended position, in which the end (19) to be inserted into the blood vessel (B) the hollow needle (10) protrudes from the housing by a length, and in that means are provided with which the hollow needle (10) can be displaced from its retracted to its extended position.

2.

24 Device according to Claim 1, characterized in that the means for displacing the hollow needle (10) from its retracted to its extended position comprise an arrangement which acts on the hollow needle (10) in a direction from the retracted to the extended position exert an acting elastic force.

3.

31 Device according to Claim 2, characterized in that the arrangement has a compression spring (14).

4.

36 Device according to Claim 2 or 3, characterized in that the arrangement has a compressed air reservoir (26).

5.

41 Device according to one of Claims 1 to 4, characterized in that the housing (1) comprises at least one internal volume (3, 4, 28-35) for receiving blood which has been removed.

6.

46 Device according to one of Claims 1 to 4, characterized in that the housing (1) comprises an adapter arrangement (39) for attaching at least one container, the internal volume (34, 35) of which is used to receive blood taken.

7.

52 Device according to Claim 5 or 6, characterized in that the means for sucking the blood through the interior of the hollow needles (10) comprise a negative pressure in the at least one interior volume (3, 4, 28-35) compared to the external environment.

8.

58 Device according to Claim 7, characterized in that the inner volume (3, 4, 28-35) is pre-evacuated and that the interior of the hollow needle (10) communicates with the inner volume (3, 4, 28-35) in its extended position.

9.

64 Device according to Claim 7, characterized in that means are provided which generate the negative pressure in the inner volume (3, 4, 28-35) when the hollow needle (10) is moved from its retracted to its extended position.

10.

70 Device according to Claim 9, characterized in that means for generating the negative pressure are a piston arrangement which is connected to the hollow needle (10) and which generates a negative pressure in a cylinder arrangement when the hollow needle (10) is moved into its extended position, and means which, in the extended Position of the hollow needle (10) connects the interior of the cylinder with the interior volume (3, 4, 28-35) for receiving the blood.

11.

78 Device according to one of Claims 1 to 10, characterized in that the side part of the housing (1) from which the hollow needle (10) protrudes in its extended position has at least one contact

surface (25) for supporting the device during use on the body surface of a patient.

12.

84 Device according to Claim 11, characterized in that the at least one contact surface (25) is designed in such a way that when the device is supported on the body surface of the patient, the hollow needle (10) forms an angle α to the body surface in the support area in the range between 5° and 30° includes.

13.

91 Device according to Claim 12, characterized in that the at least one contact surface (25) is designed such that the angle α between the hollow needle (10) and the body surface when the device is supported on the patient's body surface is adjustable.

14.

97 Device according to one of Claims 11 to 13, characterized in that the contact surface (25) has at least one recess (27) for fixing the blood vessel (B) used for taking blood.

15.

102 Device according to one of Claims 1 to 14, characterized in that the device comprises a plurality of separate inner volumes (3, 4, 28-33) for receiving the blood taken or an adapter arrangement (39) for connecting several containers for receiving blood taken includes.

16.

108 Device according to Claim 15, characterized in that the internal volumes (28, 29, 30) or the containers communicate with one another in series.

17.

113 Device according to Claim 15, characterized in that the inner volumes (31, 32, 33) or the containers communicate with one another in parallel.

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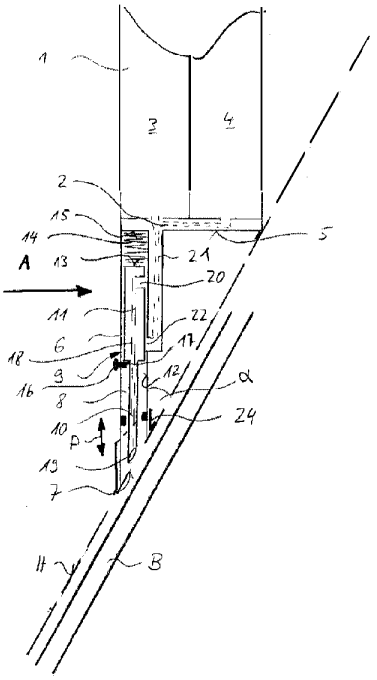
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(54) Vorrichtung zur Entnahme von Blut aus einem Blutgefäß

(57) Vorrichtung zur Entnahme von Blut aus einem Blutgefäß (B),
mit einem Gehäuse (1),
mit einer durch die Blutgefäßwandung ins Innere des Blutgefäßes (B) einführbaren Hohlnadel (10), und mit Mitteln zum Saugen des Bluts durch das Innere der Hohlnadel,
dadurch gekennzeichnet,
daß die Hohlnadel (10) zwischen einer zurückgezogenen Position, in der die Hohlnadel (10) zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß (B) einzuführende Ende (19) der Hohlnadel (10) aus dem Gehäuse um eine Länge hervorragt, verlagerbar angeordnet ist, und
daß Mittel vorgesehen sind, mit denen die Hohlnadel (10) aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist.



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Vorrichtung zur Entnahme von Blut aus einem Blutgefäß

Die Erfindung bezieht sich auf eine Vorrichtung zur Entnahme von Blut aus einem Blutgefäß der dem Oberbegriff des Anspruchs 1 entsprechenden Art.

Derartige Vorrichtungen umfassen stets eine zur Durchdringung der Haut, des zwischen Haut und Gefäß liegenden Gewebes sowie der Gefäßwandung einenends angeschrägte Hohlnadel, die an ihrem anderen Ende meist mit einer Kupplung ausgestattet ist, welche dem Ansetzen eines ein Volumen zur Aufnahme des entnommenen Blutes aufweisenden Behälters dient.

Zur Erzeugung des zur Blutentnahme erforderlichen Soges ist es bekannt, die Behältnisse als Kolben/Zylinderanordnung auszugestalten, wobei nach erfolgtem Einstich der Hohlnadel in das Blutgefäß und Ankuppeln des Behältnisses der Kolben manuell im Sinne einer Vergrößerung des Gefäßvolumens betätigt wird.

Nachteilig ist bei dieser Vorrichtung, daß ein für den Patienten nahezu schmerzloses Einstechen der Hohlnadel in das Blutgefäß nur bei erheblichem Geschick und erheblicher Übung der den Einstich vornehmenden Person möglich ist. Weiterhin kann bei manueller Betätigung des Kolbens die Nadel in der Regel nicht vollständig ruhig gehalten werden, was dazu führt, daß die Nadel im Einstechbereich die Haut, das darunter liegende Gewebe und die Gefäßwandung dehnt oder sogar verletzt, was regelmäßig zu Schmerzbeeinträchtigungen des Patienten führt.

Aus letzterem Grunde ist es ebenfalls bekannt, die das Volumen zur Aufnahme des entnommenen Blutes aufweisenden Gefäße vorzuevakuieren und in ihrem mit der Kupplung der Hohlnadel zu verbindenden Bereich mit einer Verschluß- bzw. Ventilanordnung auszustatten, die beim Ankuppeln an die Hohlnadel geöffnet wird, so daß das zu entnehmende Blut in das Volumen des Behältnisses eingesaugt wird, ohne daß es hierzu einer zusätzlichen manuellen Betätigung der Vorrichtung bedarf.

Durch diese Maßnahme wird die Gefahr, durch die manuelle Betätigung des Kolbens hervorgerufener "Wackelschmerzen" zwar verhindert, nachteilig ist jedoch, daß das Einstechen der Hohlnadel, das anschließende Ankuppeln des vorevakuierten Gefäßes und das in häufigen Fällen notwendige Auswechseln eines vollen gegen einen leeren Behälter zur Aufnahme des entnommenen Blutes wiederum zu unerwünschten, für den Patienten schmerzhaften Bewegungen der Nadel führt.

Es ist daher die Aufgabe der Erfindung, eine Vorrichtung zu schaffen, welche eine Blutentnahme aus einem Blutgefäß in für den Patienten weniger schmerzhafter Weise ermöglicht.

Diese Aufgabe wird durch die in Anspruch 1 wiedergegebene Erfindung gelöst.

Dadurch, daß bei der erfindungsgemäßen Vorrichtung die Hohlnadel zwischen einer zurückgezogenen Position, in der die Hohlnadel zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses der Vorrichtung verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß einzuführende Ende der Hohlnadel aus dem Gehäuse um eine bestimmte Länge hervorragt, verlagerbar angeordnet ist, und daß Mittel vorgesehen sind, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, ist es zum Einstechen der Nadel nicht mehr erforderlich, daß während des Einstechvorganges sowohl die Führung, als auch die Verlagerung der Nadel von der die Blutabnahme durchführenden Person bewerkstelligt werden muß. Vielmehr braucht das Gehäuse lediglich an der Stelle des Körpers, an der die Blutabnahme erfolgen soll, positioniert und anschließend die Mittel zum Ausfahren der Nadel aktiviert zu werden. Die Gefahr des "Wackelns" während des Einstiches der Hohlnadel ist daher erheblich verringert. Da zudem die Mittel zur Verlagerung der Hohlnadel derart ausgebildet sein können, daß diese mit hoher Geschwindigkeit aus ihrer zurückgezogenen in ihre ausgefahrene Position erfolgt und damit der Einstichvorgang nur eine sehr kurze Zeit dauert, ist der mit der Blutentnahme verbundene Schmerz abermals reduziert. Weiterhin ist vorteilhaft, daß durch die hohe Eindringgeschwindigkeit der Nadel der in dem Blutgefäß zum Verhindern des Kollabierens der Gefäßwandungen beim Einstechen der Nadel erforderliche Druck der meist durch Anlegen einer Druckmanschette bewerkstelligt wird, verringert ist, wodurch das Risiko paravasaler Blutergüsse reduziert ist.

Die Mittel, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, wei-

sen vorzugsweise eine Anordnung auf, die auf die Hohlnadel eine in Richtung der zurückgezogenen auf die ausgefahrene Position wirkende, elastische Kraft ausüben. Zur Durchführung des Einstiches wird die Hohlnadel dann zunächst in ihre zurückgezogene Position verlagert, in dieser durch geeignete Mittel, beispielsweise einer Verriegelungseinrichtung, gehalten, und, nachdem die Vorrichtung an die geeignete Stelle des Körpers gebracht wurde, durch Lösen der Mittel, beispielsweise der Verriegelung, in ihre ausgefahrene Position gebracht, wobei die Spitze der Hohlnadel in das Blutgefäß eindringt.

In ihrer konstruktiven Ausgestaltung kann die Anordnung zur Erzeugung der elastischen Kraft eine Druckfeder aufweisen.

Es ist jedoch ebenfalls möglich, die elastische Kraft mit Hilfe eines Druckluftreservoirs oder auch in einer gänzlich anderen Weise zu erzeugen.

Der mit der Blutentnahme für den Patienten verbundene Schmerz kann nochmals verringert werden, wenn das Gehäuse der Vorrichtung mindestens ein Innenvolumen zur Aufnahme des dem Patienten entnommenen Blutes umfaßt. Durch diese Maßnahme wird ein Ankuppeln eines Gefäßes zur Aufnahme entnommenen Blutes nach erfolgtem Einstich überflüssig, so daß "Wackelschmerzen" verhindert werden.

Sollen bereits vorhandene, handelsübliche Behälter weiterhin Verwendung finden, so empfiehlt sich eine Ausführungsform der erfindungsgemäßen Vorrichtung, bei der das Gehäuse eine Adapteranordnung zum Anschluß mindestens eines handelsüblichen Behälters zur Aufnahme entnommenen Blutes umfaßt. Durch diese Ausgestaltung können an den Adapter je nach Anforderungen entweder mehrere Behälter gleichzeitig,

oder - falls dies nicht erwünscht oder möglich ist - auch mehrere Behälter nacheinander angeschlossen werden.

Die Mittel zum Saugen des Blutes durch das Innere der Hohlnadel umfassen vorzugsweise einen Unterdruck in dem mindestens einen Innenvolumen gegenüber der äußeren Umgebung. Dieser Unterdruck kann beispielsweise dadurch erzeugt werden, daß das Innenvolumen vorevakuiert ist und das Innere der Hohlnadel in ihrer ausgefahrenen Position mit dem Innenvolumen kommuniziert, mit anderen Worten: daß erst in der ausgefahrenen Position der Hohlnadel die Verbindung deren Inneren mit dem vorevakuierten Innenvolumen erfolgt.

Es ist jedoch ebenfalls möglich, Mittel vorzusehen, die den Unterdruck erst beim Verlagern der Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position erzeugen, eine manuell oder automatisch betätigbare Kolben/Zylindereinrichtung vorzusehen oder den Unterdruck auf eine beliebige andere Weise zu bewerkstelligen.

Unabhängig davon, auf welche Weise der Unterdruck zum Saugen des Blutes bewirkt wird, ergeben sich für die Anwendung erhebliche Vorteile, wenn die Vorrichtung derart ausgebildet ist, daß der Unterdruck an der Hohlnadel anliegt, wenn diese in das Blutgefäß eindringt. Durch diese Maßnahme wird nämlich wirkungsvoll verhindert, daß infolge der Blutentnahme schmerzhafte paravasale Blutergüsse (Hämatome) entstehen, was regelmäßig dann der Fall ist, wenn während der Blutentnahme Blut an der Hohlnadel vorbei aus dem Blutgefäß in das angrenzende Gewebe austreten kann. Dadurch, daß der Sog bei dieser bevorzugten Ausführungsform der Erfindung bereits beim Eindringen der Hohlnadel in das Blutgefäß besteht, wird auch Blut, was ansonsten in das Gewebe gelangt wäre, abgesaugt, und zwar selbst dann, wenn die Öffnung der Hohlnadel nicht vollständig in das

Gefäß eingedrungen oder teilweise aus der gegenüberliegenden Gefäßwandung wieder ausgetreten ist. Als weitere Folge muß bei dieser Ausführungsform die "Eindringtiefe" der Spitze der Hohlnadel zur Durchführung des Blutentnahmeverfahrens nicht so exakt wie bislang vorgegeben werden, was die Blutentnahme auch dem Anwendungspersonal erleichtert.

Für die Handhabung der erfindungsgemäßen Vorrichtung ist es besonders vorteilhaft, das Seitenteil des Gehäuses, aus dem die Hohlnadel in ihrer ausgefahrenen Position herausragt, mit mindestens einer Anlagefläche zu versehen, über die sich die Vorrichtung während ihrer Verwendung auf der Körperoberfläche eines Patienten abstützt. Die Vorrichtung braucht zur Durchführung des Entnahmevorganges dann lediglich auf eine geeignete Körperstelle aufgesetzt und der Verlagervorgang der Hohlnadel in Gang gesetzt zu werden.

Versuche haben gezeigt, daß der Blutentnahmevorgang besonders zuverlässig und schmerzarm durchgeführt werden kann, wenn die mindestens eine Anlagefläche derart ausgestaltet ist, daß bei Abstützung der Vorrichtung auf der Körperoberfläche des Patienten die Hohlnadel zur Körperoberfläche im Abstützbereich einen Winkel im Bereich zwischen 5° und 30° - je nach Dicke des zwischen der Gefäßwandung, die die Hohlnadel durchdringen soll, und der Abstützfläche befindlichen Gewebes - einschließt.

Besonders variabel einsetzbar ist die erfindungsgemäße Vorrichtung dann, wenn die mindestens eine Anlagefläche derart ausgestaltet ist, daß der Winkel, den die Hohlnadel mit der Körperoberfläche während des Entnahmevorgangs einschließt, einstellbar ist.

Um zu verhindern, daß das jeweils für den Entnahmevorgang vorgesehene Blutgefäß beim Aufsetzen der Vorrichtung seitlich weggedrückt wird, ist bei einer besonders bevorzugten

Ausführungsform der erfindungsgemäßen Vorrichtung eine Aussparung in der mindestens einen Anlagefläche vorgesehen, in die das Blutgefäß sich zumindest teilweise hereinwölben kann und somit von den seitlichen Begrenzungsflächen der Aussparung positioniert wird.

Wird Blut eines Patienten zur Durchführung verschiedener Diagnose- bzw. Therapieverfahren benötigt, so ist es von Vorteil, eine Mehrzahl voneinander getrennter Innenvolumina oder eine Adapteranordnung zum Anschluß mehrerer Behälter zur Aufnahme entnommenen Blutes vorzusehen.

Die Innenvolumina oder die Behälter können dann wahlweise seriell oder auch parallel miteinander kommunizieren.

In der Zeichnung sind Ausführungsbeispiele der Erfindung schematisch dargestellt. Es zeigen:

Fig. 1 - ausschnittsweise und schematisch - ein erstes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung in einem Längsschnitt, wobei sich die Hohlnadel in ihrer zurückgezogenen Position befindet;

Fig. 2 dasselbe Ausführungsbeispiel in derselben Ansicht wie in Fig. 1, wobei sich jedoch die Hohlnadel in ihrer ausgefahrenen Position befindet;

Fig.. 3 - ausschnittsweise - dasselbe Ausführungsbeispiel wie in Fig. 1 in einer teilgeschnittenen Aufsicht (Ansicht A in Fig. 1);

Fig. 4 ein anderes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung in einer Fig. 3 entsprechenden Ansicht;

Fig. 5 - schematisch und ausschnittsweise - ein Fig. 1 bis 3 entsprechendes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung während eines Entnahmevorganges in einer Ansicht in Richtung des der Blutentnahme dienenden Blutgefäßes;

Fig. 6 - schematisch - verschiedene Positionen des abgeschrägten Endes der Hohlnadel relativ zur Lage des Blutgefäßes;

Fig. 7 eine Ausführungsform einer erfindungsgemäßen Vorrichtung, die mehrere seriell miteinander kommunizierende Volumina zur Aufnahme entnommenen Blutes umfaßt (schematisch);

Fig. 8 eine Ausführungsform einer erfindungsgemäßen Vorrichtung in einer Fig. 7 entsprechenden Ansicht, die mehrere parallel miteinander kommunizierende Innenvolumina zur Aufnahme entnommenen Blutes umfaßt sowie

Fig. 9 eine Ausführungsform einer erfindungsgemäßen Vorrichtung in einer Fig. 7 und 8 entsprechenden Ansicht, welche eine Adapterplatte zum Anschluß zweier externer Behältnisse zur Aufnahme entnommenen Bluts aufweist.

Die in den Fig. 1 bis 3 als Ganzes mit 100 bezeichnete, in diesen Figuren lediglich ausschnittsweise und schematisch dargestellte Ausführungsform einer erfindungsgemäßen Vorrichtung umfaßt ein Gehäuse 1, welches in seinem Inneren zwei fluidisch über einen Kanal 2 miteinander verbundene Innenvolumina 3, 4 zur Aufnahme entnommenen Blutes aufweist. Das Gehäuse 1 weist an seinen Fig. 1 nach unten weisenden Stirnseite 5 einen Gehäusefortsatz 6 auf, dessen

in Fig. 1 unten dargestelltes Ende 7 offen ausgebildet ist.

Das Innere 8 des Gehäusefortsatzes 6 dient der Aufnahme einer als Ganzes mit 9 bezeichneten Hohlnadelanordnung, die im wesentlichen aus der zum offenen Ende 7 hin gerichteten eigentlichen Hohlnadel 10 und einem der verschiebbaren Lagerung der Hohlnadelanordnung 9 in dem Inneren 8 des Gehäusefortsatzes 6 dienenden Hohlnadelträger 11 besteht, der mit der inneren Mantelfläche 12 des Gehäusefortsatzes 6 zumindest annähernd abdichtend zusammenwirkt.

Mit seiner der Hohlnadel 10 abgewandten Stirnseite 13 stützt sich der Hohlnadelträger 11 über eine vorgespannte Spiralfeder 14 an einer starren Anlagefläche 15 des Gehäuses 1 ab.

Der Arretierung der Hohlnadelanordnung 9 gegen die Druckkraft der Spiralfeder 14 in der zurückgezogenen Position dient eine Arretiereinrichtung 16, die in der zurückgezogenen Position der Hohlnadelanordnung 9 eine der Stirnseite 13 gegenüberliegende Anlagefläche 17 hintergreift.

Die Hohlnadelanordnung 9 weist einen Innenkanal 18 auf, der sich von der Spitze 19 der Hohlnadel 10 bis zu einer seitlichen Öffnung 20 des Hohlnadelträgers 11 erstreckt.

Ferner ist in der in Fig. 1 rechts dargestellten Seitenwandung des Gehäusefortsatzes 6 ein einenends in den Kanal 2 mündender Kanal 21 vorgesehen, dessen anderes Ende 22 in das Innere 8 des Gehäusefortsatzes 6 mündet.

Zur Verlagerung der Hohlnadel 10 aus ihrer in Fig. 1 dargestellten, zurückgezogenen Position in ihre in Fig. 2 dargestellte, ausgefahrene Position wird die Arretiereinrichtung 16 derart verlagert, daß die Anlagefläche 17

freigegeben wird. Durch die von der Spiralfeder 14 auf die Hohlnadelanordnung 9 ausgeübte Kraft schnellt letztere gemäß Fig. 2 nach unten, bis die Anlagefläche 17 an einem von der inneren Mantelfläche 12 nach innen ragenden Anschlag 23 anliegt und hierdurch der Verlagerungsweg begrenzt wird. In dieser Position kommuniziert der Innenkanal 18 über die Öffnung 22 mit dem Kanal 21, so daß die Innenvolumina 3 und 4 mit dem Innenkanal 18 der Hohlnadel kommunizieren und Blut durch die Kanäle 18, 21 und 2 in die Innenvolumina 3, 4 einströmen kann.

Wie ferner aus Fig. 2 ersichtlich ist, hat die Hohlnadel 10 mit ihrer Spitze 19 die Haut H im Bereich der Stelle, an der die Hohlnadel 10 in das Blutgefäß B eindringen soll, sowie eine Wandung des Blutgefäßes B durchsetzt.

Wie Fig. 6 veranschaulicht, ist eine Blutentnahme nur dann möglich, wenn die Hohlnadel 10 gerade so tief in das Gewebe des Patienten eindringt, daß ihre Spitze weder vor dem Durchdringen der Wandung des Blutgefäßes B zum Stillstand kommt (s. Fig. 6a)), noch der zur Spitze 19 hin angeschrägte Bereich der Hohlnadel 10 vollständig durch das Blutgefäß B hindurchragt (vgl. Fig. 6e)).

Um die zur Blutentnahme erforderliche "Eindringtiefe" der Spitze 19 der Hohlnadel 10 den individuellen Anforderungen anpassen zu können, ist an dem Gehäusefortsatz 6 eine in Richtung des Pfeiles P verschiebbar gelagerte Manschette 24 vorgesehen, mit der die wirksame Länge des Gehäusefortsatzes 6 und somit die Eindringtiefe der Spitze 19 der Hohlnadel 10 veränderbar ist. Die Manschette 24 und der Gehäusefortsatz 6 können mit in der Zeichnung nicht dargestellten Rastmitteln ausgestattet sein, mit denen sich die Manschette 24 in drei verschiedenen Grundstellungen arretieren läßt, bei denen die Eindringtiefe an die bei Kin-

dern, normalgewichtigen Erwachsenen bzw. übergewichtigen Erwachsenen üblichen Verhältnisse angepaßt ist.

Paravasale Blutergüsse werden auch bei Endpositionen der Hohlnadel 10, in denen die Spitze 19 nicht vollständig in das Blutgefäß B eingedrungen ist (Fig. 6b)) oder die gegenüberliegende Wandung des Blutgefäßes B teilweise durchdrungen hat (Fig. 6d)), wirksam verhindert, da der Unterdruck zum Absaugen des Blutes an der Hohlnadel bereits anliegt, sobald diese in das Gefäß eingedrungen ist. Prinzipiell ist es zwar möglich, den Einstich der Hohlnadel 10 in das Blutgefäß B im wesentlichen senkrecht zu dessen Verlauf vorzunehmen. Eine derartige Vorgehensweise setzt jedoch voraus, daß die "Eindringtiefe" nahezu exakt vorbestimmt werden muß. Um dies zu vermeiden, empfiehlt es sich, die Entnahme unter einem Winkel α zwischen der Hohlnadel 10 und dem Blutgefäß B vorzunehmen, der im Bereich zwischen 5° und 30° liegt. Hierzu weist das in den Fig. 1 und 2 dargestellte Ausführungsbeispiel der Erfindung Anlageflächen 25 auf, durch die der gewünschte Winkel α vorgegeben ist. Bei den in der Zeichnung dargestellten Ausführungsbeispielen ist der Winkel α fest eingestellt. Es liegt jedoch ebenfalls im Rahmen der Erfindung, die Anlageflächen derart variabel auszugestalten, daß der Winkel α je nach vorgesehener Anwendungsweise der Vorrichtung veränderbar ist.

Wie bereits beschrieben und in Fig. 1 nochmals im einzelnen dargestellt, kann der Erzeugung der die Hohlnadelanordnung aus ihrer zurückgezogenen in ihre ausgefahrene Position vortreibenden Kraft eine Spiralfeder 14 dienen. Es ist - wie in Fig. 4 schematisch dargestellt - jedoch ebenfalls möglich, zum Vortrieb ein Druckluftreservoir 26 zwischen der Stirnseite 13 und der Anlagefläche 15 oder andere zur Bewirkung einer elastischen Kraft geeignete Mittel vorzusehen.

Um zu verhindern, daß das Gefäß, aus dem Blut entnommen werden soll, beim Aufsetzen der Vorrichtung 100 seitlich auswandert und der Entnahmevorgang hierdurch vereitelt wird, ist bei einer bevorzugten Ausführungsform der Erfindung in den Anlageflächen eine Aussparung 27 vorgesehen, in die sich das Blutgefäß B nach dem Aufsetzen der Vorrichtung 100 auf die Haut zumindest teilweise eindrückt und somit das Blutgefäß B seitlich in der für die Blutentnahme erforderlichen Position fixiert wird (s. Fig. 5).

Wie in den Fig. 7 bis 9 verdeutlicht, können erfindungsgemäße Vorrichtungen 100 in unterschiedlicher Weise mit Volumina zur Aufnahme entnommenen Blutes ausgestattet sein. So können mehrere - in Fig. 7 drei - Volumina 28, 29, 30 in dem Gehäuse 1 vorgesehen sein, die seriell miteinander kommunizieren und somit während des Entnahmevorganges nacheinander mit Blut gefüllt werden.

Ferner ist es möglich, wie in Fig. 8 dargestellt, parallel zueinander angeordnete Innenvolumina 31, 32, 33 vorzusehen, die dementsprechend etwa zeitparallel zueinander aufgefüllt werden.

Zur Erzeugung des zum Auffüllen erforderlichen Unterdrucks können die Volumina 28 bis 33 vorevakuiert sein, oder der in selbigen erforderliche Unterdruck kann auf eine beliebige andere Weise, beispielsweise durch Verbindung der Volumina mit einer Kolben/Zylindereinheit, einer externen Pumpe usw. erfolgen. Zur Vermeidung paravasaler Blutergüsse ist es lediglich wesentlich, daß der Unterdruck bereits erzeugt ist, wenn die Spitze 19 der Hohlnadel 10 in das Gefäß eindringt.

Bei dem in Fig. 9 dargestellten Ausführungsbeispiel sind die zur Aufnahme des entnommenen Blutes vorgesehenen Volumina 34, 35 extern angeordnet und als Kolben/Zylinderein-

heiten 36/37 ausgebildet und zwar derart, daß die Kolben 36 durch manuell betätigbare Kolbenstangen 38 in den Zylinder 37 verlagerbar sind. Zur Anbringung der Kolben/-Zylindereinheit 36/37 an dieser als Ganzes mit 200 bezeichneten Vorrichtung dient eine Adapteranordnung 39, von der aus sich gemäß Fig. 9 wiederum nach unten der Gehäusefortsatz 206 erstreckt. Die Hohlnadelanordnung 209 und die Kanäle 202 entsprechen in ihrer technischen Ausgestaltung und Funktion der Hohlnadelanordnung 9 und den Kanälen 2, so wie sie anhand der Fig. 1 bis 3 beschrieben sind und bedürfen daher an dieser Stelle keiner besonderen Erörterung.

Die Blutentnahme bei der Vorrichtung gemäß Fig. 9 erfolgt in einer anhand von Fig. 1 bis 3 bereits beschriebenen Weise, wobei durch Herausziehen der Kolbenstangen 38 in die in Fig. 9 dargestellte Position, in der die Kolben 36 durch Arretiervorsprünge 40 an der Innenwandung des Zylinders 37 gegen die Wirkung des Unterdrucks gehalten werden, selbiger vor dem Vorschnellen der Nadel und Eindringen in das Blutgefäß erzeugt wird.

BEZUGSZEICHENLISTE

	1	Gehäuse	34	Volumen
5	2	Kanal	35	Volumen
	3	Innenvolumen	36	Kolben
	4	Innenvolumen	37	Zylinder
	5	Stirnseite	38	Kolbenstangen
	6	Gehäusefortsatz	39	Adapteranordnung
10	7	Ende	40	Arretiervorsprünge
	8	Inneres	100	Vorrichtung
	9	Hohlnadelanordnung	206	Gehäusefortsatz
	10	Hohlnadel	209	Hohlnadelanordnung
	11	Hohlnadelträger	202	Kanäle
15	12	innere Mantelfläche		
	13	Stirnseite	H	Haut
	14	Spiralfeder	B	Blutgefäß
	15	Anlagefläche	A	Ansicht
	16	Arretiereinrichtung	P	Pfeil
20	17	Anlagefläche		
	18	Innenkanal		
	19	Spitze		
	20	Öffnung		
	21	Kanal		
25	22	Ende		
	23	Anschlag		
	24	Manschette		
	25	Anlagefläche		
	26	Druckluftreservoir		
30	27	Aussparung		
	28	Volumen		
	29	Volumen		
	30	Volumen		
	31	Volumen		
35	32	Volumen		
	33	Volumen		

PALGEN, SCHUMACHER & KLUIN
PATENTANWÄLTE
DÜSSELDORF · ESSEN

07.08.99

UNSER ZEICHEN: 99 328 K/at

Düsseldorf, den 5. August 1999

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Schutzansprüche

1. Vorrichtung zur Entnahme von Blut aus einem Blutgefäß (B),
mit einem Gehäuse (1),
mit einer durch die Blutgefäßwandung ins Innere des Blutgefäßes (B) einführbaren Hohlnadel (10),
und mit Mitteln zum Saugen des Bluts durch das Innere der Hohlnadel,
dadurch gekennzeichnet,
daß die Hohlnadel (10) zwischen einer zurückgezogenen Position, in der die Hohlnadel (10) zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß (B) einzuführende Ende (19) der Hohlnadel (10) aus dem Gehäuse um eine Länge hervorragt, verlagerbar angeordnet ist, und
daß Mittel vorgesehen sind, mit denen die Hohlnadel (10) aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist.

2. Vorrichtung nach Anspruch 1, **dadurch gekennzeichnet**, daß die Mittel, mit denen die Hohlnadel

D-40239 DÜSSELDORF · MULVANYSTRASSE 2 · TELEFON 49 / 211 / 96 145 - 0 · TELEFAX 49 / 211 / 96 145 - 20
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(10) aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, eine Anordnung umfassen, die auf die Hohlnadel (10) eine in Richtung von der zurückgezogenen auf die ausgefahrene Position wirkende, elastische Kraft ausüben.

3. Vorrichtung nach Anspruch 2, **dadurch gekennzeichnet**, daß die Anordnung eine Druckfeder (14) aufweist.

4. Vorrichtung nach Anspruch 2 oder 3, **dadurch gekennzeichnet**, daß die Anordnung ein Druckluftreservoir (26) aufweist.

5. Vorrichtung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet**, daß das Gehäuse (1) mindestens ein Innenvolumen (3, 4, 28 - 35) zur Aufnahme entnommenen Blutes umfaßt.

6. Vorrichtung nach einem der Ansprüche 1 bis 4, **dadurch gekennzeichnet**, daß das Gehäuse (1) eine Adapteranordnung (39) zum Anschluß mindestens eines Behälters umfaßt, dessen Innenvolumen (34, 35) zur Aufnahme von entnommenem Blut dient.

7. Vorrichtung nach Anspruch 5 oder 6, **dadurch gekennzeichnet**, daß die Mittel zum Saugen des Blutes durch das Innere der Hohlnadeln (10) einen Unterdruck in dem mindestens einen Innenvolumen (3, 4, 28 - 35) gegenüber der äußeren Umgebung umfassen.

8. Vorrichtung nach Anspruch 7, **dadurch gekennzeichnet**, daß das Innenvolumen (3, 4, 28 - 35) vorevakuiert ist und daß das Innere der Hohlnadel (10) in ihrer ausgefahrenen Position mit dem Innenvolumen (3, 4, 28 - 35) kommuniziert.

9. Vorrichtung nach Anspruch 7, **dadurch gekennzeichnet**, daß Mittel vorgesehen sind, die beim Verlagern der Hohlnadel (10) aus ihrer zurückgezogenen in ihre ausgefahrene Position den Unterdruck in dem Innenvolumen (3, 4, 28 - 35) erzeugen.

10. Vorrichtung nach Anspruch 9, **dadurch gekennzeichnet**, daß Mittel zur Erzeugung des Unterdrucks eine mit der Hohlnadel (10) verbundene Kolbenanordnung, die beim Verlagern der Hohlnadel (10) in ihre ausgefahrene Position in einer Zylinderanordnung einen Unterdruck erzeugt, und Mittel, die in der ausgefahrenen Position der Hohlnadel (10) das Innere des Zylinders mit dem Innenvolumen (3, 4, 28 - 35) zur Aufnahme des Bluts verbindet, umfaßt.

11. Vorrichtung nach einem der Ansprüche 1 bis 10, **dadurch gekennzeichnet**, daß das Seitenteil des Gehäuses (1), aus dem die Hohlnadel (10) in ihrer ausgefahrenen Position herausragt, mindestens eine Anlagefläche (25) zur Abstützung der Vorrichtung während ihrer Verwendung auf der Körperoberfläche eines Patienten aufweist.

12. Vorrichtung nach Anspruch 11, **dadurch gekennzeichnet**, daß die mindestens eine Anlagefläche (25) derart ausgestaltet ist, daß bei Abstützung der Vorrichtung auf der Körperoberfläche des Patienten die Hohlnadel (10) zur Körperoberfläche im Abstützbereich einen Winkel α im Bereich zwischen 5° und 30° einschließt.

13. Vorrichtung nach Anspruch 12, **dadurch gekennzeichnet**, daß die mindestens eine Anlagefläche (25) derart ausgestaltet ist, daß der Winkel α, den die Hohlnadel (10) mit der Körperoberfläche bei Abstüt-

zung der Vorrichtung auf der Körperoberfläche des Patienten aufweist, einstellbar ist.

14. Vorrichtung nach einem der Ansprüche 11 bis 13, **dadurch gekennzeichnet**, daß die Anlagefläche (25) mindestens eine Aussparung (27) zur Fixierung des der Blutentnahme dienenden Blutgefäßes (B) aufweist.

15. Vorrichtung nach einem der Ansprüche 1 bis 14, **dadurch gekennzeichnet**, daß die Vorrichtung eine Mehrzahl von einander getrennter Innenvolumina (3, 4, 28 - 33) zur Aufnahme des entnommenen Bluts umfaßt oder eine Adapteranordnung (39) zum Anschluß mehrerer Behälter zur Aufnahme entnommenen Blutes umfaßt.

16. Vorrichtung nach Anspruch 15, **dadurch gekennzeichnet**, daß die Innenvolumina (28, 29, 30) oder die Behälter seriell miteinander kommunizieren.

17. Vorrichtung nach Anspruch 15, **dadurch gekennzeichnet**, daß die Innenvolumina (31, 32, 33) oder die Behälter parallel miteinander kommunizieren.

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Fig. 1

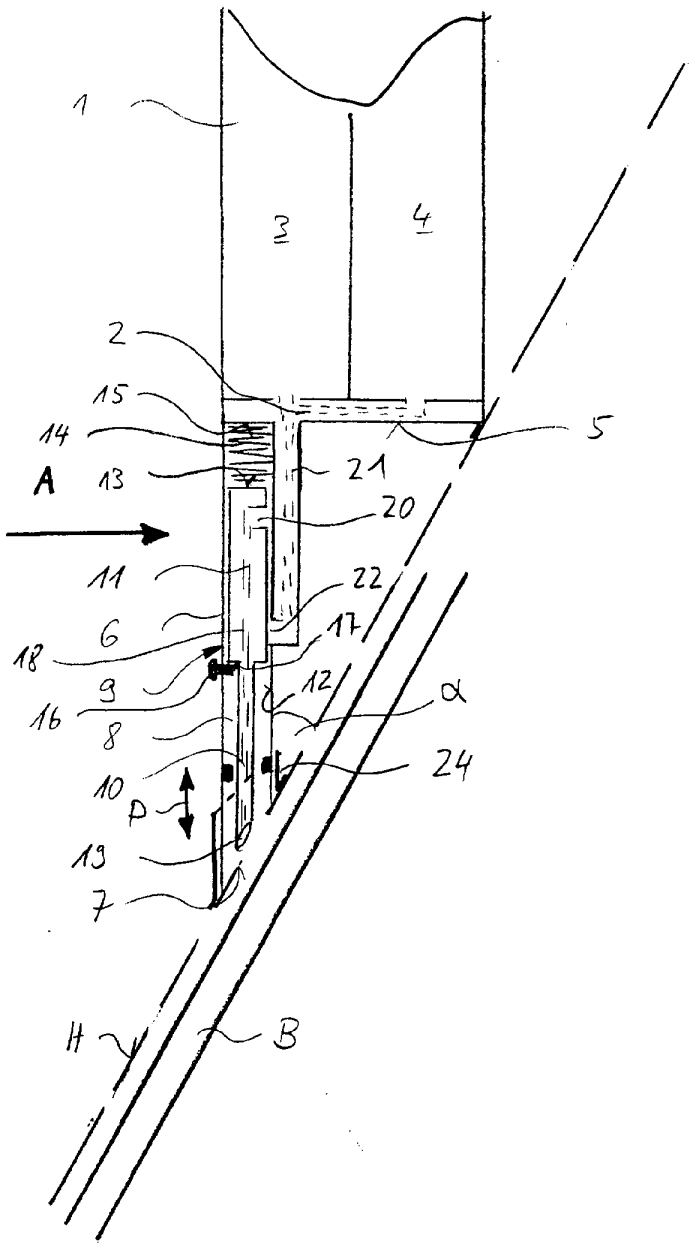
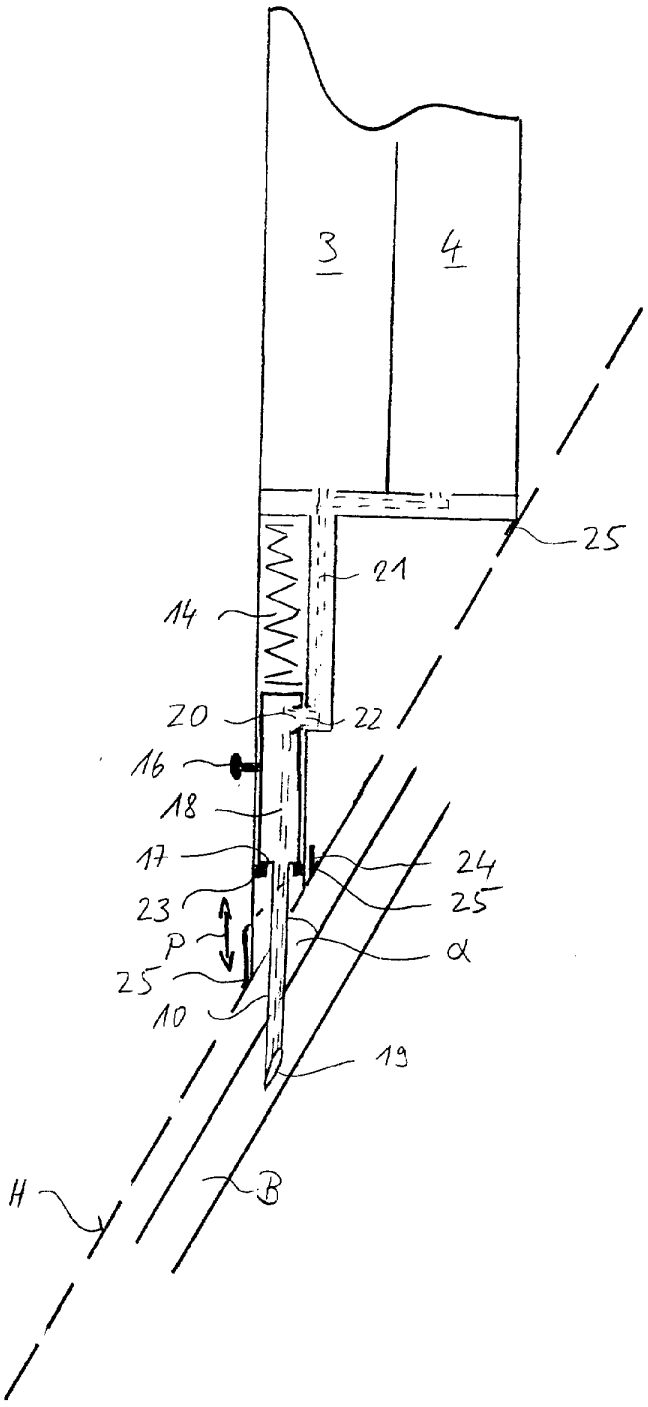


Fig. 2



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Fig.3

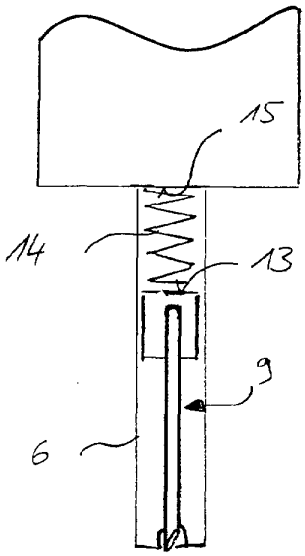
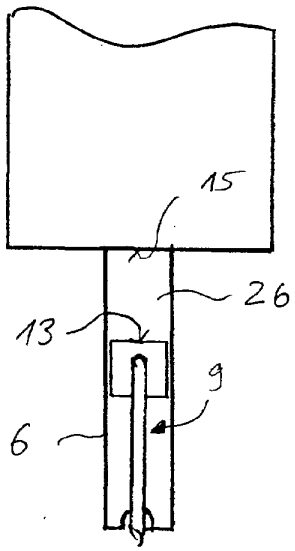


Fig.4



DE 299 13 417 U1

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Fig. 5

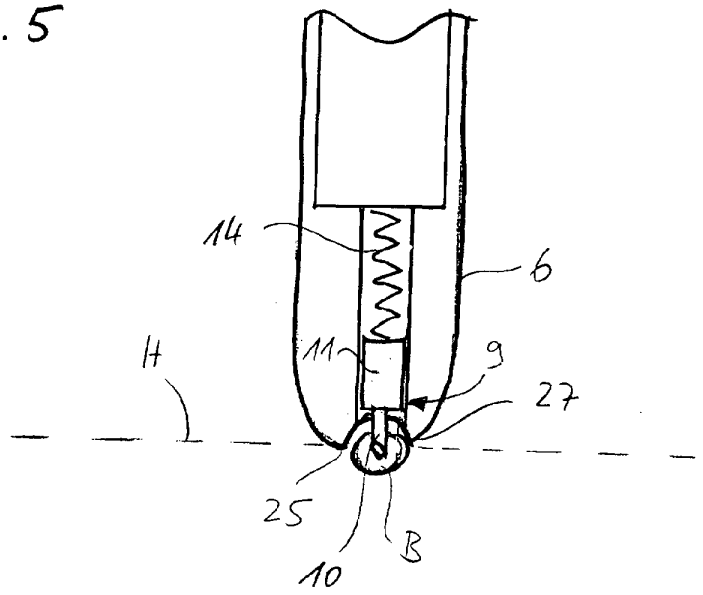
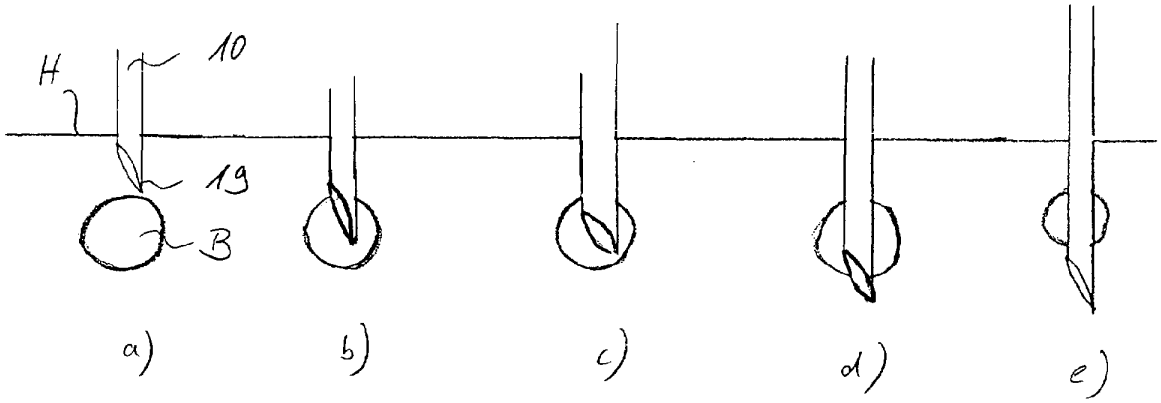


Fig. 6



DE 299 13 417 U1

07.08.99

Fig. 7

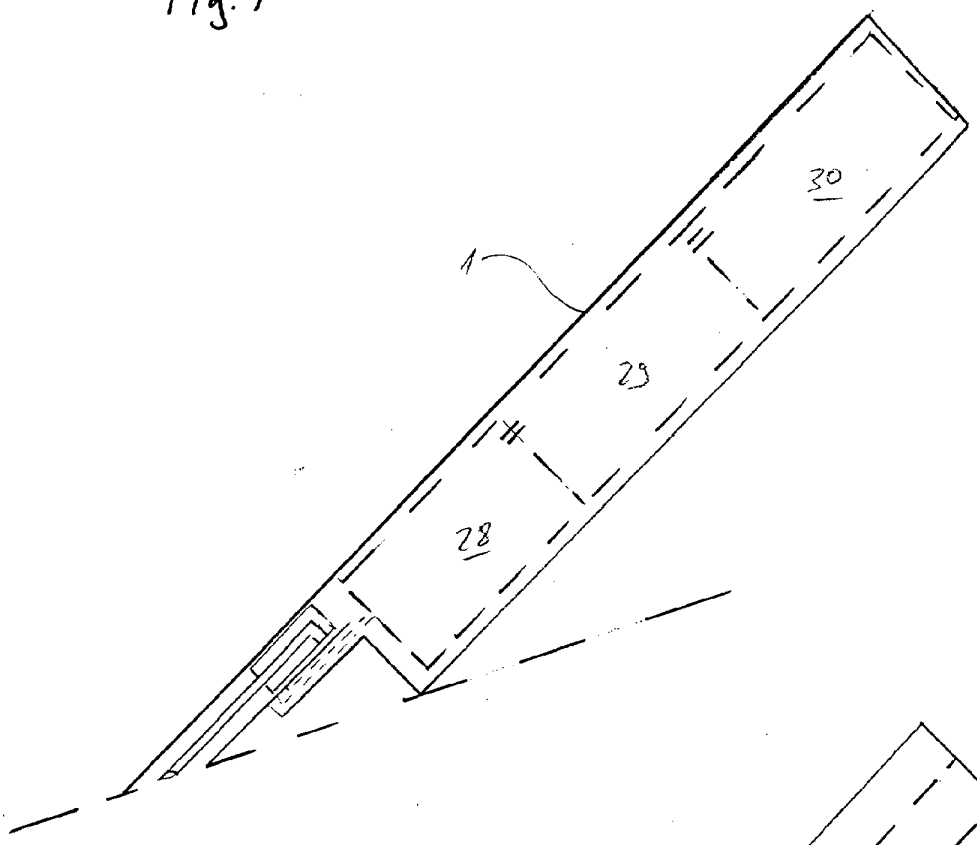
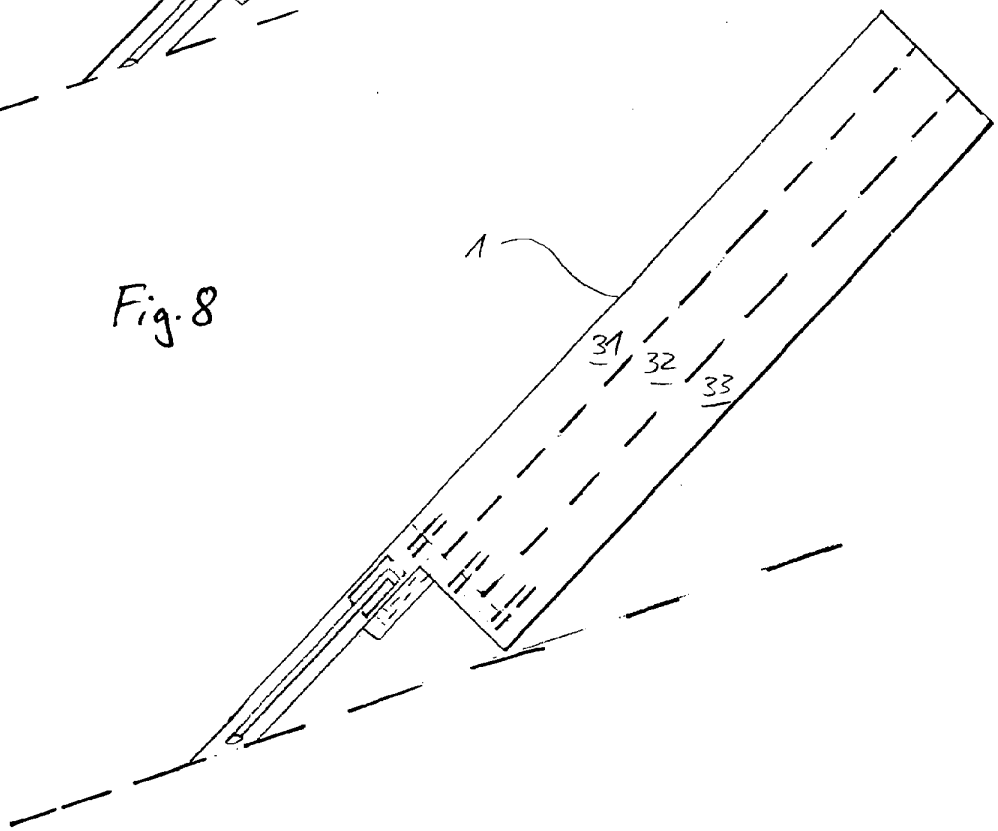
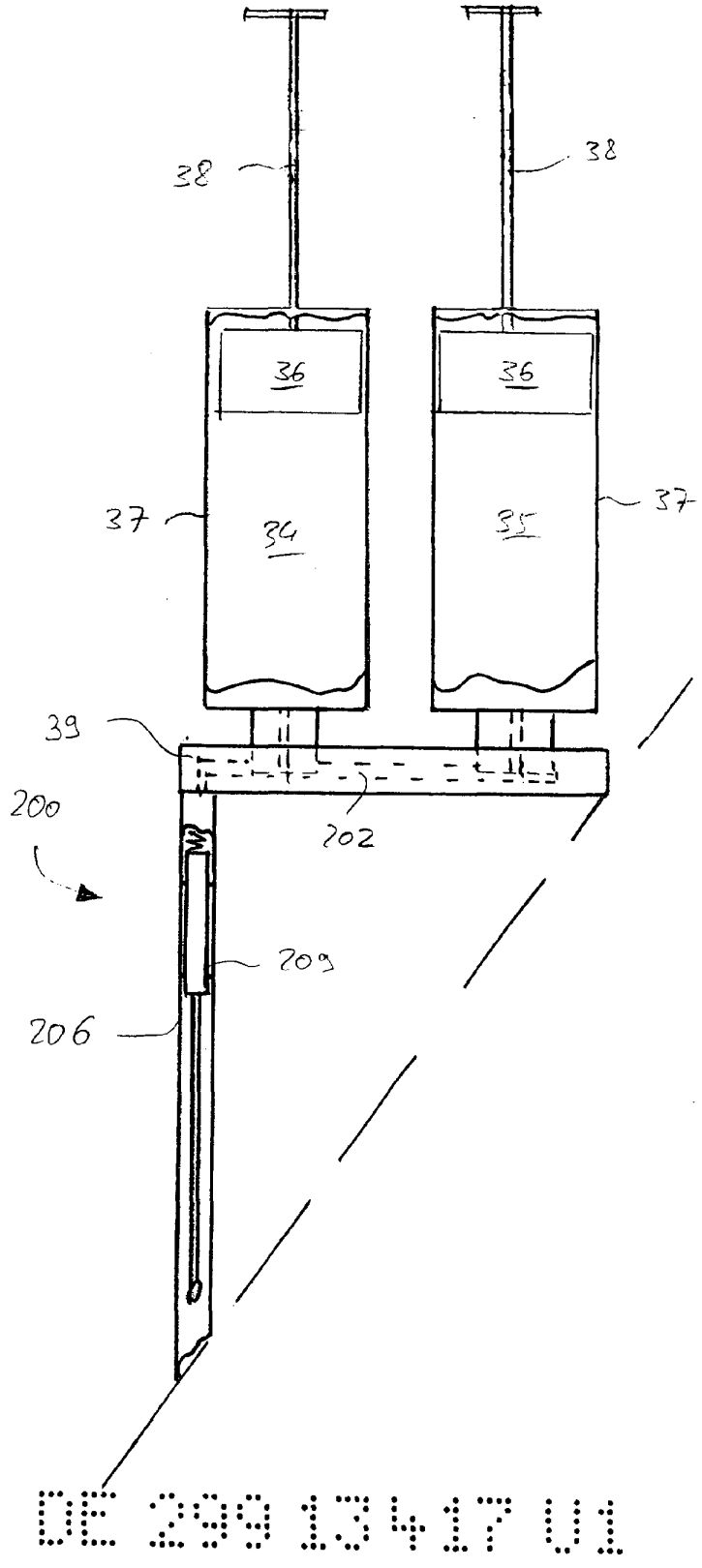


Fig. 8



07.08.99

Fig. 9



DE 299 13 417 U1

Europäisches Patentamt
European Patent Office
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European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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ALLEMAGNE

WUESTHOFF & WUESTHOFF
Patentanwälte PartG mbB
02. Dez. 2019
EINGEGANGEN / RECEIVED

Date: 02.12.19

Reference	Application No./Patent No.
EPA-148 105	19200766.4 - 1132

Applicant/Proprietor: Kurin, Inc.

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the European search report (R. 61 EPC) or the partial European search report/ declaration of no search (R. 63 EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☑ 0 additional set(s) of copies of such documents is (are) enclosed as well.

The following have been approved:

☐ Abstract ☑ Title

☑ The Abstract was modified and the definitive text is attached to this communication.

The following figure(s) will be published together with the abstract: 15C

Refund of search fee
If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued once the date of publication of the European search report has been mentioned in the European Patent Bulletin (R. 69(1), R. 70(2) EPC).

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Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 96/05875 A1 (BAXTER INT [US]) 29 February 1996 (1996-02-29) * the whole document *	1-14	INV. A61B5/15 A61B5/153 A61B5/154
A	WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011 (2011-12-29) * paragraph [0070] * * figure 15 * * abstract *	1-14	
A	US 2009/227953 A1 (TAN CHEE LEONG [SG] ET AL) 10 September 2009 (2009-09-10) * the whole document *	1-14	
A	JP H08 257018 A (NISSHO KK) 8 October 1996 (1996-10-08) * abstract; figures *	1-14	
A	US 4 416 290 A (LUTKOWSKI LAWRENCE [US]) 22 November 1983 (1983-11-22) * abstract; figures *	1-14	TECHNICAL FIELDS SEARCHED (IPC) A61B
A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) * abstract; figures *	1-14	
A	EP 1 665 986 A1 (BECTON DICKINSON CO [US]) 7 June 2006 (2006-06-07) * figures 13,14 *	1-14	
A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) * abstract; figures *	1-14	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	18 November 2019	Schultz, Ottmar

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) * paragraphs [0084] - [0094] * * figures 16-18 *	1-14	

TECHNICAL FIELDS SEARCHED (IPC)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	18 November 2019	Schultz, Ottmar

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 19 20 0766

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

18-11-2019

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9605875 A1	29-02-1996	AT 208640 T	15-11-2001
		AU 686450 B2	05-02-1998
		CA 2173331 A1	29-02-1996
		DE 69523887 D1	20-12-2001
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		EP 0725658 A1	14-08-1996
		JP H09504726 A	13-05-1997
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US 2013317391 A1	28-11-2013	US 2013317391 A1	28-11-2013
		US 2015099996 A1	09-04-2015
		US 2015351678 A1	10-12-2015
		US 2018092584 A1	05-04-2018
		US 2019209066 A1	11-07-2019

EPO FORM P0459

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
EP 19 20 0766

TITLE: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE

APPLICANT: Kurin, Inc.

IPC CLASSIFICATION: A61B5/15, A61B5/153, A61B5/154

EXAMINER: Schultz, Ottmar

CONSULTED DATABASES: EPODOC, WPI, COMBI, TXT+

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B5/15003, A61B5/150213, A61B5/150389, A61B5/150473, A61B5/150572, A61B5/153, A61B5/154

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:
See claims.

EPO FORM P0A42

ABSTRACT / ZUSAMMENFASSUNG / ABRÉGÉ

19200766.4

Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

The examination is being carried out on the **following application documents**

Description, Pages

1-43 as originally filed

Claims, Numbers

1-14 as originally filed

Drawings, Sheets

1/50-50/50 as originally filed

+++++

Reference is made to the following document; the numbering will be adhered to in the rest of the procedure.

D1: WO 96/05875 A1 (BAXTER INT [US]) 29 February 1996.

1 The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1 and 6 are not new in the sense of Article 54(1) and (2) EPC.

The reasons are as follows:

1.1 Document D1 discloses (the references in parentheses applying to this document) all the features of claim 1, namely:

"A blood sequestration device (see figure 1: ref. sign 10 *"closed system blood sampling device"*) **comprising;**

an inlet port (see figure 1: ref. sign 14 *"cannula tip"*);

a junction (see fig. 1: the area where the bore 36 connects with bore 18) **connected with the inlet port;**

a sequestration chamber (see figure 1: ref. sign 22 *"blood disposal chamber"*) **having a vent** (see figure 1: ref. sign 30 *"liquid tight, air permeable hydrophobic membrane"*) **comprising an air permeable blood barrier;**

a sampling channel (see figure 1: ref. sign 36 *"bore"*) **having a proximal end connected with the inlet port via the junction and a distal end connected with an outlet port** (see fig. 1: ref. sign 42 *"luer"*); **and**

a housing (see fig. 1) **that houses and defines the inlet port, the junction, the sequestration chamber, and the sampling channel, and the outlet port,**

whereby the sequestration chamber (see figure 1: ref. sign 22 *"blood disposal chamber"*) **is connected** (see fig. 1) **with the inlet port via the junction which is configured to direct** (see page 3, lines 1 to 4: *"... It also feeds an initial fraction of withdrawn blood to a communicating blood disposal chamber which has an air permeable liquid sealed end ..."*) **the first portion of blood to the sequestration chamber** (see figure 1: ref. sign 22 *"blood disposal chamber"*), **and the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with a portion of the first portion of blood"**.

Claim 1 is thus not novel (Art. 54(1)(2) EPC).

1.2 Document D1 also discloses (the references in parentheses applying to this document) all the features of claim 1, namely:

"A system of a blood sequestration device (see figures 1, 2: ref. sign 10 *"closed system blood sampling device"*), **a blood sampling pathway** (see figures 2: ref. sign 50 *"venipuncture device"*) **having a patient needle, and a sample collection device** (see figures 2: ref. sign 70 *"syringe"*), **the blood sequestration device comprising;**

an inlet port (see figure 1: ref. sign 14 *"cannula tip"*) **connected with the patient needle;**

a junction (see fig. 1: the area where the bore 36 connects with bore 18) **connected with the inlet port opposite the blood sampling pathway;**

a sequestration chamber (see figure 1: ref. sign 22 *"blood disposal chamber"*) **having a vent** (see figure 1: ref. sign 30 *"liquid tight, air permeable hydrophobic membrane"*) **comprising an air permeable blood barrier;**

a sampling channel (see figure 1: ref. sign 36 *"bore"*) **having a proximal end connected with the inlet port; and**

an outlet port (see fig. 1: ref. sign 42 *"luer"*) **connected with a distal end of the sampling channel and with the sample collection device; and**

a housing (see fig. 1) **that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel,**

whereby the sequestration chamber is connected with the inlet port and the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood".

Claim 6 is thus not novel (Art. 54(1)(2) EPC).

2 The dependent claims 2 to 5 and 7 to 14 do not appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty (Art. 54(1)(2), EPC) and/or inventive step (Article 56, EPC), the reasons being as follows:

Ad claims 2, 12, 13: Not novel, see D1, figure 1;

Ad claims 3, 4: Not novel, see D1, figures 1, 2;

Ad claims 5, 14: Not inventive to design the housing from two parts, see D1, figure 1;

Ad claims 7, 8, 9, 10, 11: Not novel, see D1, figures 2.

3 Further objections:

3.1 The closest prior art (see document D1) is not acknowledged in the description (Rule 42(1)(b) EPC).

3.2 Claim-like clauses appended at the end of the description (see pages 39 to 43) must also be deleted prior to grant, since they otherwise may lead to unclarity as to the actual scope of protection (Guidelines F-IV, 4.4).

3.3 "Incorporation by reference" is not an option in the European procedure since the concerned subject-matter does not fall within the scope of the claims (Article 84 EPC); the description thus requires amendment in this respect at paragraph [0001].

4 It is not at present apparent which part of the application could serve as a basis for a new, allowable claim.

5 If, however, filing an amended set of claims, **arguments in support of inventive step in the form of a problem-solution approach according to the Guidelines G-VII, 5 should be provided in an accompanying letter**.

6 Since the present description will not be consistent with the subject-matter as defined by such an amended set of claims, **to expedite the examining procedure** the applicant should then at the same time bring **all affected passages** of entire description into conformity with such an amended set of claims, i.e. the applicant should limit the application to the embodiment of the invention, namely as defined by an amended independent claim, and to the preferred embodiments, namely as defined by amended dependent claims.

In this respect, it is noted that terms like ***"... may ..."***, ***"... can ..."***, **etc.** as used throughout the description are not allowed if the related feature is part of the invention as defined by the independent claims. **Appropriate amendments are required.**

It is noted that anything denoted *"... embodiment ..."* and *"... invention ..."* must fall under the scope of protection sought, otherwise it is not an embodiment and not an invention.

Therefore, all the terms like *"... aspect of the invention ..."*, *"... embodiment ..."*, *"... invention ..."*, *"... variation of the invention ..."*, etc. related to all further inventions and further features or methods not covered by the amended set of claims should be replaced by the term *"... **example not being part of the invention** ..."*, if not then the remaining embodiments are to be excised from the amended set of claims, description and drawings or to be denoted not forming part of the present invention but represent background art that is useful for understanding the invention (see Guidelines F-IV, 4.3(iii)).

The subject-matter concerning the embodiments to be excised may be made the subject of one or more divisional applications according to Rule 36 EPC.

7 Care should then also be taken during revision of the description and the claims not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

Intermediate generalisations should also be avoided (Art. 123(2) EPC and Guidelines H-V, 3.2.1).

To make sure that the new set of claims meets the requirements of Art. 123(2) EPC and Guidelines H-V, 3.2.1, the applicant is requested to double check and provide basis for the amendments by references to the application as filed in the accompanying letter in his own interest.

+++++

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
50828-501001WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2016/043709	22 July 2016 (22-07-2016)	24 July 2015 (24-07-2015)
Applicant		
CALLIOPE SOLUTIONS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 15C
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011 (2011-12-29)	1-5, 7-13, 15-20
A	paragraph [0070] figure 15 abstract	6,14
A	US 2009/227953 A1 (TAN CHEE LEONG [SG] ET AL) 10 September 2009 (2009-09-10) the whole document	1-20
A	JP H08 257018 A (NISSHO KK) 8 October 1996 (1996-10-08) abstract; figures	1-20

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2016	19/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schultz, Ottmar

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 416 290 A (LUTKOWSKI LAWRENCE [US]) 22 November 1983 (1983-11-22) abstract; figures	1-20
A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) abstract; figures	1-20
A	EP 1 665 986 A1 (BECTON DICKINSON CO [US]) 7 June 2006 (2006-06-07) figures 13,14	1-20
A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) abstract; figures	1-20
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) paragraphs [0084] - [0094] figures 16-18	1-20

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011162772 A1	29-12-2011	NONE	
US 2009227953 A1	10-09-2009	US 2009227953 A1	10-09-2009
		US 2010262038 A1	14-10-2010
		US 2012330187 A1	27-12-2012
JP H08257018 A	08-10-1996	NONE	
US 4416290 A	22-11-1983	NONE	
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		US 2015351678 A1	10-12-2015

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2016/043709	22.07.2016	24.07.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61B5/15 A61B5/153 A61B5/154

Applicant
CALLIOPE SOLUTIONS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	see form PCT/ISA/210	Schultz, Ottmar Telephone No. +49 30 25901-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 6, 7, 11, 14
	No:	Claims	1, 3-5, 8-10, 12, 13, 15-20
Inventive step (IS)	Yes:	Claims	6, 14
	No:	Claims	1-5, 7-13, 15-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

+++++

Reference is made to the following document:

D1: WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011.

+++++

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

+++++

1 INDEPENDENT CLAIMS 1, 8, 17

1.1 Claims 8 seeks to define a blood sequestration device by being connected with a blood sampling pathway having a patient needle and a sample collection device whereby said blood sampling pathway does not form part of the claimed blood sequestration device.

This would only be the case if e.g. claim 8 defined e.g. "A system of a blood sequestration device and a blood sampling pathway having a patient needle and a sample collection device, whereby the blood sequestration device is connected with the blood sampling pathway, said blood sequestration device comprising...".

The technical features and the related definitions of the blood sampling pathway can therefore not be used to render the subject-matter of claim 8 either novel or inventive.

Since the intended limitation does not belong to the subject-matter claimed, namely the blood sequestration device, this said limitation leads to uncertainty with regard to the actual protection sought, contrary to the requirements of Article 6 PCT.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 17, which therefore is also considered not meeting the requirements of Article 6 PCT.

1.2 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT. The reason is the following:

Document D1 discloses (the references in parenthesis applying to this document) in figure 15 all the features of independent claim 1, namely:

"A blood sequestration device (see figure 15) comprising;

an inlet port (see ref. sign 117 "well");

an outlet port (see ref. sign 330 "sleeve connector");

a sequestration chamber (see ref. sign 117 "guide tube aperture") connected with the inlet port, the sequestration chamber having a vent (see ref. sign 117 "venting member") comprising an air permeable blood barrier;

a sampling channel (see the channel formed in the sleeve connector 330) having a proximal end connected with the inlet port and a distal end connected with the outlet port; and

a housing (see ref. sign 116 "guide tube") that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel".

1.3 The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 8 an 17, which therefore are also considered not new (Article 33(1) and (2) PCT).

2 DEPENDENT CLAIMS 2-7, 9-16, 18-20

2.1 Dependent claims 2 to 5, 7, 9 to 13, 15, 16 and 18 to 20 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty (Article 33(2) PCT) and/or inventive step (Article 33(3) PCT), the reasons being as follows:

As far as the features of these said dependent claims are not already explicitly anticipated by document D1 (for further details, see the relevant passages as cited in the International Search Report and in the above-mentioned paragraph 1), these features would be chosen by a person skilled in the art simply by routine trial and error or these said features are at least generally known by a person skilled in the art either to be one of several straightforward possibilities from which this said person would select or to be regarded by this said person as a normal design option and thus would not add any inventive merit to the subject-matter of the these said dependent claims.

2.2 The features of dependent claims 6 and 14 in combination with the features of any claim to which these said claims refer, seem neither to be known from, nor rendered obvious by, the available prior art.

+++++

Re Item VII

Certain defects in the international application

+++++

1 The independent claims are not in the two-part form in accordance with Rule 6.3(b) PCT with those features known in combination from the prior art (e.g. one of the documents cited in the International Search Report) being placed in the preamble (Rule 6.3(b)(i) PCT) and with the remaining features being included in the characterising part (Rule 6.3(b)(ii) PCT).

2 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents cited in the International Search Report is not mentioned in the description, nor are at least some of these documents identified therein.

3 The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

+++++

Re Item VIII

Certain observations on the international application

+++++

Claims 8 seeks to define a blood sequestration device by being connected with a blood sampling pathway having a patient needle and a sample collection device whereby said blood sampling pathway does not form part of the claimed blood sequestration device.

This would only be the case if e.g. claim 8 defined e.g. "A system of a blood sequestration device and a blood sampling pathway having a patient needle and a sample collection device, whereby the blood sequestration device is connected with the blood sampling pathway, said blood sequestration device comprising...".

The technical features and the related definitions of the blood sampling pathway can therefore not be used to render the subject-matter of claim 8 either novel or inventive.

Since the intended limitation does not belong to the subject-matter claimed, namely the blood sequestration device, this said limitation leads to uncertainty with regard to the actual protection sought, contrary to the requirements of Article 6 PCT.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claim 17, which therefore is also considered not meeting the requirements of Article 6 PCT.

+++++

拒絶理由通知書

特許出願の番号	特願２０１８－５２３３８４
起案日	令和　１年　７月１６日
特許庁審査官	清水　裕勝　　５２６２　２Ｑ００
特許出願人代理人	三好　秀和（外　３名）　様
適用条文	第２９条第１項、第２９条第２項

この出願は、次の理由によって拒絶をすべきものです。これについて意見がありましたら、この通知書の発送の日から３か月以内に意見書を提出してください。

理由

１．（新規性）この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において、頒布された下記の刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明であるから、特許法第２９条第１項第３号に該当し、特許を受けることができない。

２．（進歩性）この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において、頒布された下記の刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明に基いて、その出願前にその発明の属する技術の分野における通常の知識を有する者が容易に発明をすることができたものであるから、特許法第２９条第２項の規定により特許を受けることができない。

記　　（引用文献等については引用文献等一覧参照）

●理由１（新規性）、理由２（進歩性）について

・請求項１－２、５、７－９、１１－１２、１４
・引用文献等１
・備考
引用文献１には、静脈に穿刺した針から真空採血管に血液を採取するシステムが記載されている。（特に、特許請求の範囲、第６頁左上欄第２０行－同頁左下欄第１行、第７図等参照）
そして、第７図を参酌すると、引用文献１に記載された発明は、空気透過性血液不透過性の多孔性プラグ５２（本願発明の「空気透過性血液バリア」に相当。

）と横孔４８との間に空間を有し、かつ、プラグ５２で血液をブロックしてから真空採血管を挿入して横孔４８を通じて、プラグ５２を迂回して血液を採取するものであるから、当該「空間」は、血液サンプルの最初の量を受け入れる「隔離チャンバ」としても機能すると認められる。

そうしてみると、本願請求項１－２、５、７－９、１１－１２、１４に係る発明の構成と、引用文献１に記載された発明の構成との間に差異があるとは認められない。

したがって、本願請求項１－２、５、７－９、１１－１２、１４に係る発明は、引用文献１に記載された発明であるか、引用文献１に記載された発明に基づいて、当業者が容易になし得たものといえる。

●理由２（進歩性）について

・請求項６、１６
・引用文献等１
・備考
採血経路の形状や材質は、発明を具体化する際に当業者が適宜決定する事項と認められる。

したがって、本願請求項６、１６に係る発明は、引用文献１に記載された発明に基づいて、当業者が容易に想到し得たものといえる。

・請求項３－４、１３
・引用文献等１－２
・備考
引用文献２に記載されているように、真空採血管を用いて採血する技術分野において、サンプル針に真空採血管によって穿孔されるシールを設けることは周知技術である。（特に、第２図等参照）

したがって、本願請求項３－４、１３に係る発明は、引用文献１－２に記載された発明に基づいて、当業者が容易になし得たものである。

・請求項１０、１５
・引用文献等１、３
・備考
引用文献３に記載されているように、採血時の最初の血流が通る流路を設けることは周知技術である。（特に、段落[００１１]－[００１２]等参照）

したがって、本願請求項１０、１５に係る発明は、引用文献１、３に記載された発明に基づいて、当業者が容易になし得たものである。

＜引用文献等一覧＞

１．特開昭５８－２５１４６号公報
２．特開昭５８－６７２３８号公報（周知技術を示す文献）
３．特開２０１２－１６４９６号公報（周知技術を示す文献）

－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－－

＜先行技術文献調査結果の記録＞

・調査した分野　　ＩＰＣ　Ａ６１Ｂ５／１５３－５／１５４

・先行技術文献　　特開昭５７－８９８６９号公報
特表平９－５０４７２６号公報
特開平２－２２４７４２号公報
米国特許第４２０７８７０号明細書

この先行技術文献調査結果の記録は拒絶理由を構成するものではありません。

＜補正をする際の注意＞
（１）明細書、特許請求の範囲について補正をする場合は、補正により記載を変更した個所に下線を引いてください（特許法施行規則様式第１３備考６、７）。
（２）補正は、この出願の国際出願日における国際特許出願の明細書若しくは図面（図面の中の説明に限る。）の翻訳文、国際出願日における国際特許出願の請求の範囲の翻訳文（特許協力条約第１９条（１）の規定に基づく補正後の請求の範囲の翻訳文が提出された場合にあっては、当該翻訳文）又は国際出願日における国際特許出願の図面（図面の中の説明を除く。）（以下、翻訳文等という。）（誤訳訂正書を提出して明細書、特許請求の範囲又は図面について補正をした場合にあっては、翻訳文等又は当該補正後の明細書、特許請求の範囲若しくは図面）に記載した事項の範囲内で行わなければなりません。また、意見書で、各補正事項について補正が適法なものである理由を、根拠となる翻訳文等（誤訳訂正書を提出して明細書、特許請求の範囲又は図面について補正をした場合にあっては、翻訳文等又は当該補正後の明細書、特許請求の範囲若しくは図面）の記載箇所を明確に示したうえで主張してください。
（３）特許請求の範囲について補正をする際には、特許法第１７条の２第４項に違反する補正とならないよう、注意してください。

この拒絶理由通知の内容に関するお問合せ又は面接のご希望がありましたら次の連絡先までご連絡ください。

審査第一部　分析診断（医学診断）　清水裕勝
ＴＥＬ．０３－３５８１－１１０１　内線３２９１
ＦＡＸ．０３－３５８５－２０５５

Japanese Patent Application No. 2018-523384
Your Ref: KURIN2JP
Our Ref: TS/KRN-C0137JP01
August 26, 2019

Translation of "Notice of Reasons for Rejection"

Patent Application Number:	JP 2018-523384
Date of Delivery:	July 23, 2019
Applied Provision:	Patent Law Articles 29(1), and 29(2)

The present application should be rejected for the following reasons. The applicant may present an argument against the reasons within three months from the date of delivery of this notice.

Reasons

1. The inventions of the following claims should not be granted a patent under Patent Law Article 29(1)(iii) as lacking novelty over the documents listed below.

2. The inventions of the following claims should not be granted a patent under Patent Law Article 29(2) as lacking inventive step over the documents listed below.

Remarks (See the Document List below)

- Reasons 1 and 2
- Claims 1-2, 5, 7-9, 11-12 and 14
- Document D1

D1 discloses a system for collecting blood in an evacuated blood collection tube from a needle punctured into a vein. (See especially the claims, page 6, upper left column, line 20 to lower left column, line 1, Figure 7, etc.)

Referring to FIG. 7, the invention disclosed in D1 has a space between an air-permeable blood-impermeable porous plug 52 (corresponding to the "air permeable blood barrier" of the present invention) and a side hole 48, the blood is blocked by the plug 52 before the evacuated blood collection tube is inserted, the blood is collected through the side hole 48 to bypass the plug 52, and thus the "space" functions as a "sequestration chamber" for receiving a first amount of blood sample.

As a result, it is not recognized that there is a difference between the invention of claims 1-2, 5, 7-9, 11-12 and 14 and the invention disclosed in D1.

Therefore, the inventions of claims 1-2, 5, 7-9, 11-12 and 14 are the inventions disclosed in D1 or could have been easily made by those skilled in the art based on the invention disclosed in D1.

- Reason 2

- Claims 6 and 16
- Document D1

The shape and material of the blood sampling pathway are matters that could have been appropriately determined by those skilled in the art when the invention is embodied.

Therefore, the inventions of claims 6 and 16 could have been easily conceived by those skilled in the art based on the invention disclosed in D1.

- Claims 3-4 and 13
- Documents D1 and D2

As disclosed in D2, in the technical field of collecting blood using an evacuated blood collection tube, it is a well-known art to provide a sample needle with a seal to be pierced by an evacuated blood collection tube. (See especially Figure 2 etc.)

Therefore, the invention of claims 3-4 and 13 could have been easily made by those skilled in the art based on the invention disclosed in D1 and D2.

- Claims 10 and 15
- Documents D1 and D3

As disclosed in D3, it is a well-known art to provide a channel through which an initial blood flow passes during blood collection. (See especially paragraphs [0011]-[0012] etc.)

Therefore, the invention of claims 10 and 15 could have been easily made by those skilled in the art based on the invention disclosed in D1 and D3.

Document List

D1: JP S58-25146A
D2: JP S58-67238A (Document disclosing well-known art)
D3: JP 2012-16496A (Document disclosing well-known art)

Record of the Result of Prior Art Search

Technical field(s) searched	IPC A61B 5/153-5/154
Prior art document(s)	JP S57-89869A
	JP H9-504726A
	JP H2-224742A
	US 4,207,870B

This record is not a component of the reasons for rejection.

Contamination Rates of Blood Cultures Obtained by Dedicated Phlebotomy vs Intravenous Catheter

Alonna Norberg, MD
Norman C. Christopher, MD
Maria L. Ramundo, MD
John R. Bower, MD
Shirley A. Berman, RN

Context Blood culture is the criterion standard for identifying children with bacteremia. However, elevated false-positive rates are common and are associated with substantial health care costs.

Objective To compare contamination rates in blood culture specimens obtained from separate sites vs through newly inserted intravenous catheters.

Design, Setting, and Participants Observational study conducted January 1998 through December 1999 among patients aged 18 years or younger who were seen at a US children's hospital emergency department and had a blood culture obtained as part of their care. Medical records were reviewed in all cases with a positive blood culture. Patients with indwelling vascular catheters were excluded.

Intervention All phlebotomy was performed by emergency department registered nurses. During the baseline phase, blood specimens for culture were obtained simultaneously with intravenous catheter insertion. During the postintervention phase, specimens were obtained by a separate, dedicated procedure.

Main Outcome Measure Contamination rate in the postintervention period compared with the baseline period.

Results A total of 4108 blood cultures were evaluated, including 2108 during the baseline phase and 2000 in the postintervention phase. The false-positive blood culture rate decreased from 9.1% to 2.8% ($P<.001$). A statistical process control chart demonstrated a steady-state process in the baseline phase and the establishment of a significantly improved steady state in the postintervention phase. Young age was associated with increased contamination rate in both the baseline and postintervention periods.

Conclusion Blood culture contamination rates were lower when specimens were drawn from a separate site compared with when they were drawn through a newly inserted intravenous catheter.

JAMA. 2003;289:726-729 www.jama.com

FEVER IS THE PRIMARY COMPLAINT in up to 20% of children presenting to emergency departments,[1] and bacteremia is the source of fever in 1.5% to 2.3% of these patients.[2,3] Blood culture is the criterion standard for identifying children with bacteremia[4-7]; however, false-positive blood cultures are common and may add significantly to health care costs.[8-11] High rates of contamination are common among pediatric patients, likely related to difficulties inherent to phlebotomy in young patients.[12] To minimize the number of venipunctures in children, blood culture specimens are obtained simultaneously with intravenous catheter placement in many emergency departments. The impact of using intravenous catheters to obtain blood cultures is unclear.[13-16] We hypothesized that the blood culture contamination rate would be less when blood culture specimens were obtained from a remote site rather than through a newly inserted intravenous catheter.

METHODS

A preintervention and postintervention observational study of patients who had a blood culture obtained as part of their routine emergency department course was conducted. Patients 18 years old or younger who presented to the emergency department at a free-standing tertiary care children's hospital that evaluates more than 65 000 children annually and required a blood culture as part of their routine care were eligible. Patients were identified by computerized search of the hospital database.

Laboratory specimens were obtained based on clinical and laboratory indications and were drawn by an emergency department registered nurse. The protocols for skin antisepsis and

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KUR-MAG-DE004378

for specimen collection and inoculation were standardized and remained unchanged during the study. Nursing staff members were unaware of ongoing data collection and analysis. In cases where a positive blood culture was reported, the patient's medical record was reviewed. Patients with indwelling devices (central venous lines, ventricular catheters) were excluded.

Baseline Phase

During the baseline phase (January 1, 1998-November 19, 1998), culture specimens were obtained through a newly inserted peripheral intravenous catheter using the standard over-the-needle approach. A sterile 5-mL syringe was attached to the catheter hub, and blood for both culture and for laboratory studies was withdrawn; the first portion of the sample was used for culture.

During the first 4 months of the baseline phase, focused efforts to decrease the contamination rate were implemented. Because these interventions failed to reduce the contamination rate, the standard technique was abandoned in favor of obtaining specimens from a separate phlebotomy site. Data from a 6-week implementation phase (November 20, 1998-December 31, 1998) were not included in the analysis.

Postintervention Phase

During the postintervention phase (January 1, 1999-December 31, 1999), culture specimens were obtained by venipuncture at a dedicated site. If a patient required an intravenous catheter, it was placed using the standard approach at a site distant from the blood culture venipuncture site. While laboratory specimens were sometimes obtained through the newly inserted intravenous catheter, all specimens for culture were obtained by phlebotomy dedicated to that procedure.

Classification of Blood Culture Isolates

Blood culture isolates were categorized as contaminants or pathogens. In all cases, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Salmonella* species, *Haemophilus influenzae*, and group A or group B β-hemolytic streptococci were considered pathogens. A contaminant was defined as a nonpathogenic microorganism.[15] If pathogenicity was uncertain or variable, assignment was made in consultation with an infectious disease expert (J.R.B.), with consideration of patient demographics and the clinical setting. Assignment was made without knowledge of the intervention phase. Because the presence of even a single nonpathogenic species in the blood culture specimen represented improper phlebotomy technique, a specimen with multiple bacteria was considered contaminated.

Decisions regarding treatment and follow-up of patients were made by clinicians in the emergency department based on current practice. The institutional review board of the Children's Hospital Medical Center of Akron approved the study protocol. Consent was not obtained from families. The intervention was adopted as our standard of care, and data was collected in a blinded database for analysis.

Data Analysis

Data were analyzed using STATA Version 7.0 (Dallas, Tex, 2001). Univariate analysis was performed unless stated otherwise. Pearson χ^2 was used to analyze categorical data. Descriptive analysis of continuous data was performed. $P<.05$ was the level of significance.

Statistical process control methodology was also used to examine the impact of the intervention over time. A run chart was constructed showing the blood culture contamination rate for each month of the study ([number of contaminated specimens × 100]/[number of blood cultures obtained]). The mean blood culture contamination rate and the upper and lower control limits were established based on the preintervention data, with control limits representing ±3 SD from the mean.[16-18]

Table 1. Patient Demographics

	Baseline (n = 2106)	Postintervention (n = 2000)
Age, median (IQR), y	1.4 (0.47-3.8)	1.4 (0.42-3.4)
Emergency department disposition, No. (%)		
Admit	1099 (52.0)	1042 (52.0)
Discharge	1009 (48.0)	958 (48.0)
Age category, No. (%)		
<12 wk	385 (18.3)	353 (17.7)
3 mo-≤2 y	887 (42.1)	891 (44.6)
>2 - ≤5 y	391 (18.5)	381 (19.1)
>5 y	445 (21.1)	375 (18.8)

Abbreviation: IQR, interquartile range.

RESULTS

During the study, 4448 blood culture specimens were obtained. We excluded 289 specimens obtained during the 6-week implementation phase, 14 with incomplete data in the medical record and 37 because of the presence of central venous catheters, leaving 4108 emergency department visits for analysis (2108 in the baseline phase and 2000 in the postintervention phase). Overall, there were 324 positive blood culture specimens.

Patient demographics are presented in TABLE 1. There were no statistically or clinically important differences between patients in the baseline and in the postintervention phases.

During the baseline phase, 223 positive blood culture specimens were reported; of these, 32 specimens grew a pathogen. In the 191 blood culture specimens categorized as contaminated, 243 organisms were cultured (TABLE 2). The overall false-positive rate was 9.1% and the true-positive rate was 1.5%. In the postintervention period, there were 101 positive blood cultures; of these, 45 grew a pathogen. In the 56 contaminated specimens, 65 organisms were cultured (Table 2). The overall false-positive rate during the

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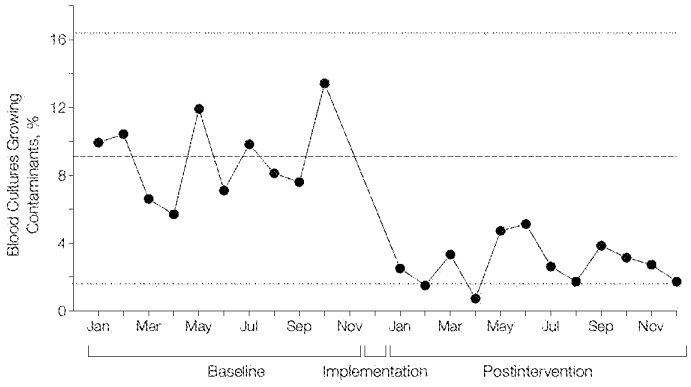
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Table 2. Blood Culture Contaminants in the Baseline and Postintervention Periods of Study

Contaminants	No. of Organisms (% of Total Contaminated Specimens)	
	Baseline*	Postintervention
Coagulase-negative staphylococci	140 (73)	37 (67)
Streptococcus viridans	57 (30)	8 (14)
Corynebacterium species	13 (7)	7 (12)
Micrococcus species	13 (7)	5 (8)
Bacillus species	3 (1.6)	3 (5)
Propionibacterium acnes	4 (2)	0
Neisseria species	3 (1.6)	0
Others	10 (5)	5 (8)
Total No. of Organisms	**243**	**65**

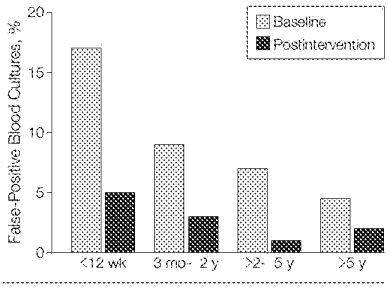
*There were 191 contaminated specimens growing 243 organisms in the baseline phase and 56 contaminated specimens growing 65 organisms in the postintervention phase of the study.

Figure 1. Statistical Process Control Chart Showing the Percentage of All Blood Cultures Growing Contaminants by Month, for the 2-Year Study Period



The upper and lower control limits (dotted lines) represent ±3 SD from the mean (dashed line). The mean, upper control limit, and lower control limit are calculated based on data in the baseline phase of the study.

Figure 2. Blood Culture Contamination Rate, by Age Category, During the Baseline and Postintervention Phases of Study



postintervention period was 2.8%, with a true-positive rate of 2.3%. Using a 2-sample test of proportions, the contaminated blood culture rate in the postintervention phase is significantly decreased when compared with the baseline phase ($P<.001$). The increase in true-positive rates did not reach statistical significance ($P=.20$).

The statistical process control chart (FIGURE 1) shows 12 consecutive data points below the mean established in the baseline phase in the postintervention phase, indicating a special cause effect (the intervention) and a significant change in the measured outcome (the contamination rate).[19]

The contamination rates in the baseline and postintervention phases are higher the younger the child (FIGURE 2). For example, in the baseline phase, the contamination rate in patients younger than 12 weeks was 17%, compared with 4.5% in those older than 5 years.

COMMENT

The contamination rates were significantly lower when blood culture specimens were drawn from a separate and dedicated venipuncture site compared with through a newly inserted intravenous catheter in children seen in a busy emergency department. The low rates have been sustained since the end of the study.

The statistical quality control methodology we applied provides a simple graphical display of process data that enhances our ability to understand outcomes that occur over time.[17] This methodology has been used increasingly in the evaluation of processes occurring in the health care setting.[16,20,21] The premise is that when a process achieves steady state, it is likely to remain there until events cause it to shift to a new steady state.[18,19]

This study addresses a common problem that has been linked to substantial and unnecessary resource utilization.[9,10,22-24] The contamination rate in our emergency department was resistant to change in spite of several specific interventions intended to address the problem. The sole procedural change was in the method by which blood culture specimens were obtained. During the baseline phase, the overall false-positive blood culture rate was 9.1% compared with a rate of 2.8% after the intervention, representing a decrease of 70%. While not statistically significant, the true-positive rate increased from 1.5% at baseline to 2.3% after the intervention. We believe that at least some of this increase is due to more selective ordering of blood cultures during the postintervention phase, when all cultures were obtained in response to other diagnostic tests obtained during the patient's emergency department evaluation. Since it is easier to obtain blood for culture from an intravenous catheter, cultures may have been obtained more indiscriminately in the baseline phase.

Previous studies comparing contamination rates in specimens obtained through newly inserted intravenous catheters or by phlebotomy at a remote

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site suggest that the 2 techniques are essentially equivalent. Smart and Baggoley[22] failed to show a difference in the contamination rate in 940 adult patients randomized to phlebotomy by either venipuncture or by placement of an intravenous catheter. Isaacman and Karasic[14] prospectively evaluated a convenience sample of 99 pediatric patients, each of whom had 2 blood cultures obtained, one by venipuncture and one through a newly inserted intravenous catheter. The authors demonstrated a low contamination rate with both techniques, concluding that newly inserted intravenous catheters offer an alternative to a separate venipuncture procedure in patients requiring blood culture. The small number of patients enrolled and the impact of the nursing staff's awareness of the study protocol may have biased the results.

On the other hand, a study by Ramsook et al[15] suggested that blood culture contamination rates were decreased when using dedicated phlebotomy compared with those obtained through a newly inserted intravenous catheter. Importantly, this study demonstrated the highest contamination rates in patients younger than 3 months of age, regardless of the collection method used, a finding confirmed in our study. Because staff members were aware of ongoing data collection, the potential effect on their phlebotomy technique is unknown.

However, our study also has limitations; because medical records were reviewed only for those patients with positive blood cultures, detailed information about patients with negative blood cultures is not known. In particular, information about antibiotic pretreatment is unknown. While it is likely that some patients were prescribed systemic antibiotic therapy prior to or during their emergency department evaluation, the rates of antibiotic pretreatment in the baseline and postintervention phases of the study are likely to be similar and unlikely to affect the study's conclusions. In addition, this protocol was implemented in a single unit and may not be generalizable to other settings. Finally, no concurrent control group was included to account for secular temporal changes.

Obtaining blood cultures from a separate site requires the patient to undergo an additional procedure for phlebotomy, but the overall benefit in terms of costs associated with a high contamination rate is likely to be substantial. During the baseline period, there were 6 contaminated specimens for every true-positive blood culture, compared with a ratio of 1.2:1 after implementation of the intervention. If subsequent patient management is based on preliminary blood culture results, false-positive test results will result in repeat emergency department visits, unnecessary medical interventions, unnecessary antibiotic therapy, and even hospital admission. One study[5] found that 26% of children followed as outpatients who had false-positive blood cultures were hospitalized unnecessarily, and that unnecessary use of antibiotics was significantly increased in the presence of false-positive blood culture results. Additional costs that are more difficult to quantify include staff effort and time required to arrange follow-up for patients, exposure of patients to unnecessary procedures, and cost and inconvenience related to repeat emergency department and/or hospital visits.[10,24]

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Analysis and interpretation of data: Norberg, Christopher, Bower.
Drafting of the manuscript: Norberg, Christopher, Bower.
Critical revision of the manuscript for important intellectual content: Norberg, Christopher, Ramundo, Bower, Berman.
Statistical expertise: Christopher.
Administrative, technical, or material support: Norberg, Berman.
Study supervision: Christopher, Ramundo, Bower.

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Innovation for Reducing Blood Culture Contamination: Initial Specimen Diversion Technique

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ABSTRACT

We hypothesized that diversion of the first milliliter of venipuncture blood—the initial specimen diversion technique (ISDT)—would eliminate incompletely sterilized fragments of skin from the culture specimen and significantly reduce our blood culture contamination rate (R). We studied our hypothesis prospectively beginning with our control culture (C) definition: one venipuncture with two sequentially obtained specimens, 10 ml each, the first specimen (M1) for aerobic and the second (M2) for anaerobic media. The test ISDT culture (D) was identical, with the exception that each was preceded by diverting a 1-ml sample (D_S) from the same venipuncture. During the first of two sequential 9-month periods, we captured D versus C data ($n = 3,733$), where $D_{MX}R$ and $C_{MX}R$ are R for D and C specimens. Our hypothesis predicted D_S would divert soiled skin fragments from D_{M1}, and therefore, $C_{M1}R$ would be significantly greater than $D_{M1}R$. This was confirmed by $C_{M1}R$ (30/1,061 [2.8%]) less $D_{M1}R$ (37/2,672 [1.4%]; $P = 0.005$), which equals 1.4%. For the second 9-month follow-up period, data were compiled for all cultures ($n = 4,143$), where $AD_{MX}R$ is R for all (A) diversion specimens, enabling comparison to test ISDT. Our hypothesis predicted no significant differences for test ISDT versus all ISDT. This was confirmed by $D_{M1}R$ (37/2,672 [1.4%]) versus $AD_{M1}R$ (42/4,143 [1.0%]; $P = 0.17$) and $D_{M2}R$ (21/2,672 [0.80%]) versus $AD_{M2}R$ (39/4,143 [0.94%]; $P = 0.50$). We conclude that our hypothesis is valid: venipuncture needles soil blood culture specimens with unsterilized skin fragments and increase R, and ISDT significantly reduces R from venipuncture-obtained blood culture specimens.

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As a clinical laboratory test, blood culture has played a major diagnostic role in medicine for decades. One limitation of this diagnostic role is false-positive results, which increase expenses and have an adverse patient safety impact (1, 2). Consequently, numerous interventions with blood culture processes have been employed by laboratories to reduce contamination (5, 6). The purpose of this report is to introduce a new blood culture technique that significantly reduced the blood culture contamination rate (*R*) in this study. This innovation, the initial specimen diversion technique (ISDT), omits the first approximately 1-ml portion of venipuncture blood from the culture specimen without compromising or diminishing the volume of blood optimum for culture. The basis for ISDT is the hypothesis that skin fragments incompletely sterilized by skin surface antisepsis and dislodged by venipuncture increase *R*. We evaluated our hypothesis prospectively first with test ISDT versus control cultures for a 9-month period (group 1; $n = 3,733$ cultures). Next, we collected data for a second 9-month period with an all-cultures ISDT (group 2; $n = 4,143$) for comparison to test ISDT.

MATERIALS AND METHODS

Patients and phlebotomists. The blood cultures in this study were from adults suspected of having sepsis who were hospitalized, evaluated in the emergency room, or seen as outpatients in a not-for-profit urban community hospital setting. Venipunctures (peripheral vein sites only) were performed by laboratory-trained and supervised phlebotomists who wore safety gloves during the procedure. No indwelling-catheter-obtained specimens were included in this study. Our standard procedure of monitoring needle puncture and other laboratory staff issues was continued during and after the study.

Skin preparation. Prior to venipuncture, the skin antisepsis agent 2% chlorhexidine-70% alcohol (Medi-Flex Hospital Products, Inc., Overland Park, KS) was applied with a sponge using vertical and horizontal strokes in a washboard manner for 30 s over a 5- by 5-cm area. The scrubbed area was allowed to dry and was not repalpated prior to venipuncture.

Blood culture definition and initial specimen diversion technique. A blood culture was defined as two separate 10-ml specimens obtained serially from one venipuncture for sequential inoculation of bottled media, M1 (aerobic) and M2 (anaerobic). Medium bottle stoppers were cleaned with a 70% isopropyl alcohol wipe, which was left in place prior to inoculation. The culture medium bottles were incubated in an automated computer-monitored system (BacT/Alert SN Microbial Detection System; bioMérieux S.A, Durham, NC) and in the event of growth were Gram stained and subcultured for identification. We used a pushbutton blood collection apparatus (Becton Dickinson and Company, Franklin Lakes, NJ) with a 21-gauge venipuncture needle for blood culture specimen collection and inoculation (Fig. 1). The apparatus included a venipuncture needle (1), wings (2) to aid insertion of the venipuncture needle, tubing (3) for blood transfer, and a protective adapter (4) that facilitated medium bottle inoculation. Inoculation was enabled within the adapter by a second needle (Fig. 1, inset). The venipuncture and inoculation needles had safety covers. The inoculation needle cover was rubberized and re-covered the needle between medium inoculations. Blood culture specimens (10 ml each) were collected sequentially directly to M1 and then to M2 (Fig. 2). The medium bottle volume in 5-ml increments was shown on the medium bottles, providing precision in measuring the culture specimen volume. The medium bottles were held vertically, and the desired 10-ml increment was marked with a pen or the phlebotomist's thumb nail. The procedure was the same for ISDT blood culture (D), with the exception that each was preceded by diverting the first milliliter (D_S) of the same venipuncture blood into a 3-ml sterile Vacutainer collection tube (Becton Dickinson and Company, Franklin Lakes, NJ) (Fig. 1). For patients with small veins, syringes and 23-gauge needles were used for blood collection as

follows. The collection needle/adapter attachment apparatus (Fig. 1, inset, 5) was removed, enabling a syringe connector (6) to be attached. Syringes (3 ml and 10 ml) collected the 1-ml D_S and culture samples, respectively. A separate safety needle was attached to the 10-ml syringes for transferring culture specimens to medium containers. The medium bottles were placed in racks for the syringe/safety needle inoculation; hand-held medium inoculation was not permitted.

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FIG. 1.

ISDT diversion step prior to culture. 1, venipuncture needle; 2, wings to aid insertion of the venipuncture needle; 3, tubing for blood transfer; 4, protective adapter to facilitate medium bottle inoculation; 5, collection needle/adapter attachment apparatus; 6, syringe connector; 7, diversion tube. (Inset) Diversion inoculation needle detail.

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FIG. 2.

ISDT direct-to-medium inoculation step.

Blood cultures were classified as false positive if one or more of the following organisms were isolated from only one of a series of blood culture specimens: coagulase-negative *Staphylococcus* spp., *Propionibacterium acnes*, *Micrococcus* spp., "viridans" group streptococci, *Corynebacterium* spp., or *Bacillus* spp. (2).

Data groups. For the first of two 9-month periods, June 2007 through February 2008, culture specimen collection was tracked for test ISDT versus C (group 1). Training for ISDT commenced prior to and continued at the beginning of the period, followed by randomization of test-ISDT versus C. Before randomization was fully implemented, significant reduction of *R* by ISDT became obvious; therefore, in the best interest of our patients and our institution, randomization was discontinued and all cultures were obtained with ISDT. For a second 9-month period, April through December 2008, blood culture specimens were obtained with all ISDT (group 2). Confirmation of receipt in the laboratory and the blood volume of D_S were also tracked. D_S was not cultured.

Statistical method. Pearson's chi-square test was used to evaluate the significance of the blood culture groups compared; significance was defined as a *P* value of ≤ 0.05.

RESULTS

During the first of two sequential 9-month periods, we captured test ISDT data, D versus C data (n = 3,733), which can be expressed as

$$D_T R = D_S R + D_{M1} R + D_{M2} R \quad (1)$$

and

$$C_T R = C_{M1} R + C_{M2} R \quad (2)$$

where $D_{MX}R$, $C_{MX}R$, and $D_S R$ are R for D, C, and D_S specimens and $D_T R$ and $C_T R$ are total R for D and C. Our ISDT hypothesis predicted that D_S would divert soiled skin fragments from D_{M1}, and therefore, $C_{M1}R$ would be significantly greater than $D_{M1}R$. This was confirmed by $C_{M1}R$ (30/1,061 [2.8%]) less $D_{M1}R$ (37/2,672 [1.4%]; $P = 0.005$) equaling 1.4%. Also predicted was that ISDT would show no significant difference between $C_{M2}R$ and $D_{M2}R$. Confirmation came as $C_{M2}R$ (11/1,061 [1.0%]) less $D_{M2}R$ (21/2,672 [0.8%]; $P = 0.31$) equaling 0.2%. Additionally, we assumed $D_T R$ was equal to $C_T R$, and therefore,

$$D_S R = C_{M1} R + C_{M2} R - D_{M1} R - D_{M2} R \quad (3)$$

Thus, $D_S R$ was discrete, could be calculated, and was 1.6%. Regarding the second 9-month follow-up period for comparison to test ISDT, ISDT data were compiled for all (A), $AD_T R$, and $AD_{MX}R$, cultures ($n = 4,143$),

$$AD_T R = AD_{M1} R + AD_{M2} R \quad (4)$$

Our hypothesis predicted no significant differences for test ISDT versus all ISDT. This was confirmed by $D_{M\,1}R$ (37/2,672 [1.4%]) versus $AD_{M\,1}R$ (42/4,143 [1.0%]; $P = 0.17$) and $D_{M2}R$ (21/2,672 [0.80%]) versus $AD_{M2}R$ (39/4,143 [0.94%]; $P = 0.50$). The data are shown in Table 1 for all cultured specimens, as are comparison contamination rates for control versus test ISDT and all ISDT versus test ISDT. The only significant comparison difference was test ISDT M_1 versus control M_1 (1.4%). This difference can be attributed to the diversion of unsterilized skin fragments from control M_1 by ISDT (formulas 1 and 2), and this difference in the study can be quantified (formula 3) as 1.6%. The lack of significant differences between test ISDT M_1 and M_2 and AD M_1 and M_2 rates are consistent with our hypothesis: ISDT significantly reduces contamination in venipuncture-obtained blood culture specimens.

TABLE 1.

Comparison of R for control versus test ISDT and all ISDT versus test ISDT culture groups

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[a]Test ISDT rate from first 9 months less all ISDT rate from second 9 months used for comparison.

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For one randomly chosen month (February 2008), the diversion volume distribution was 152 (40%) >0.5 ml and ≤1.0 ml, 256 (68%) ≤1.5 ml, 351 (93%) ≤2.0 ml, and ≤3.0 ml (100%) (n = 376).We conclude that ≥0.5 ml and ≤2.0 ml is adequate diversion volume to significantly reduce contamination.

The clinical service distribution of blood cultures during the study was inpatients 77.2%, emergency department 15.9%, and outpatients 6.9% (n = 11,330). None of these were ≤16 years of age.

Phlebotomists did not suffer needle sticks or other injuries as a result of this study.

DISCUSSION

Every pathologist who has examined numerous needle aspirations of bone marrow and other viscera has observed skin fragments (mini-biopsy specimens) contaminating these aspiration specimens. Based on this experience, we sought improvement in our blood culture contamination rate. We hypothesized that small fragments of skin dislodged by a venipuncture needle harbor bacteria not killed by skin surface antisepsis and that they are a discrete cause of contamination. Additionally, we hypothesized that diverting the first milliliter of venipuncture blood and subsequently obtaining a culture specimen from the same venipuncture would eliminate some of these fragments from the culture specimen and significantly reduce contamination and that it would do so without compromising blood culture sensitivity. We refer to this diversion method as ISDT.

Our results show that ISDT significantly reduces contamination of blood cultures by excluding contaminants from the first portion of venipuncture-obtained culture specimens. Given this, several questions arise. What other studies have been done that may corroborate our findings? What is the optimum volume of blood for diversion? What is the cost of ISDT, and are there laboratory worker safety issues? Finally, do we recommend ISDT to other laboratories?

Regarding other studies, to our knowledge, reduction of contamination by diversion has not been previously studied in detail or quantified for venipuncture-obtained blood culture specimens. In contrast, diversion has been extensively studied and quantified for donor blood components. Diversion of the first part of donor blood to reduce the risk of bacterial contamination in recipients is a worldwide standard. Diversion volumes ranging from 10 to 50 ml are credited with having reduced contamination of blood components by 40 to 90% between 1995 and 2007 (7). Similar reductions in contamination of blood cultures may be realized with less diversion volume, as a blood culture needle is commonly a smaller gauge than a donor needle. The usual 16-gauge donor needle (bore, 1.19 mm) captures numerous plugs of skin contaminants (3). One would expect less contamination from our 21-gauge culture needle (bore, 0.514 mm), which has a cross-sectional area less than 1/5 that of the donor needle.

As for the optimum diversion volume for blood cultures, this study showed significant improvement in contamination with a volume of ≥0.5 ml and ≤2 ml. More diversion volume is likely better. Our data show that all specimens subsequent to ≥2.0 ml of diversion (C_{M2}, D_{M1}, D_{M2}, AD_{M1}, and AD_{M2}) had an average R of 1%. Hence, 20 ml of diversion would very likely decrease contamination further. However, with meticulous oversight, increased experience with diversion, and both initial and remedial training using a video of our diversion technique, our phlebotomists have achieved an R of <1% in the first 6 months of 2010, an R which a short time ago we would have thought impossible. We are satisfied with our current diversion volume but are considering increasing the volume to 3 or possibly 5 ml. Another improvement tactic is drawing blood for other tests (blood counts, chemistry, etc.) prior to blood culture.

ISDT can be cost-effective by lowering patient care charges. Recently, in a large emergency department (ED), patient charges were increased by $8,720 for each contaminated blood culture (4). If our IDST procedure were implemented in this ED, with 5,432 blood cultures in 13 months, annual charges would decrease by $699,575 for an increase in supply costs of $3,510. Our costs for ISDT supplies are minimal (blood collection apparatus, $1.28, and diversion tube, $0.07), replacing a theoretical 20-ml syringe and two safety needles ($0.65). Reduced contamination is based on our calculated $D_S R$ of 1.6%, and these cost savings can accrue without employee safety issues. We had no needle sticks or other injuries to our phlebotomists or other laboratory workers during this study.

For venipuncture-obtained specimens, we believe ISDT significantly reduces blood culture contamination, has a high benefit/cost ratio, is practical and safe for laboratory personnel and patients, and does not compromise blood culture sensitivity. We recommend ISDT to other laboratories.

ACKNOWLEDGMENTS

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FOOTNOTES

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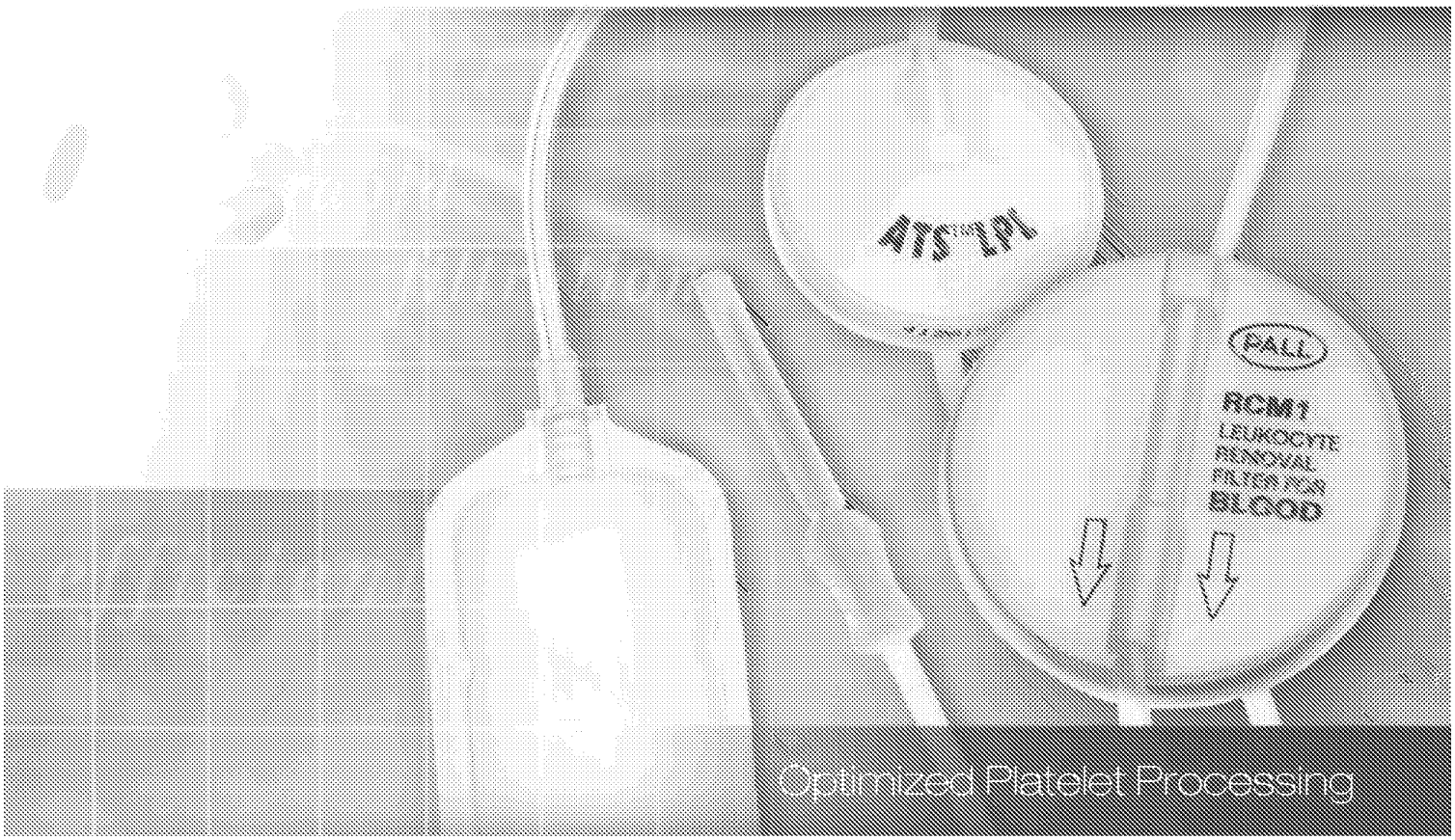
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Leukotrap® Filtration Systems for Whole Blood Derived Platelets

Leukotrap RC PL and Leukotrap PL Systems



Better Blood, Better Care.℠

Improving the Availability of Safer Whole Blood Derived Platelets

Pall offers the Only In-line Collection, Filtration and Storage Systems Capable of Producing Leukocyte Reduced Whole Blood Derived Platelets



Leukotrap® RC PL System produces leukocyte reduced red blood cells, platelets, and plasma.

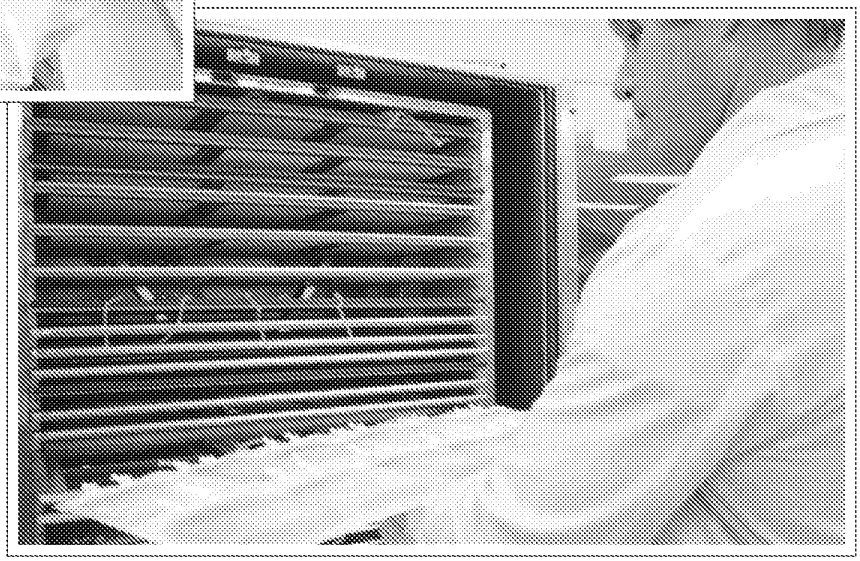
Leukotrap PL System produces leukocyte reduced platelets and plasma.

- Fits into routine operating procedures without additional labeling and handling
- Requires no sterile connection which eliminates the rework process of clockable leukoreduction and associated errors and product loss
- Features easy, snap-open closures for fast opening of fluid paths between bags

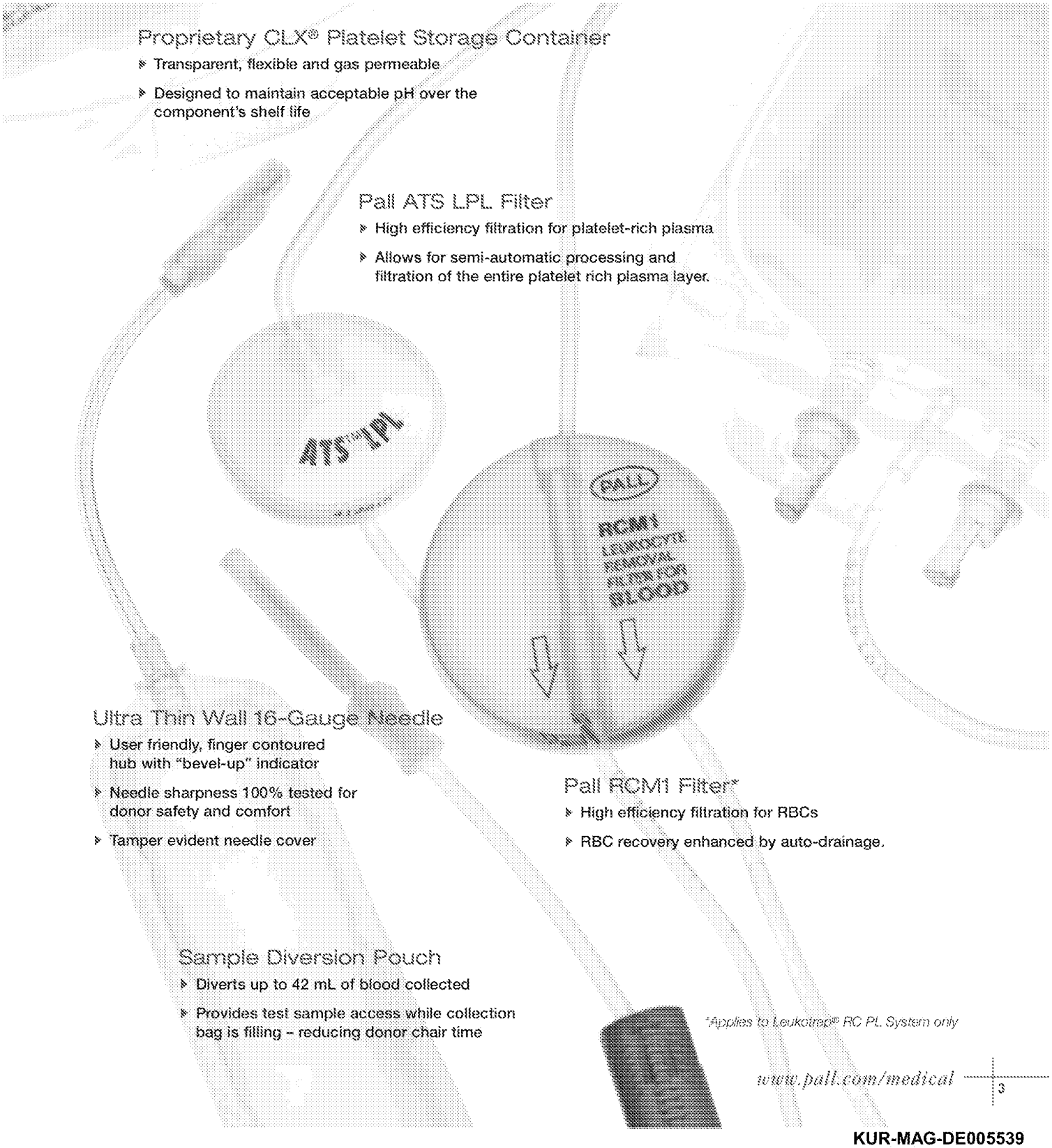
Makes cGMP compliance easier than ever.

- High efficiency filtration providing consistently low residual leukocytes in processed RBC*, platelets and plasma
- RBC recovery enhanced by auto-drainage*
- Allows for semi-automatic processing and filtration of the entire platelet rich plasma layer
- Greater QC assurance of meeting platelet recovery requirements

**Applies to Leukotrap RC PL System only.*



A Unique Combination of Technologies to Enhance Transfusion Safety and Operating Efficiency



Proprietary CLX® Platelet Storage Container

- Transparent, flexible and gas permeable
- Designed to maintain acceptable pH over the component's shelf life

Pall ATS LPL Filter

- High efficiency filtration for platelet-rich plasma
- Allows for semi-automatic processing and filtration of the entire platelet rich plasma layer.

Ultra Thin Wall 16-Gauge Needle

- User friendly, finger contoured hub with "bevel-up" indicator
- Needle sharpness 100% tested for donor safety and comfort
- Tamper evident needle cover

Pall RCM1 Filter*

- High efficiency filtration for RBCs
- RBC recovery enhanced by auto-drainage.

Sample Diversion Pouch

- Diverts up to 42 mL of blood collected
- Provides test sample access while collection bag is filling – reducing donor chair time

*Applies to Leukotrap® RC PL System only

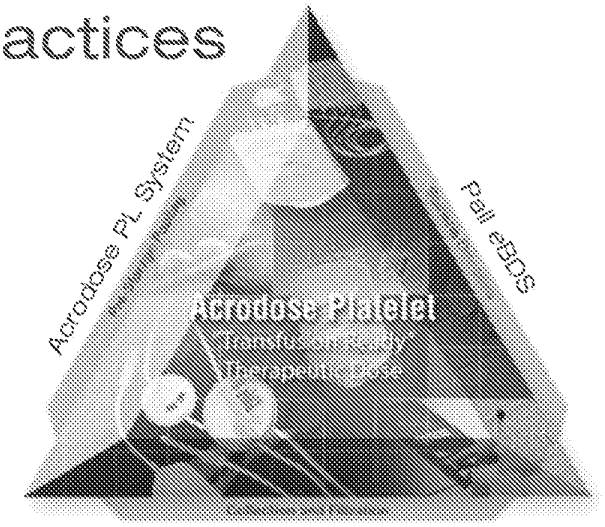
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KUR-MAG-DE005539

A Synergy of Best Practices

Supports your Bacteria Risk Management Program.

- Pre-donation Diversion Pouch Sampling System: Up to 72% predicted reduction in bacteria contamination by diverting initial 13.5 mL[1]
- Leukocyte reduction filters have been shown to reduce bacteria from blood components[2,3,4]
- Produce leukoreduced platelets ready for bacterial testing with the Pall eBDS



Leukotrap RC PL and
Leukotrap PL Systems

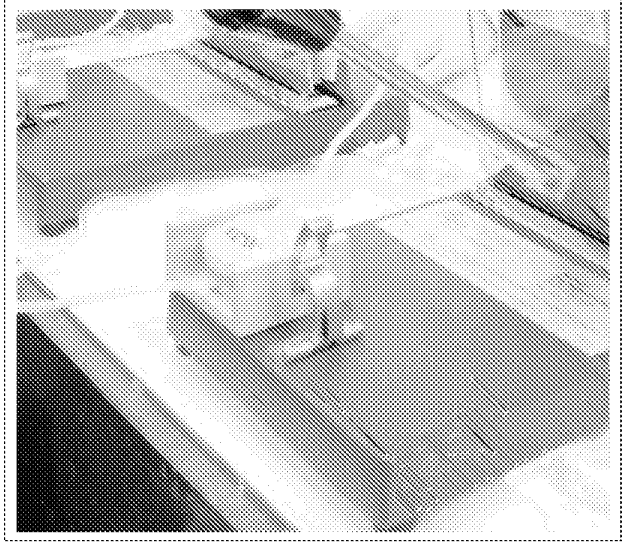
Collection and Filtration

Pall Sample Diversion Pouch



1 Automatically divert initial blood with the Pall Sample Diversion Pouch

Leukotrap RC PL or Leukotrap PL System



2 Prepare leukoreduced platelets with the Leukotrap RC PL or PL System

Provide Greater Platelet Transfusion Safety

Greater QC Assurance of Meeting Guidelines for Detecting Bacteria in *all* Platelet Products

- The American Association of Blood Banks (AABB)[5] and College of American Pathologists (CAP)[6] have issued guidelines for the detection of bacteria in all platelet products.
- All market cleared systems for detecting bacteria in platelet products require that these platelet products must be leukoreduced.
- The same standard of testing should be applied to all platelet products to make cGMP compliance easier.
- The Leukotrap RC PL System is the only closed system that can produce leukoreduced whole-blood derived platelet products.

Pre-storage Pooling and Bacteria Detection

Acrodose™ PL System



3 Pool leukoreduced platelets with the Pall Acrodose PL System.

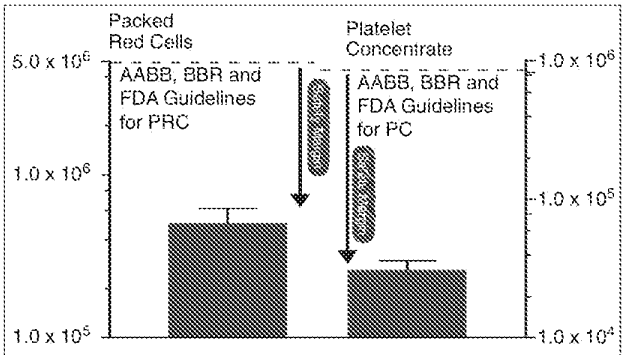
Pall eBDS and Pall Data



4 Detect bacteria with Pall eBDS, a market cleared quality control culture based system.

Consistent and Reliable Performance

Greater QC Assurance of Meeting White Blood Cell Residual Requirements



Safety margins for residual leukocytes in packed cells and platelet concentrates prepared with the Leukotrap RC PL System

Figure 1

Consistency of performance with RCM1 and ATS LPL Filters using the Leukotrap® RC PL System.

Data from actual field use.

Shown are mean residual WBC/unit and 95% confidence interval.

Greater QC Assurance of Platelet Recovery Requirements

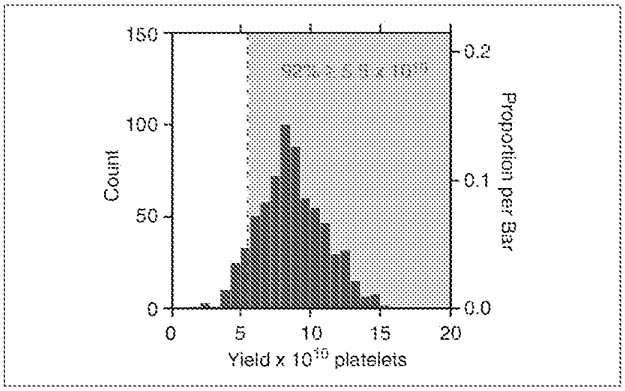


Figure 2

Platelet yield distribution of individual platelet concentrates (PC) prepared using the Leukotrap RC PL System.

Data from 500 mL WB (n=700) collections processed with the Leukotrap RC PL System.

Mean platelet yield = 8.87 x 10^{10} with a standard deviation of 2.42 x10^{10} platelets.

Ninety-two percent (92%) of PCs had a platelet count greater than the AABB Standards[7] for platelets prepared from whole blood (≥5.5 x 10^{10}).

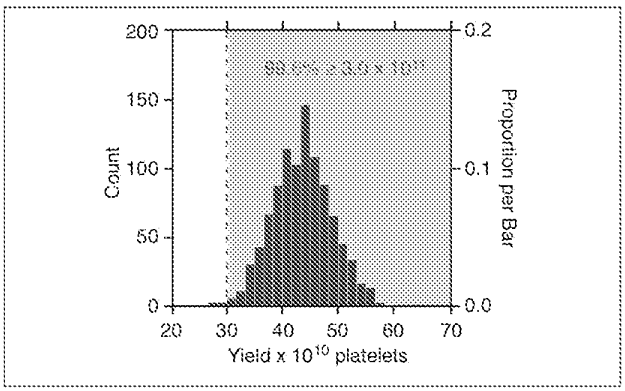


Figure 3

Platelet yield distribution of a pool of five (5) individual platelet concentrates (PC) prepared using the Leukotrap RC PL System.

The distribution was obtained by computer simulation using the individual PC yield data shown in Figure 2.

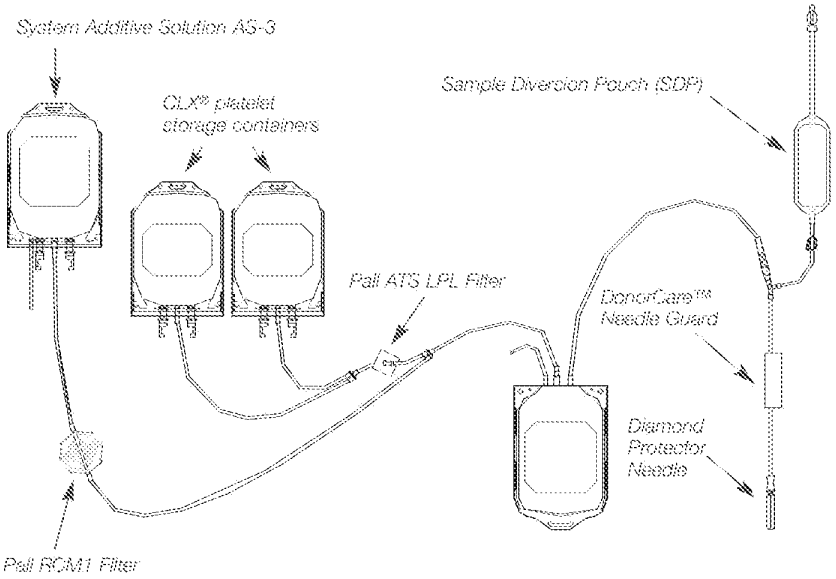
Mean platelet yield with a pool of 5 = 4.3 x 10^{11} with a standard deviation of 5.3 x 10^{10} platelets.

Over ninety-nine percent (99.6%) of the PC pools had a platelet yield greater than the AABB Standard for platelets prepared by cytapheresis[8] (≥3.0 x 10^{11}).

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Leukotrap® RC PL System

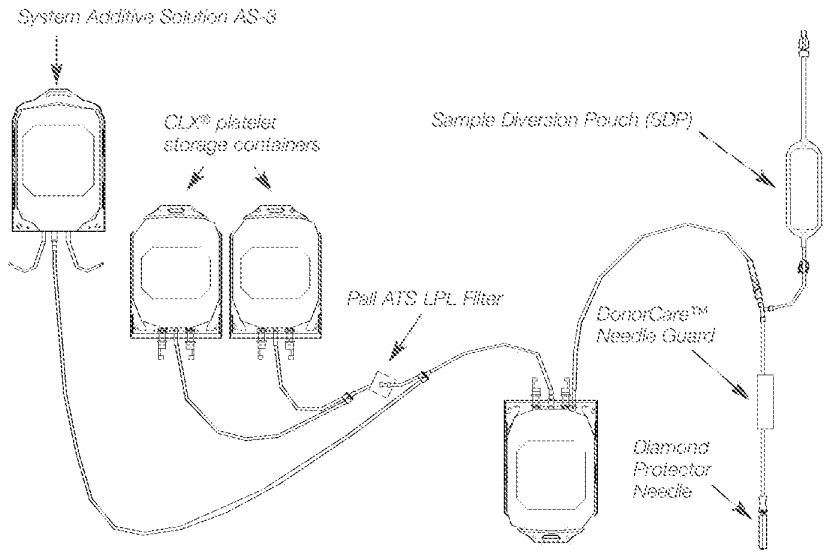


Ordering Information*

Leukotrap RC PL System

Reorder Code	Packaging
With SDP	
723-93	CP2D/AS-3, 450 mL capacity, Triple
123-93	CP2D/AS-3, 500 mL capacity, Triple
123-94	CP2D/AS-3, 500 mL capacity, Quad

Leukotrap PL System

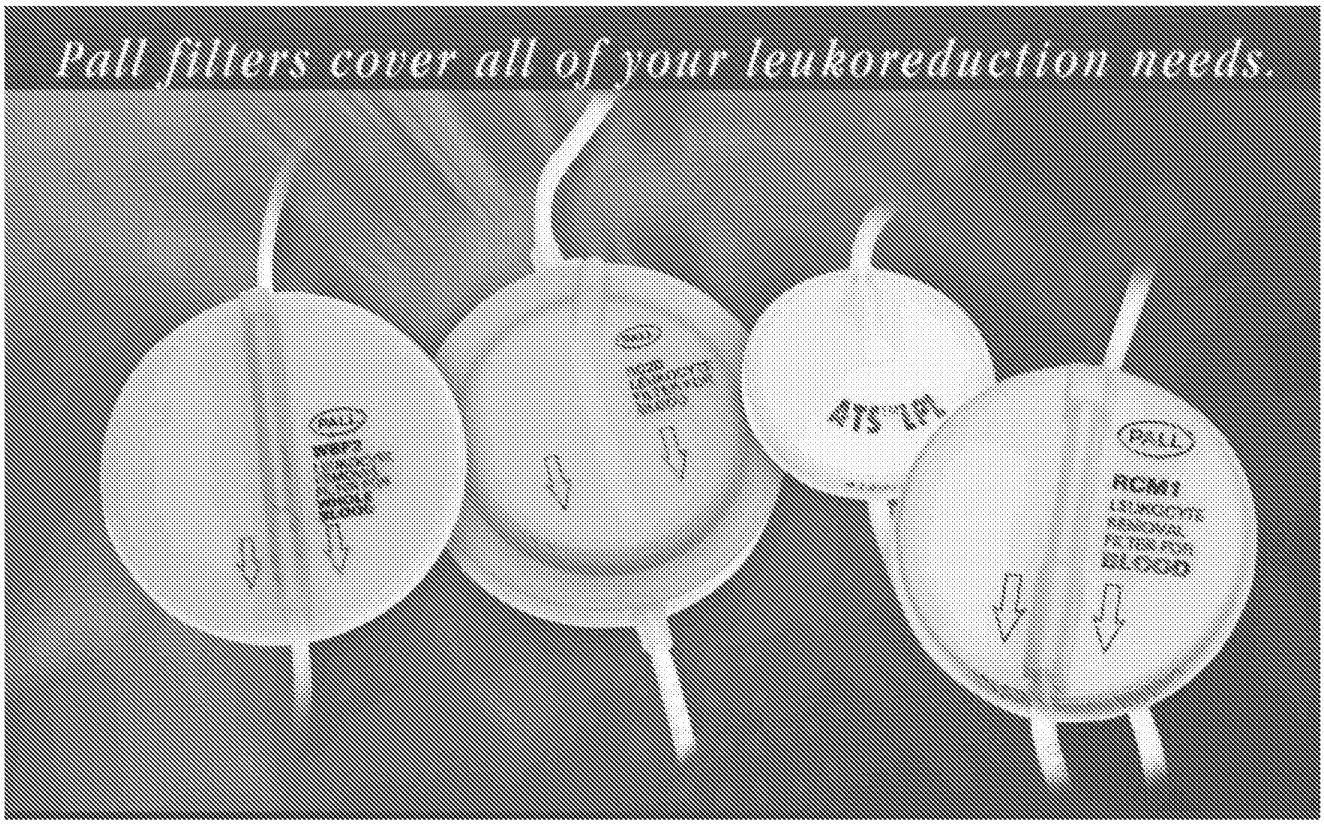


Ordering Information*

Leukotrap PL System

Reorder Code	Packaging
With SDP	
125-93	CP2D/AS-3, 500 mL capacity, Triple

**All sets come with DonorCare™ Needle Guard for reducing needlestick injury, enhanced paper labels for improved adhesion of overlabels and a QC leg on the collection bag for improved QC sampling. The System Additive Solution AS-3 (Nutricel® System) for RBC maintains viability for 42 days without manitol.*



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[FI]
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[Name] Hiroaki Kubota
[Examiner] Yukio Tanaka
(56) [Reference]
[Reference] JP-A-2009-265778 (JP, A) [Reference] JP-A-2008-015958 (JP, A) (58)) [Investigated field] (Int.Cl., DB name) G06F 9/50

The scope of the claims open —

(57) [Claims]
[Claim 1] In a system that distributes and executes
requested processing to a plurality of virtualized
computer nodes, a computer node that manages tasks executed in the system comprises: When a processing request with a specified delivery date is received, the management information stored in the storage unit for managing the tasks executed by the computer nodes of the system is referred to, and the task of the processing request is assigned to the computer node.

A simulation is performed, and

the simulation of the assignment shows that there is no computer node that can complete th e processing of the task of the processing request within the delivery date, and even if anothe r computer node moves the task that can complete the processing within the delivery date, th e processing will be performed. An auto-scaling method characterized by executing a proces s of increasing the number of computer nodes in the system when it is determined that a com puter node capable of completing the processing of the requested task within the deadline can not be prepared. 2. The computer node that manages the task further refers to the manag ement information and executes a simulation of moving a task running on one computer node to another computer node, and simulating the movement of the task . If it is determined tha t a computer node that does not have a task to be executed can be prepared by moving tasks that can be completed within the deadline on other computer nodes, the other computer node s can also complete the processing within the deadline. move the task,

2. The autoscaling method of claim 1, further comprising removing from the system compu ter nodes that have no tasks to execute .

3.

The computer node that manages the tasks further

moves tasks that can be completed by other computer nodes within the delivery date by sim ulating the movement so that the number of tasks to be executed is equal to or less than a pr edetermined number. If it is determined that a computer node can be prepared to meet the pr ocessing request, tasks that can be completed within the deadline are moved to other comput er nodes, and computer

nodes with a predetermined number or less of tasks to be executed are assigned to the proc essing request task.

3. The auto-scaling method according to claim 2, further comprising executing a process of s etting the object to be excluded from allocation .

4.

In the process of adding a computer node to the system, the task of the processing request can be completed within the deadline even if the setting of the computer node set to be exclu ded from the assignment of the task of the processing request is cancelled.

4. The autoscaling method according to claim 3, further comprising adding a computer node to said system when it is determined that a computer node capable of completing processing cannot be prepared.

5. In a system that distributes and executes

requested processing to a plurality of virtualized computer nodes, a computer node that manages tasks executed in the system includes:

When a processing request with a specified delivery date is received, the management information stored in the storage unit for managing the tasks executed by the computer nodes of the system is referred to, and the task of the processing request is assigned to the computer node. A simulation is performed, and

the simulation of the assignment shows that there is no computer node that can complete the processing of the task of the processing request within the delivery date, and even if another computer node moves the task that can complete the processing within the delivery date, the processing will be performed. An auto-scaling program for increasing the number of computer nodes in the system when it is determined that a computer node capable of completing the processing of the requested task within the deadline cannot be prepared. 6. In a system comprising a plurality of virtualized computer nodes, a computer node that manages tasks executed in the system, and management information that manages the tasks executed by the computer nodes in the system a storage unit, a schedule processing unit that, when receiving a processing request with a specified delivery date, refers to the management information and executes a simulation that allocates the task of the processing request to a computer node ; , Even if there is no computer node that can complete the processing of the task of the processing request within the delivery date, and even if another computer node moves the task that can complete the processing of the task within the delivery date, the processing of the task of the processing request can be completed within the delivery date. If it is determined that a sufficient computer node cannot be prepared, the system

A computer node, comprising: a scale-out processing unit that executes processing for increasing the number of computer nodes.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to an autoscaling method, an autoscaling

program, and computer nodes for controlling the number of computer nodes provided in a system. [Background technology]

[0002]

In a conventional on-premise system, the resource amount of the system was fixed, and therefore it was not possible to accept processing requests from clients exceeding the resource amount of the system.

[0003]

On the other hand, in a system using cloud computing, which has been developed in recent years, the amount of resources possessed by the system can be changed dynamically. Therefore, even if the amount of system resource consumption exceeds the available resources of the system by executing the processing requested by the client, requests from the client can be accepted by dynamically increasing the system resources. It becomes possible.

As a technique for increasing or decreasing such system resources, there is a technique called scale-up/scale-down for increasing or

decreasing the amount of resources of virtualized computer nodes in the system. However, increasing the resources of virtualized computer nodes is limited by the amount of physical machine resources.

Another

technique for increasing or decreasing system resources is called scale-out/scale-shrink, which increases or decreases the number of computer nodes in the system. With this technology, there is no limit to the amount of physical machine resources when increasing the amount of system resources. There is also a technology called autoscaling that automatically scales out and scales down according to the resource consumption rate of the system.

[0006]

In a distributed batch system, when a new batch process is requested, the batch process being executed by a certain processing server is transferred to another server, and the new batch process is executed by the server that is ready for processing. There is known a technique for managing deadlines for batch processing by doing so.

[Patent Document] [Patent

Document 1] Japanese Unexamined Patent Application Publication No. 2002-342098 [Summary of the Invention] [Problems to be Solved by the Invention] When auto-scaling is performed according to the resource consumption rate, unnecessary computer nodes may be added due to scale-out, and processing being executed by the system may be forcibly interrupted due to incorrect scale-shrink. In cloud computing, when pay-as-you-go billing is performed according to the number of computer nodes, useless scale-out may result in unnecessary billing. [0009] In one aspect, the object of the present invention is to provide a technique that enables

the operation of a system with good billing efficiency. [0010] In one aspect, an autoscaling method distributes requested processing to a plurality of virtualized

In a system in which execution is distributed to computer nodes, when a computer node that manages tasks to be executed in the system receives a processing request with a specified de livery date, the computer node that is stored in the storage unit is referring to management in formation for managing tasks to be executed, executing a simulation of allocating the task of t he processing request to a computer node; Furthermore, even if a task that can be completed within the deadline is moved to another computer node, a computer node that can complete t he processing of the requested task within the deadline is used.
If it is determined that the number of computer nodes in the system cannot be increased, pro cessing is executed to increase the number of computer nodes in the syste
m. EFFECTS OF THE INVENTION [0011] According to one a spect, it is possible to operate a system with good billing efficiency. BRIEF DESCRIPTION OF T HE DRAWINGS [0012] FIG. 1 is a diagram explaining a problem of a system realized on-premi ses; FIG. 2 is a diagram explaining a problem of a system realized by cloud computing; FIG. 3 is a diagram showing a configuration example of a system according to this embodiment; FIG. 4 is a diagram showing an example of functional configuration of each node according to the e mbodiment; FIG. 5 is a diagram showing an example of a virtual machine system that implem ents a node according to this embodiment; FIG. 6 is a diagram illustrating an example of a si mulation of assignment of processing-requested tasks by a scheduler in a master node accord ing to the present embodiment; FIG. 7 is a diagram illustrating an example of a simulation of assignment of processing request tasks by a schedule processing unit in a master node accord ing to the present embodiment; FIG. 8 is a diagram illustrating an example of a simulation of assignment of processing request tasks by a schedule processing unit in a master node accord ing to the present embodiment; FIG. 9 is a diagram illustrating an example of a simulation of assignment of processing request tasks by a schedule processing unit in a master node accord ing to the present embodiment;

FIG. 10 is a diagram illustrating an example of a task migration simulation by a rescheduling processor in a master node according to the embodiment;
FIG. 11 is a diagram illustrating an example of a task movement simulation by a rescheduling processor in a master node according to the embodiment;
12A and 12B are diagrams for explaining an example of lock setting for a slave node by a resc heduling processor in a master node according to the present embodiment; FIG.
13A and 13B are diagrams for explaining an example of lock setting for a slave node by a resc heduling processor in a master node according to the present embodiment; FIG.
14A and 14B are diagrams illustrating an example of unlocking of a slave node by a schedule processing unit in the master node according to the present embodiment; FIG.
FIG. 15 is a processing flowchart when a processing request is accepted by the master node a ccording to the embodiment;
16 is a processing flowchart when a processing request is received by the master node accord ing to the embodiment; FIG.
FIG. 17 is a flowchart of rescheduling by the master node according to the embodiment; BEST MODE FOR CARRYING OUT THE INVENTION The present embodiment will be described belo w with reference to the drawings. [0014] FIG. 1 is a diagram for explaining problems of a sy stem implemented on-premise. In the example shown in FIG. 1, the vertical length of a grap hic representing a task indicates the resource consumption of the task, and the horizontal len gth indicates the processing time of the task. In the example shown in FIG. 1, the vertical axi s of the graph indicates the resource consumption of the system, and the horizontal axis indic ates the passage of time. t0 _

~ t 3 indicates the times at equal intervals.

[0016]

In an on-premise system, the amount of resources that the system has is fixed. That is, it is not possible to process resource consumption that exceeds the amount of resources that the system has in advance. In the example shown in Figure 1, the System Resources line represents the amount of resources the system has.

indicate. For example, in FIG. 1A, it is assumed that the processing requests for tasks #1 to #4 are issued to the system at approximately the same

time t0 . At this time, the system starts processing in the order in which the processing requests are accepted, here in the order of task #1, task #2, task #3, and task #4. However, as shown in FIG. 1A, when the processing of task #3 is started, the resource consumption of the system reaches the amount of resources that the system has, and the processing of task #4 cannot be started. will not be able to accept processing requests for The example shown in FIG . 1B is an example of a scheduling system. In a scheduling system, the task processing time is estimated at the time a processing request is received, and even if there are no available resources at the time the processing request is generated, the task of the processing request that is received after the completion of other tasks in progress. Schedule tasks to execute For example, it is assumed that the deadline for processing task #4, which is finally accepted, is time t3 . As shown in FIG. 1B, the processing end time of task #3, which has the earliest processing end time, is t1, so if task #4 is scheduled after task #3, the processing end time of task #4 is is t3 , and the deadline is met. In this case, the processing request for task #4 can be accepted by the system. [0020]

However, in the example shown in FIG. 1(C), if task #4 is scheduled after task #2, which has the earliest processing end time, the processing end time of task #4 will exceed t3, and the deadline will not be met . In this case, the processing request for task #4 is not accepted by the system. On-premises systems may not be able to accept processing requests even after scheduling. Cloud computing technology exists at the opposite end of such on-premise technology

.

The amount of system resources realized by cloud computing is variable. In cloud computing, each computer node provided in the system is realized by, for example, a virtual machine (VM)

.

In the following description, the computer nodes included in the system are simply referred to as nodes. In cloud computing, there is, for example, a scale-up/scale-down technique as a t echnique for changing the amount of system resources

.

Scaling up is a technique for increasing the resource amount of a node. Also, scaling down is a technique to reduce the resource amount of a node. By using scale-up technology, for exam ple, even if a task with a new processing request cannot be executed in time with the current resources, by increasing the amount of node resources, the new processing request can be ful filled. Be able to complete tasks on time.

[0024]

However, since the resources that can be scaled up are limited to the resources of the physic al machines that implement the nodes, which are virtual machines, there is a limit to how mu ch nodes can be scaled up. In addition, usually multiple virtual machine nodes are arranged o n one physical machine, and if there is no surplus after allocating the resources of the physica l machine to each node, it can be specified without reducing the performance of other nodes. It becomes impossible to increase the performance of the nodes of For example, in a multi-te nant environment, multiple tenants' virtual machines are running on a single physical machin e, and in order to increase the resource amount of one tenant's virtual machine, it is possible to reduce the resource amount of other tenants. cannot be done easily. Therefore, even if scal e-up techniques are used, the required processing

Not all tasks can be executed with a guaranteed delivery date. In cloud computing, there is a scale-out/scale-shrink technique in addition to the scale-up/scale-down technique as a tech nique for changing the amount of system resources

.

Scale-out is a technique for adding nodes to a system. Scale shrink is a technique for removin g nodes from a system. By using scale-out technology, it is almost certain that all requested p rocessing tasks can be executed with a guaranteed delivery date.

[0026]

However, in the world of cloud computing, the service usage fee is normally based on a pay-as-you-go system, and as the number of nodes provided in the system increases due to scale-out, the service usage fee increases.

FIG.

2 is a diagram for explaining problems of a system realized by cloud computing.

In the example shown in FIG. 2, the

vertical length of a graphic representing a task indicates the resource consumption of the tas k, and the horizontal length indicates the processing time of the task. In the example shown i n FIG. 2, the vertical axis of the graph indicates the total amount of resource consumption of the nodes that make up the system, and the horizontal axis indicates the passage of time. t_0 to t_3 indicate times at equal intervals. In the example shown in FIG. 2, the system resource li

ne indicates the total amount of resources possessed by the nodes that make up the system.

[0029]

In FIG. 2A, it is assumed that the system initially has three nodes VM#1 to VM#3. Here, it is assumed that the processing requests of task #1 to task #4 are issued to the system at approximately the same time t0 . At this time, in the system, tasks are assigned to the nodes in the order in which the processing requests are accepted, here in the order of task #1, task #2, task #3, and task #4, and processing is started. However, as shown in FIG. 2A, when task #3 is assigned to node VM#3, the resource consumption of all nodes in the system becomes the upper limit, and task #4 can be assigned. node disappears. At this time, as shown in FIG. 2A, for example, the system is scaled out and a VM#4 node is added to the system

.

As shown in FIG. 2A, by adding a VM#4 node to the system by scale-out, the processing of the requested task #4 can be executed. For example, in cloud computing, as a service of an IaaS (Infrastructure as a Service) vendor that provides infrastructure such as virtual machines and networks as a service, it automatically scales out when the resource consumption rate of the system exceeds a predetermined level. There is service. In cloud computing, the technology for automatically expanding/reducing the system is also called autoscaling. Here, it is assumed that the deadline for processing task #4 is

time t3 . As shown in FIG. 2A, the processing end time of task #3, which has the earliest processing end time, is t 1

Therefore, if task #4 is scheduled after task #3, the processing end time of task #4 will be t 3, and the deadline will be met . If task scheduling can be performed in this way, it is possible to execute the processing of task #4 in time for the delivery date without increasing the number of nodes for VM #4 due to scale-out

.

. However, such a judgment cannot be made just by looking at resource consumption as in the case of the IaaS service described above. As mentioned above, in cloud computing, the usage fee increases as the number of nodes increases. I have a request.

[0033]

Further, in order to suppress useless node usage charges, a scale shrink is performed on a node that is determined not to be in operation in the system, and the node is removed from the system. For example, in cloud computing, as a service of an IaaS vendor, when the CPU (Central Processing Unit) usage rate of a node falls below a predetermined level, task processing is not performed at the node and only middleware such as the OS operates. There is a service that automatically scales and shrinks if it judges that it is not.

[0034]

However, even if the resource consumption of a node is low, it does not necessarily mean that the requested task is not being processed. For example, in the example shown in FIG. 2B, in the node of VM#3, the amount of resource consumption is drastically reduced after the proc

essing of task #3 is completed. However, in the example shown in FIG. 2B, in the node of VM #3, task #4, which consumes less resources, is being executed in parallel with task #3. If the node of VM#3 is scale-shrinked at the same time as the processing of task #3 ends, the proce ssing of task #4 will be forcibly terminated. In this way, if scale shrinkage is determined just b y looking at resource consumption as in the above-mentioned IaaS vendor service, for exampl e, task #4 shown in FIG. It is possible to accidentally remove a running node.

[0035]

The auto-scaling technique according to the present embodiment for solving such problems will be described below.

FIG.

3 is a diagram showing a configuration example of a system according to this embodiment.

[0037]

In this embodiment, the system 100 shown in FIG. 3 is assumed to be a computer system c omposed of virtual machine nodes provided from the IaaS side in cloud computing. The syste m 100 distributes and executes the processing requested by the client 200 over a plurality of nodes. The system 100 and the client 200 are connected by a network 300 such as a LAN (Lo cal Area Network) or the Internet. The system 100 comprises a master node 110 and slave no des 120 .

The master node 110 receives processing requests from the client 200 , assigns

tasks to each slave node 120 , and manages tasks to be executed in the system 100 . Note t hat the master node 110 according to this embodiment performs auto-scaling processing such as scale-out and scale-shrink of the slave node 120 . Note that the master node 110 may be o ne of the slave nodes 120 at the same time.

The slave node 120 is a computer node that

executes tasks requested by the master node 110 . The slave node 120 is capable of parallel processing of multiple tasks. The slave node 120 is added to the system 100 or deleted from t he system 100 by autoscaling processing. For example, in FIG. 3, when the slave node 120a #a and the slave node 120b #b are executing task processing, if there is a processing request that cannot be executed by those slave nodes 120, #c A slave node 120 c is added to system 100 . Also, for example, when there are no more tasks to be executed by the #c slave node 1 20c, the #c slave node 120c is deleted from the system 100 .

[0040]

The client 200 is a computer having a high-level application that requests the system 100 to execute processing provided by the system 100 . In the example shown in FIG. 1, the client 2 00 is an external device of the system 100.

Node 200 may be a node within system 100 .

FIG.

4 is a diagram showing an example of the functional configuration of each node according to this embodiment.

The master

node 110 comprises a client communication section 111 , a schedule processing section 112 , a schedule information storage section 113 , a scale-out processing section 114 , a slave co mmunication section 115 , a rescheduling processing section 116 and a scale shrink processin g section 117 .

[0043]

The client communication unit 111 receives a processing request from the client 200 . If the processing of the received request is executable within the system 100, the client communicat ion unit 111 passes it to the schedule processing unit 112. FIG. If the processing of the receiv ed request cannot be processed within the system 100, the client communication unit 111 res ponds to that effect to the client 200. FIG. Processes that cannot be executed within the syste m 100 include, for example, application processes that are not present in the slave node 120 and large-scale processes that cannot be completed by the slave node 120 of one virtual mac hine by the due date. The technique of distributing and executing large-scale processing on a plurality of nodes is outside the scope of the technique according to the present embodiment, and will not be described here. The client communication unit 111 notifies the client 200 of th e processing result received from the slave node 120 . When the client communication unit 1 11 receives a processing request with a specified delivery date, the schedule processing unit 1 12 refers to the management information stored in the schedule information storage unit 113 and slaves the task of the processing request

.

Run the simulation assigned to node 120 .

[0045]

The schedule information storage unit 113 is a management information storage unit for ma naging tasks executed by the slave nodes 120 provided in the system 100 . The management information stored in the schedule information storage unit 113 records schedules of tasks to be executed by all the slave nodes 120 .

More

specifically, the schedule processing unit 112 first detects the slave node 120 that can compl ete the processing of the received processing request within the specified delivery date in the current state. Here, the schedule processing unit 112 not only selects the slave nodes 120 tha t can immediately execute the processing, but also the slave nodes 120 that can complete the processing within the deadline even if the processing request task is executed after the proces sing of other tasks is completed. To detect. The schedule processing unit 112 selects the slave node 120 to which the task of the processing request is to be assigned from among the slave nodes 120 detected here. Note that the locked slave node 120 is excluded from detection her e. In the present embodiment, locking refers to setting the slave node 120 as a non-allocation target for the task of the processing request.

[0047]

In the current state, if there is no slave node 120 that can complete the processing of the requested task within the deadline, the schedule processing unit 112 detects a task that can complete the processing within the deadline even if the task is moved to another slave node 120. . By moving the detected task, the schedule processing unit 112 determines whether or not the slave node 120 capable of completing the processing of the requested task within the delivery date can be prepared. If it is determined that by moving the task, the slave node 120 capable of completing the processing of the task requested by the deadline can be prepared, the schedule processing unit 112 performs the process of moving the task to another slave node 120 as follows: It is executed via the slave communication unit 115 . The task may be moved by, for example, stopping the processing of the task at the source slave node 120 and restarting it at the destination slave node 120. A method of transferring data to the destination slave node 120 may also be used. In this embodiment, the task is moved by a method of restarting the processing of the task in the destination slave node 120 . Schedule processing unit 11
In step 2, the slave node 120 that has become free due to the movement of the task is determined as the target slave node 120 to which the task of the processing request is to be assigned. If the schedule processing unit 112 cannot prepare a slave node 120 capable of completing the processing of the requested task within the delivery date even if the task is moved, the schedule processing unit 112 unlocks the locked slave node 120 if any

.

For example, it is determined whether the processing of the requested task can be completed within the deadline. When it is determined that the processing of the requested task can be completed within the due date by unlocking, the schedule processing unit 112 unlocks the locked slave node 120 . The schedule processing unit 112 determines the unlocked slave node 120 as the target slave node 120 to which the task of the processing request is to be assigned.

[0049]

If the slave node 120 to which the task of the processing request is to be assigned is not found in the processing up to this point, the schedule processing unit 112 determines that the slave node 120 should be added to the system 100 by scale-out.

The scale-out processing unit 114 performs processing for

adding computer nodes to the system 100 by scale-out. More specifically, the scale-out processing unit 114 accesses the management computer on the IaaS side using an interface prepared by the IaaS side and requests scale-out to the own system 100 .

[0051]

The slave communication unit 115 communicates with the slave node 120 . For example, the slave communication unit 115 requests the slave node 120 to which the task of the received processing request is to be assigned to process the task. The slave communication unit 115 also receives the processing result of the requested task from the slave node 120 as a response. When a task is moved, the slave communication unit 115 notifies the source slave node 120 of the stop of the task, and notifies the destination slave node 120 of the execution of the task.

. The rescheduling processing unit 116, for example, periodically refers to the management i nformation stored in the schedule information storage unit 113, and targets slave nodes 120 t hat do not have tasks to be executed

. The rescheduling processing unit 116 also refers to the management information stored in the schedule information storage unit 113 and executes a simulation of migrating a task runni ng on a certain slave node 120 to another slave node 120 . . The rescheduling processing unit 116 detects tasks that can be completed within the deadline even if they are moved to anothe r slave node 120 . [0054]

The rescheduling processing unit 116 determines whether or not the slave node 120 having no task to be executed can be prepared by moving the detected task. If it is determined that a slave node 120 that does not have a task to be executed can be prepared by moving the tas k, the rescheduling processing unit 116 transfers the task to another slave node 120 via the sl ave communication unit 115. to run. The movement of tasks is the same as in the case of the schedule processing unit 112 described above. The rescheduling unit 116 targets the slave no de 120, which no longer has tasks to be executed due to the movement of tasks, for scale shr ink.

The rescheduling processing unit 116 also determines whether or not it

is possible to prepare a slave node 120 in which the number of tasks to be executed is equal to or less than a predetermined number by moving the detected tasks. If it is determined that a slave node 120 can be prepared in which the number of tasks to be executed by task move ment is equal to or less than a predetermined number, the rescheduling processing unit 116 p erforms the process of moving the corresponding task to another slave node 120 via slave co mmunication. 115. Reschedule processing part

116 sets a lock on the slave node 120 for which the number of tasks to be executed due to ta sk movement is equal to or less than a predetermined number. As a general rule, the locked sl ave node 120 is not assigned a task with a new processing request, so it becomes the target of scale shrink after the processing of the remaining tasks is completed. The scale shrink pro cessing unit 117 performs processing for deleting the target slave node 120 from the system 100 by scale shrink

.

More specifically, the scale shrink processing unit 117 uses an interface prepared by the IaaS side to access the management computer on the IaaS side and request scale shrinking of the target slave node 120 . The slave node 120 has a master communication section 121 and an application 122

.

As shown in FIG. 4, the slave node 120 can run multiple types of applications 122a, b, . When the task of the processing request is assigned, the task processing is executed by the applicati on 122 corresponding to the processing request.

[0058]

The master communication unit 121 communicates with the master node 110 . For example, the master communication unit 121 receives a task execution request or a stop request from t he master node 110, and performs processing for starting or stopping task execution. Further, when task processing is completed, the master communication unit 121 returns a processing r esult response to the master node 110 .

FIG.

5 is a diagram showing an example of a virtual machine system that implements a node acc ording to this embodiment.

[0060]

The virtual machine system shown in FIG. 5 is, for example, a system in which one or more virtual machines operate on one physical machine. In the example of the virtual machine syst em shown in FIG. 5, a plurality of virtual machines 30 including a master node 110 and slave nodes 120 are operating using the resources of the computer 10, which is a physical machine, such as the CPU 11 and memory 12. . In the virtual machine system shown in FIG. 5, the ma ster node 110 and slave nodes 120 are realized by the same physical machine, but in a cloud computing environment, the master node 110 and each slave node 120 are different. It is ofte n implemented on a physical machine.

In the virtual machine system shown in FIG .

5, the hypervisor 20 is software that implements a virtual environment using the computer 1 0 . A virtual machine 30 including the master node 110 and slave node 120 can be constructe d on the hypervisor 20 . The computer 10, which implements the master node 110 and slave node 120 shown in FIG

.

, an input device 16, an output device 17, and other hardware. The storage device 13 is, for e xample, an external storage device such as a HDD (Hard Disk Drive) or an auxiliary storage d evice. The medium reading/writing device 15 is, for example, a CD-R (Compact Disc Recordab le) drive or a DVD-R (Digital Versatile Disc Recordable) drive. The input device 16 is, for exam ple, a keyboard/mouse. The output device 17 is, for example, a display device such as a displ ay. Note that the hardware configuration of the computer 10 can be arbitrarily designed as re quired.

The master node 110, slave node 120, and functional units provided in each node shown in F IG. 4 can be realized by hardware such as the CPU 11 and memory 12 provided in the comput er 10, and software programs . A program executable by the computer 10

The gram is stored in the storage device 13, for example, read out to the memory 12 when ex

ecuted, and executed by the CPU 11. FIG.

The computer 10

can also read a program directly from a portable recording medium and execute processing according to the program. The computer 10 can also execute processing according to the received program every time the program is transferred from the server computer. Furthermore, this program can be recorded in a computer-readable recording medium.

Processing by the master node 110 according to this embodiment will now be described using a

more specific example.

FIGS.

6 to 9 are diagrams for explaining an example of a simulation of assignment of processing request tasks by the schedule processor in the master node of this embodiment.

FIG .

6A shows an example of notation of tasks. In FIG. 6A, solid figures represent task processing. The vertical length of the figure indicating task processing indicates the resource consumption of the task, and the horizontal length indicates the processing time of the task. Also, in FIG. 6A, the right end of the outline figure indicates the due date of the task. The due date is the deadline for completing the processing of the task designated by the client 200 . In the following description, all tasks are represented as shown in FIG. 6(A).

FIG . 6B shows the time t_0

from the client 200. shows the schedule of tasks executed by the slave nodes 120a and 120b included in the system 100 when a processing request is received. As shown in FIG. 6(B), the system 100 has two slave nodes 120 at this time: #a slave node 120a and #b slave node 120b. Note that the schedule information storage unit 113 stores management information in which the schedule of tasks executed by the slave nodes 120 included in the system 100 is converted into data, for example, as shown in the graph of FIG. 6B. In FIG. 6B, the vertical axis of the graph indicates the amount of resources consumed by the slave node, and the horizontal axis indicates the passage of time. t_{-1} to t_3 indicate times at equal intervals.

FIG. 6C

is a diagram showing the task X of the processing request received from the client 200 at time t_0 . As shown in FIG. 6(C), the processing of the processing request task X is indicated by hatching so as to be distinguished from other tasks. As shown in FIG. 6C, the due date of time t3 is specified for task X of the processing request .

[0070]

Note that there are many well-known techniques for estimating the task processing time and resource consumption, such as methods based on past results and theoretical methods, so a detailed description is omitted here. Estimation of the processing time of a task differs depending on the target processing of the task. For example, the image processing time is affected by the image file size. Processing using a database is affected by the number of accesses to th

e database. As for the resource consumption of a task, for example, if a value is determined f or each application 122 that processes the task, that value can be used. The resource consum ption amount may be inquired of the slave node 120 . In addition, various well-known techniq ues can be used.

In the master node 110 , when the schedule processing unit 112 receives a processing reques t, it

first verifies whether the task of the processing request can be assigned to the slave node 1 20 under the current circumstances.

FIG .

7(A) shows the execution of the process request task X at #a so that the process execution i s started at time t0 .

An example of verification assigned to a slave node 120a is shown. Also, FIG. 7B shows an ex ample of verification in which the task X of the processing request is assigned to the #b slave node 120b so as to start processing execution at time t0 . In either case, the resource consum ption of the node exceeds the resource limit of the node, so the verification result is NG.

FIG. 7C

shows an example of verification in which task X requesting processing is scheduled after tas k A#1 executed by slave node 120a of #a, which finishes processing the earliest, is complete d. In this case, the verification result is NG because the processing end time of the processing request task X exceeds the due date t3 . Next, the schedule processing unit 112 performs ver ification to move a task whose processing can be completed by the due date even if the task i s restarted with another task

.

As shown in FIG. 8A, task B#3 executed by the #b slave node 120b can be moved to the #a s lave node 120a in terms of resource consumption. Processing can be completed by the due da te even if the system is restarted. FIG. 8(B) shows an example of verification in which the pro cessing request task X is assigned to the #b slave node 120b whose resource consumption ha s decreased due to the movement of the tasks shown in FIG. 8(A). Even if the task is moved, the resource consumption of the node exceeds the resource limit of the node, so the verificati on result is NG.

[0075]

Since there is no other locked slave node 120 , the schedule processing unit 112 determines that the slave node 120 will be added by the scale-out processing by the scale-out processing unit 114 . FIG. 9 shows a state in which the task X requesting processing is assigned to the # c slave node 120 c added by the scale-out processing unit 114 . As described above, the ma ster node 110 according to the present embodiment performs verification including scheduling in the current state of the slave node 120, and furthermore, even if verification including task migration is performed, the task can be completed within the deadline

.

Scale out only if the task of the processing request cannot be assigned so that the processing is finished. As a result, useless scale-out can be suppressed, so that the system 100 can be o perated efficiently without unnecessary billing.

10 and 11 are diagrams for explaining an

example of task movement simulation by the rescheduling processor in the master node of t his embodiment.

FIG .

10 shows the schedule of tasks executed by the slave nodes 120a, 120b, and 120c of the sy stem 100 at time t0 . As shown in FIG. 10, at this point, the system 100 has three slave node s 120: #a slave node 120a, #b slave node 120b, and #c slave node 120c.

[0079]

First, in the master node 110, the rescheduling processing unit 116 periodically refers to the schedule information storage unit 113 to check whether there is a slave node 120 that has no task to be executed. As shown in FIG. 10, all the slave nodes 120 are executing processing at this point, so there is no slave node 120 that has no task to execute. At this time, the resched uling processing unit 116 determines that there is no slave node 120 that can be scaled down as it is.

Next, the rescheduling processing unit 116 performs verification to move the task that can be completed by the due date even if it

is restarted by another task.

FIG. 11A

shows an example of verification in which task B#1 executed by slave node 120b of #b is re started by slave node 120a of #a. As shown in Figure 11(A), the task

If B#1 is restarted by another slave node 120, the processing end time will exceed the deliver y date t2 , so the verification result will be NG. The rescheduling unit 116 determines that it is not possi ble to move the task and perform scale shrinking on the #b slave node 120b.

FIG. 11B

shows an example of verification in which task C#1 executed by slave node 120c of #c is res tarted by slave node 120a of #a. As shown in FIG. 11B, task C#1 can be completed by the de adline t3 even if the slave node 120a of #a is restarted. Furthermore, when task C#1 is move d to the slave node 120a of #a, there is no task to be executed by the slave node 120c of #C, so scale shrinking can be performed on the slave node 120c of #C. The rescheduling unit 11 6 instructs the #C slave node 120c to stop task C#1 and the #A slave node 120a to execute t ask C#1 via the slave communication unit 115

.

do. Since there are no more tasks to be executed by the #C slave node 120c, the reschedulin g unit 116 targets the #C slave node 120c for scale shrink. The scale shrink processing unit 1 17 executes scale shrink processing for the #C slave node 120c.

[0084]

In this way, the master node 110 according to the present embodiment actively creates slav e nodes 120 that do not have tasks to be executed by moving tasks to other slave nodes 120, and executes scale shrink. As a result, it is possible to positively delete useless slave nodes 12 0, so that it is possible to operate the system 100 efficiently without unnecessary billing. 12 and 13 are diagrams for explaining an example of setting a lock on a slave node by the resche duling processor in the master node of this embodiment

. FIG . 12 shows the schedule of tasks executed by the slave nodes 120a and 120b of the sy stem 100 at time t0 . As shown in FIG. 12, the system 100 has two slave nodes 120 at this ti me: #a slave node 120a and #b slave node 120b. In the master node 110, when the slave no de 120 that has no tasks to be executed cannot be prepared even if the tasks are moved, th e rescheduling processing unit 116 reduces the number of tasks to be executed by moving the tasks to a predetermined number or less. Verifies whether the slave node 120 can be prepare d. For example, the predetermined number is 1 here. FIG. 13A shows an example of verifica tion in which task B#2 executed by the #b slave node 120b is restarted by the #a slave node 120a. As shown in FIG. 13(A), task B#2 has a deadline of t 3 even if the slave node 120a of #a is restarte d.

Processing can be completed by Even if task B#1 executed by slave node 120b of #b is to be restarted by slave node 120a of #a, task B#1 will be moved because the processing end time will exceed the due date t2 . Can not.

Assuming that task B#2 is

moved to #a slave node 120a, as shown in FIG. . At this time, the rescheduling processing u nit 116 instructs the #B slave node 120b to stop the task B#2 and instructs the #A slave nod e 120a to execute the task B#2 via the slave communication unit 115. do.

Also, as shown in FIG. 13(B), a lock is set for the slave node 120b of #b, for which the only task to be executed is B#1 . Information on the slave node 120 that has set the lock is record ed in a storage unit such as the schedule information storage unit 113 that can be accessed b y the schedule processing unit 112 . As a general rule, the #b slave node 120b is not assigne d a new processing request task. can be deleted. As described above, the master node 110 according to the present embodiment moves tasks to other slave nodes 120, actively creates slave nodes 120 with fewer tasks to be executed, and creates new slave nodes 120 for those slave nodes 120

.

Suppress task allocation for processing requests. As a result, the environment of the system 1 00 becomes an environment where it is easy to create slave nodes 120 that do not have tasks to be executed, and it is possible to positively delete useless slave nodes 120, so it is efficient to avoid unnecessary billing. Operation of the system 100 becomes possible.

FIG.

14 is a diagram for explaining an example of unlocking a slave node by the schedule process ing unit in the master node of this embodiment.

[0093]

Here, it is assumed that the system 100 receives a processing request for task X shown in FI G. 6(C) from the client 200 in the state shown in FIG. 13(B). At this time, the schedule proces sing unit 112 attempts to allocate the processing request task X to the unlocked #a slave nod e 120a as shown in FIG. Cannot be allocated because it would exceed the resource limit. Furt hermore, there is no other slave node 120 to which the task can be transferred. At this time, the schedule processing unit 112 verifies whether or not task X requested by the slave node 1 20b of #b can be completed by the due date by unlocking the locked slave node 120b of #b

.

do. As shown in FIG. 14B, the slave node 120b of #b can complete the processing of the task X of the processing request by the due date. is released, and the task X of the processing req uest is assigned to the #b slave node 120b.

As described above, the slave node 120 that is locked is assigned

a task requesting processing only when the task requesting processing cannot be assigned t o another slave node 120 . As a result, it is possible to suppress the occurrence of scale-out w hile maintaining an environment that facilitates scale-shrinking to the very limit, so that the s ystem 100 can be operated efficiently without unnecessary billing.

The master node 110 according to this embodiment gives the highest priority to completing ta sk processing within the deadline, so the system 100

always maintains the minimum processing performance.

[0097]

15 and 16 are processing flowcharts when the master node of this embodiment accepts a pr ocessing request. In the master node 110, the client communication section 111 receives a processing request from a client (step S10)

.

A delivery date is specified in the processing request received here. The client communication unit 111 determines whether the processing request can be accepted (step S11). If the proce ssing request is not acceptable (NO in step S11), the client

The communication unit 111 responds to the client that the processing request cannot be acc epted (step S12), and terminates the processing. If the processing request can be accepted (YES in step S11), the schedule processing unit 112 refers to the management information in the schedule information storage unit 113 and performs a simulation of allocating the task of t

he processing request to the current slave node 120

.

(step S13). Here, for example, verification including scheduling is performed as shown in FIG. The

schedule processing unit 112 determines whether or not it is possible to allocate the task of the processing request to the current slave node 120 (step S14). If the task of the processing request can be assigned (YES in step S14), the schedule processing unit 112 determines the s lave node 120 to which the task of the processing request is assigned (step S15). The slave c ommunication unit 115 requests the determined slave node 120 to process the task of the pro cessing request (step S22).

If it is not possible to assign the task of the processing request (NO in step S14), the schedule processing unit

112 refers to the management information in the schedule information storage unit 113, mo ves the existing task, and A simulation of assigning tasks is performed (step S16). Here, for e xample, as shown in FIG. 8, if there is an existing task that can be completed within the deliv ery date even if it is moved to another slave node 120 and re-executed, the existing task is m oved and resource It is verified whether the task of the processing request can be assigned to the slave node 120 that has become free.

[0102]

The schedule processing unit 112 determines whether it is possible to allocate the task of th e processing request by moving the existing task (step S17). If the task of the processing req uest can be assigned (YES in step S17), the schedule processing unit 112 moves the correspo nding existing task (step S18). More specifically, the schedule processing unit 112 requests, vi a the slave communication unit 115, the slave node 120 from which the existing task is move d to stop the task. Also, the schedule processing unit 112 requests the slave node 120 to whic h the existing task is moved to execute the task via the slave communication unit 115 . The sl ave communication unit 115 requests the slave node 120, whose resource becomes available due to the migration of the existing task, to process the requested task (step S22).

If it is not possible to allocate the task of the processing request (NO in step S17), the schedu le processing unit 112 determines that there is a locked slave node 120 ,

and if the slave node 120 is unlocked, It is determined whether or not the task of the proces sing request can be assigned (step S19). If the lock is released and it becomes possible to all ocate the task of the processing request (YES in step S19), the schedule processing unit 112 unlocks the locked slave node 120 (step S20). The slave communication unit 115 requests the unlocked slave node 120 to process the requested task (step S22). This case is the case show n in the example of FIG.

[0104]

If there is no locked slave node 120 or if it is not possible to allocate the processing request task even if the lock is released (NO in step S19), the scale-out processing unit 114 executes

scale-out processing (step S21). A slave node 120 is added to the system 100 by scale-out. T he slave communication unit 115 requests the added slave node 120 to process the requested task (step S22). This case is the case shown in the example of FIG. The slave communicatio n unit 115 receives a processing result response to the processing request from the slave nod e 120

.

is received (step S23), the client communication unit 111 transmits the response to the client (step S24).

FIG.

17 is a flow chart of rescheduling by the master node of this embodiment. In the master no de 110, the rescheduling processing section 116 starts this processing at a predetermined tim ing

. The rescheduling processing unit 116 refers to the management information in the schedul e information storage unit 113 and determines whether there is a slave node 120 that current ly has no task to be executed (step S30). If there is a slave node 120 that does not have a ta sk to be executed (YES in step S30), the scale shrink processing unit 117 executes scale shrin k processing for that slave node 120 (step S31). The scale shrink removes the slave node 120 from the system 100 . The rescheduling processing unit 116 refers to the management infor mation in the schedule information storage unit 113 and performs a task migration simulation (step S32). Here, for example, as shown in FIG. 11, if there is a task that can be completed w ithin the deadline even if it is moved to another slave node 120 and re-executed, there is no t ask to move and execute the task. It is verified whether the slave node 120 can be created. F or example, as shown in FIG. 13, if there is a task that can be completed within the deadline even if it is moved to another slave node 120 and re-executed, a predetermined number of ta sks are moved and executed. It is verified whether the following slave nodes 120 can be gene rated. [0110]

The rescheduling unit 116 determines whether it is possible to generate a slave node 120 th at does not have a task to be executed by moving the task, that is, whether it is possible to m ove the task and perform scale shrinking (step S33). If scale shrinking becomes possible by m oving the task (YES in step S33), the rescheduling processor 116 moves the task (step S34). More specifically, the rescheduling processing unit 116 requests the slave node 120 from whic h the task is moved to stop the task via the slave communication unit 115 . Also, the resched

uling processing unit 116 requests the slave node 120 to which the task is moved to execute t he task via the slave communication unit 115 . The scale shrink processing unit 117 executes scale shrink processing for the slave node 120 that has no tasks to be executed due to the mo vement of the tasks (step S35). The scale shrink removes the slave node 120 from the syste m 100 . If scale shrinking is not possible even after the task is moved (NO in step S33), the rescheduling processing unit 116 determines that there is a slave node 120 where the number of tasks to be executed by moving the task is less than the predetermined number

.

It is determined whether or not (step S36). If there is no slave node 120 whose number of tas ks to be executed is equal to or less than the predetermined number even after the task is mo ved (NO in step S36), the rescheduling processing unit 116 ends the process.

[0112]

If there is a slave node 120 in which the number of tasks to be executed by migrating tasks i s equal to or less than the predetermined number (YES in step S36), the rescheduling process ing unit 116 migrates the tasks (step S37). More specifically, the rescheduling processing unit 116 requests the slave node 120 from which the task is moved to stop the task via the slave c ommunication unit 115 . Also, the rescheduling processing unit 116 requests the slave node 1 20 to which the task is moved to execute the task via the slave communication unit 115 . The rescheduling processing unit 116 locks the slave node 120 for which the number of tasks to b e executed by moving tasks is less than a predetermined number.

is set (step S38). If all tasks remaining without being unlocked are processed, the slave node 120 to which the lock is set becomes the target of scale shrink in subsequent steps S30 and S 31.

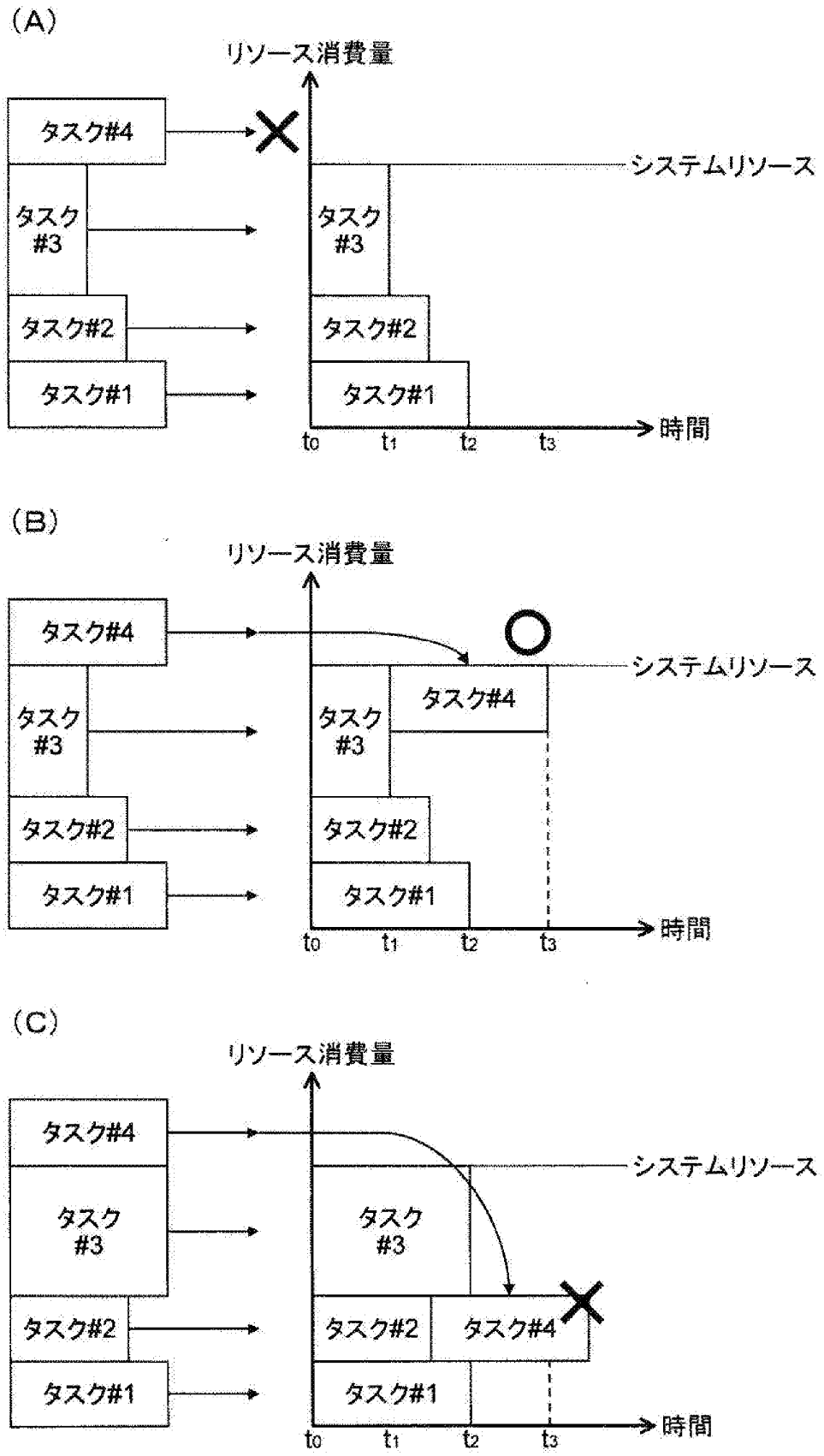
Although the present embodiment has been described above

, it is a matter of course that the present invention can be modified in various ways within th e spirit and scope of the invention. 100

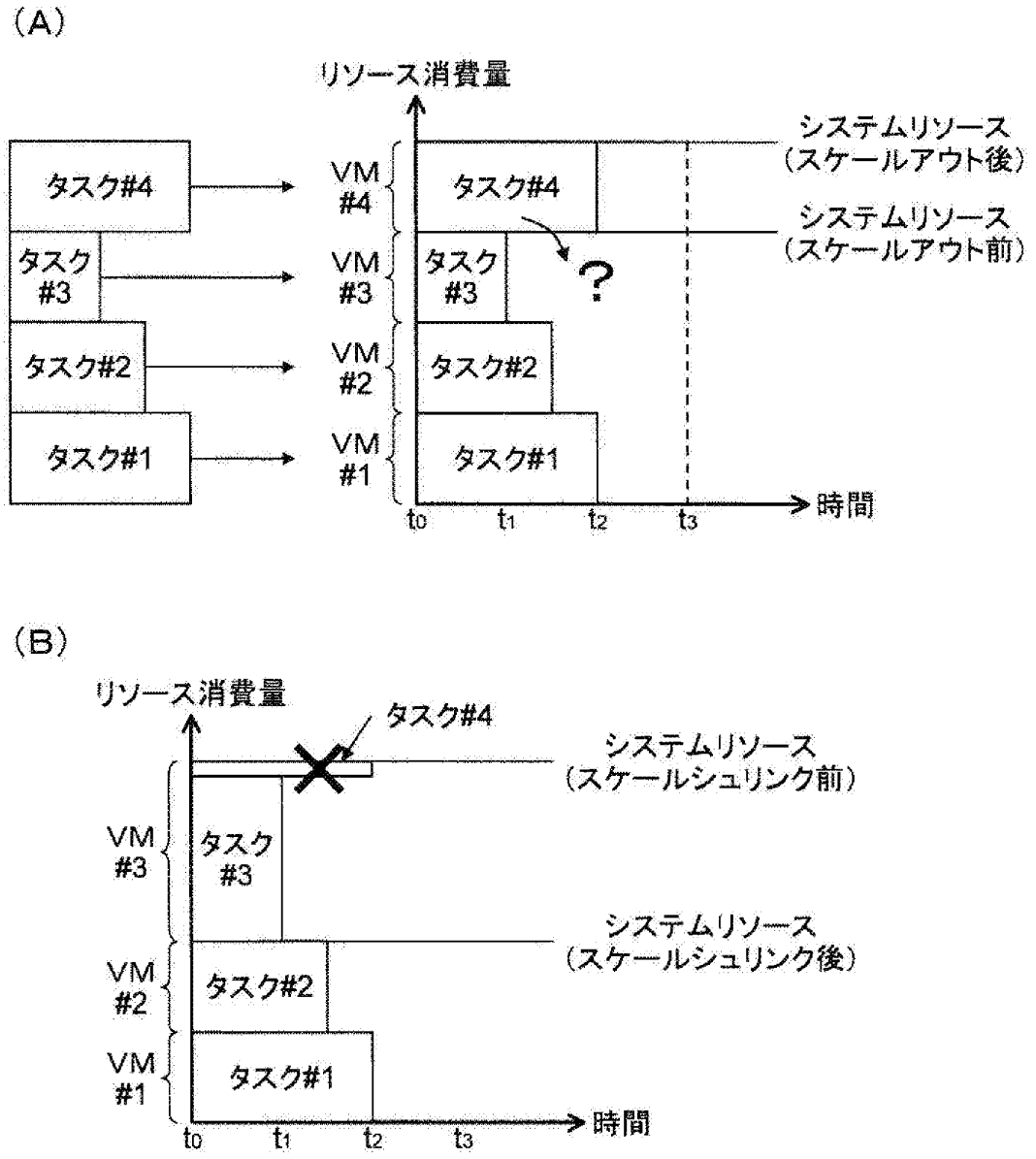
System 110 Master node 111 Client communication unit 112 Schedule processing unit 113 Schedule information storage unit 114 Scale-out processing unit 115 Slave communic ation unit 116 Reschedule processing unit 117 Scale shrink processing unit 120 Slave nod e 121 Master Communication unit 122 Application 200 Client 300 Network

drawing open —

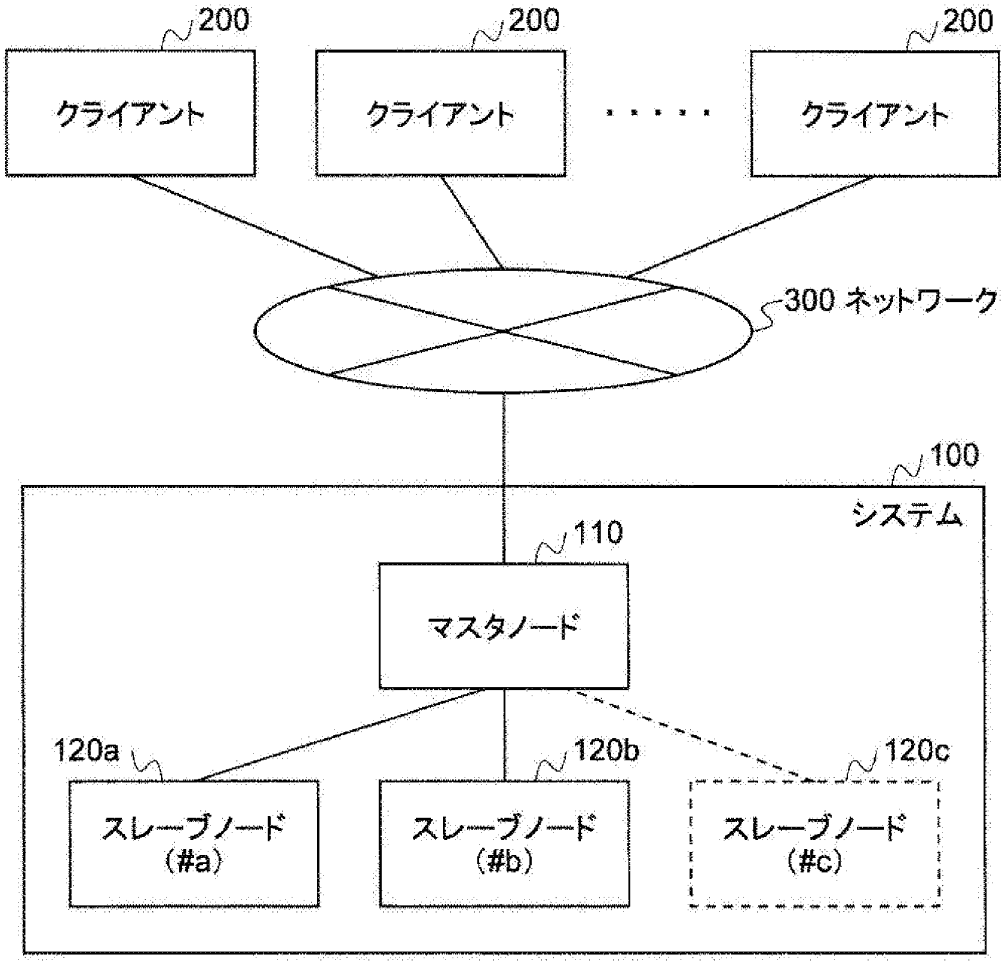
[Fig. 1]


(A)
リソース消費量
タスク#4
タスク#3
タスク#2
タスク#1
システムリソース
タスク#3
タスク#2
タスク#1
時間
t0
t1
t2
t3
(B)
リソース消費量
タスク#4
タスク#3
タスク#2
タスク#1
システムリソース
タスク#4
タスク#3
タスク#2
タスク#1
時間
t0
t1
t2
t3
(C)
リソース消費量
タスク#4
タスク#3
タスク#2
タスク#1
システムリソース
タスク#3
タスク#2
タスク#4
タスク#1
時間
t0
t1
t2
t3

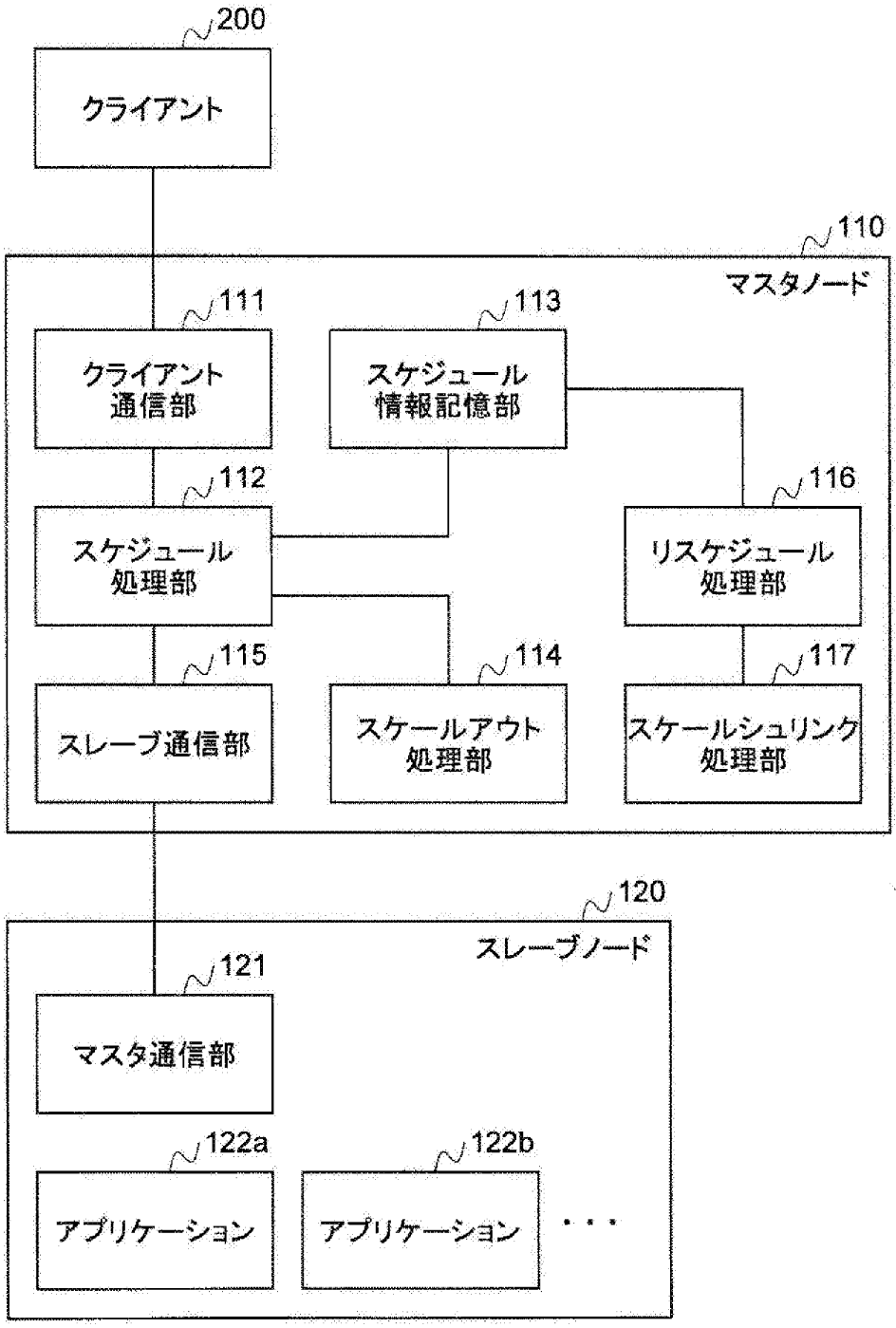
[Figure 2]


(A)
リソース消費量
タスク#4
タスク
#3
タスク#2
タスク#1
VM
#4
VM
#3
VM
#2
VM
#1
タスク#4
タスク
#3
?
タスク#2
タスク#1
システムリソース
(スケールアウト後)
システムリソース
(スケールアウト前)
時間
t0
t1
t2
t3
(B)
リソース消費量
タスク#4
システムリソース
(スケールシュリンク前)
VM
#3
タスク
#3
システムリソース
(スケールシュリンク後)
VM
#2
タスク#2
VM
#1
タスク#1
時間
t0
t1
t2
t3

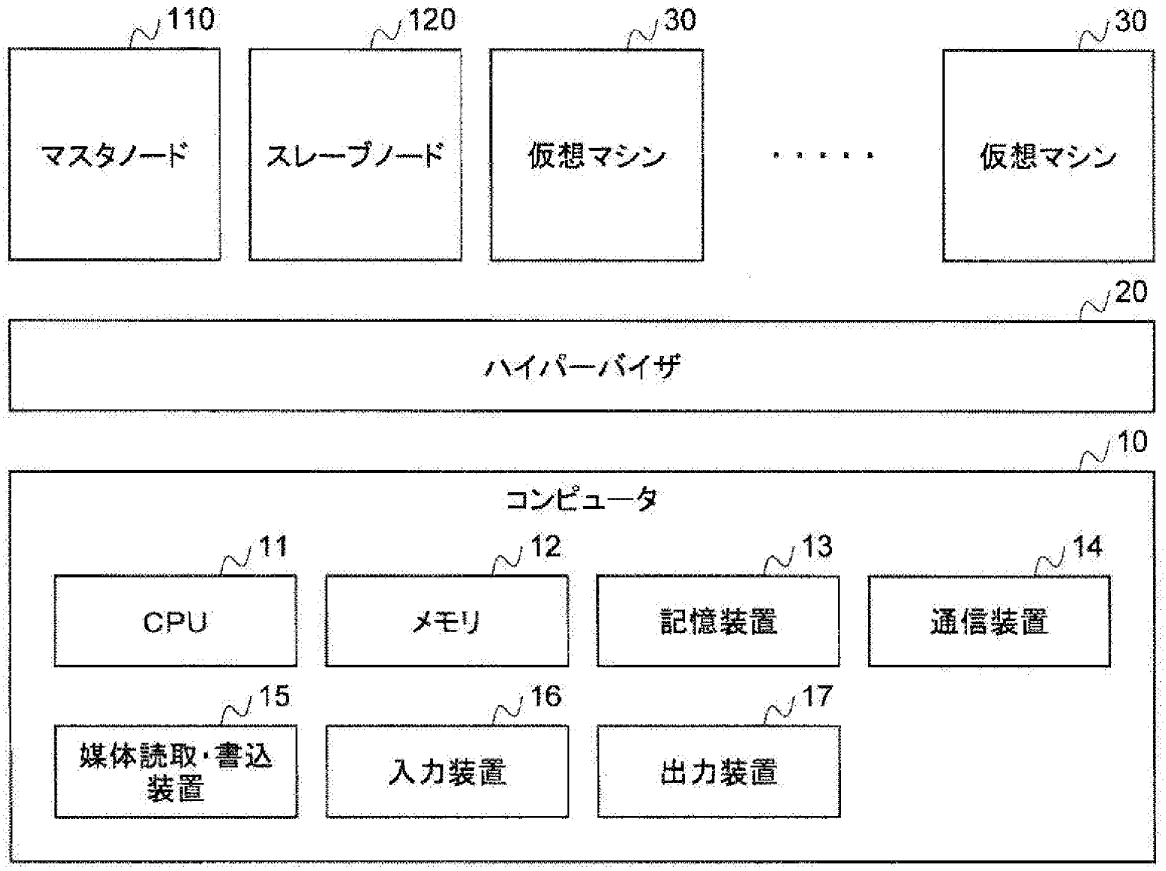
[Figure 3]


200
クライアント
200
クライアント
・・・・・
200
クライアント
300 ネットワーク
100
システム
110
マスタノード
120a
スレーブノード
(#a)
120b
スレーブノード
(#b)
120c
スレーブノード
(#c)

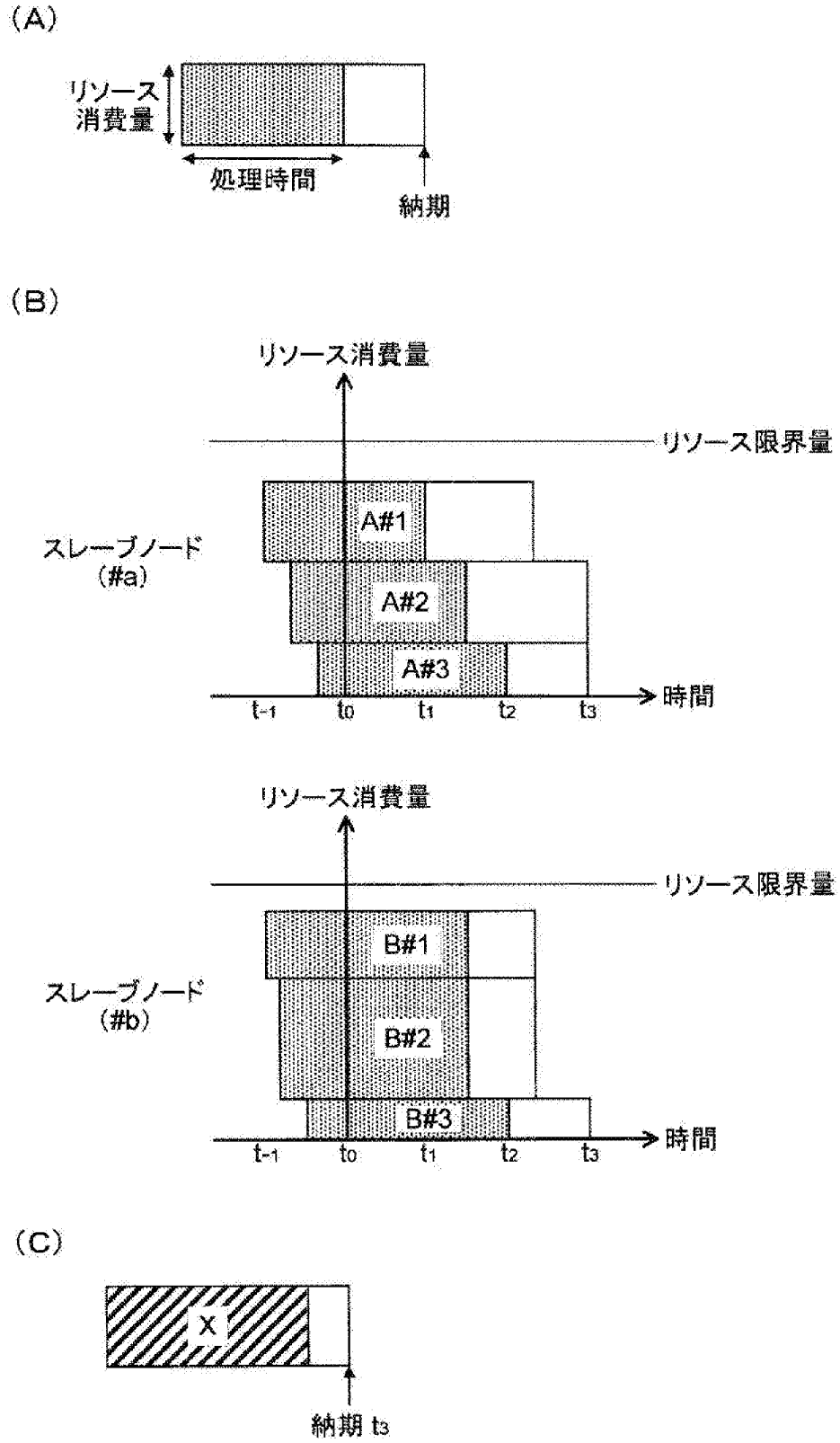
[Figure 4]


200
クライアント
110
マスタノード
111
クライアント
通信部
113
スケジュール
情報記憶部
112
スケジュール
処理部
116
リスケジュール
処理部
115
スレーブ通信部
114
スケールアウト
処理部
117
スケールシュリンク
処理部
120
スレーブノード
121
マスタ通信部
122a
アプリケーション
122b
アプリケーション
・・・

[Figure 5]

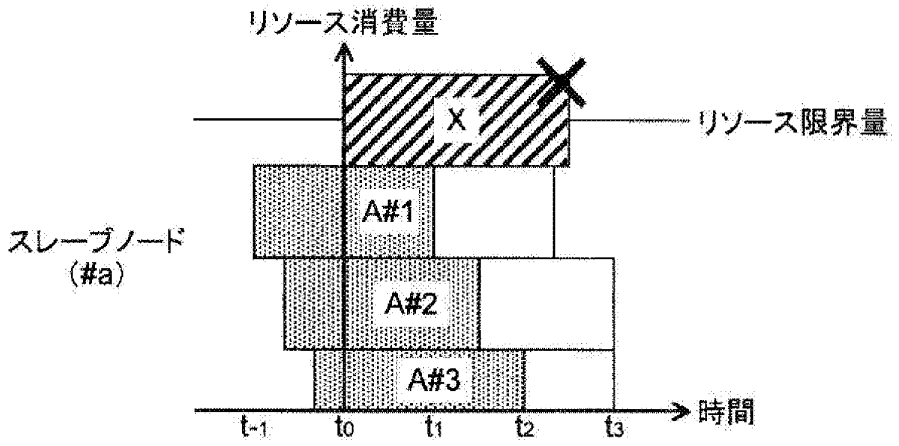

110
120
30
30
マスタノード
スレーブノード
仮想マシン
・・・・・
仮想マシン
20
ハイパーバイザ
10
コンピュータ
11
12
13
14
CPU
メモリ
記憶装置
通信装置
15
16
17
媒体読取・書込装置
入力装置
出力装置

[Fig. 6]

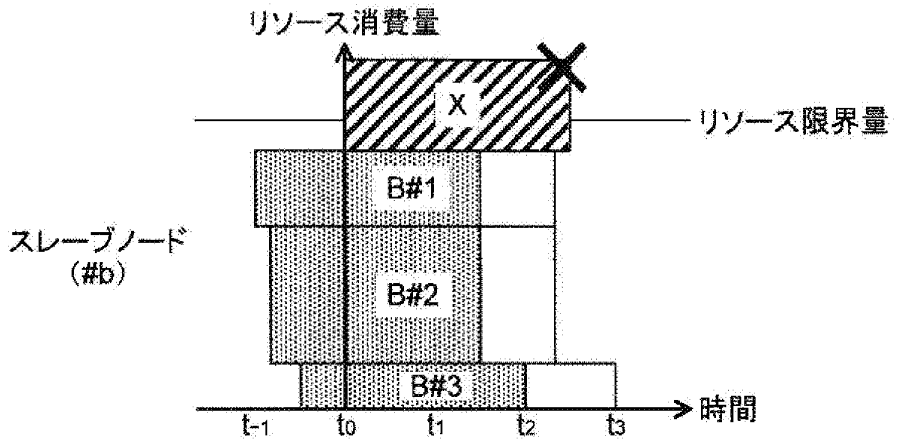

(A)
リソース
消費量
処理時間
納期
(B)
リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
t-1
t0
t1
t2
t3
(C)
X
納期 t3

[Fig. 7]

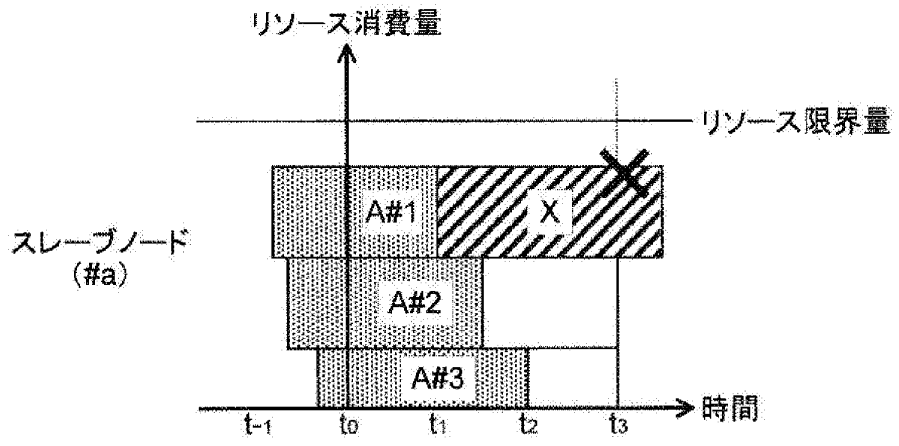
（A）


リソース消費量
X
リソース限界量
スレーブノード
（#a）
A#1
A#2
A#3
時間
t-1
t0
t1
t2
t3

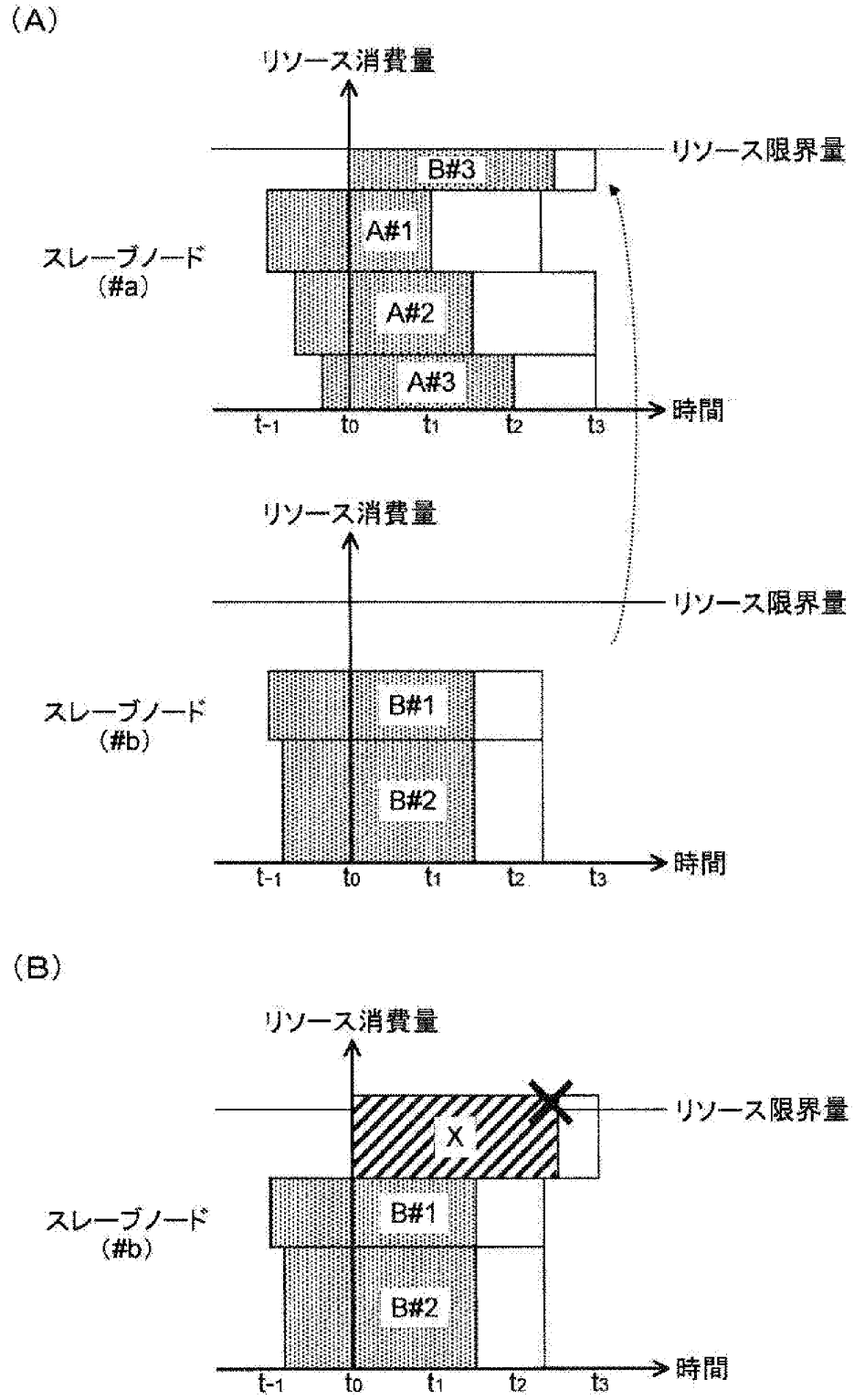
（B）


リソース消費量
X
リソース限界量
スレーブノード
（#b）
B#1
B#2
B#3
時間
t-1
t0
t1
t2
t3

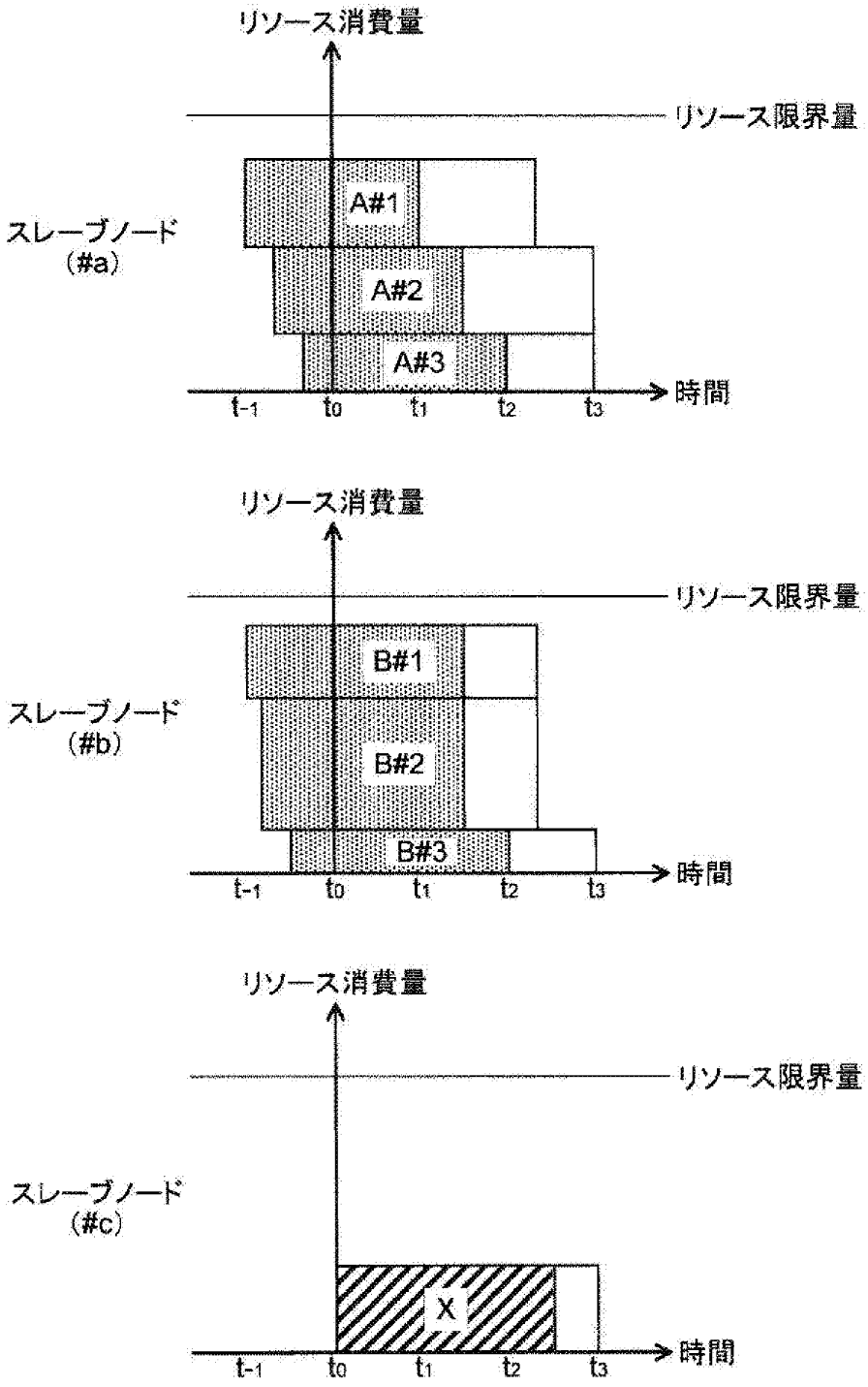
（C）


リソース消費量
リソース限界量
スレーブノード
（#a）
A#1
X
A#2
A#3
時間
t-1
t0
t1
t2
t3

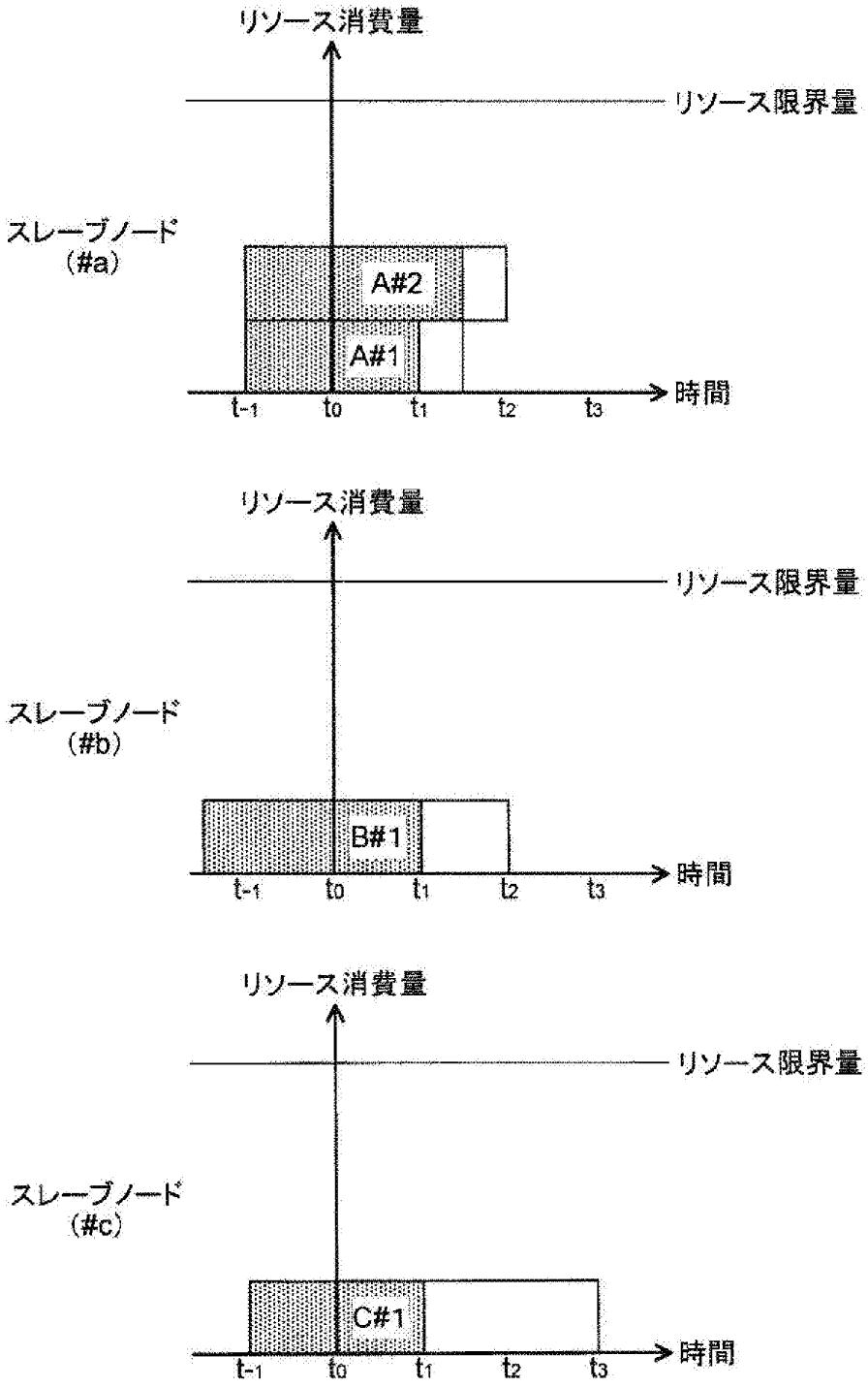
[Fig. 8]


(A)
リソース消費量
リソース限界量
B#3
A#1
スレーブノード
(#a)
A#2
A#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
時間
t-1
t0
t1
t2
t3
(B)
リソース消費量
リソース限界量
X
スレーブノード
(#b)
B#1
B#2
時間
t-1
t0
t1
t2
t3

[Fig. 9]

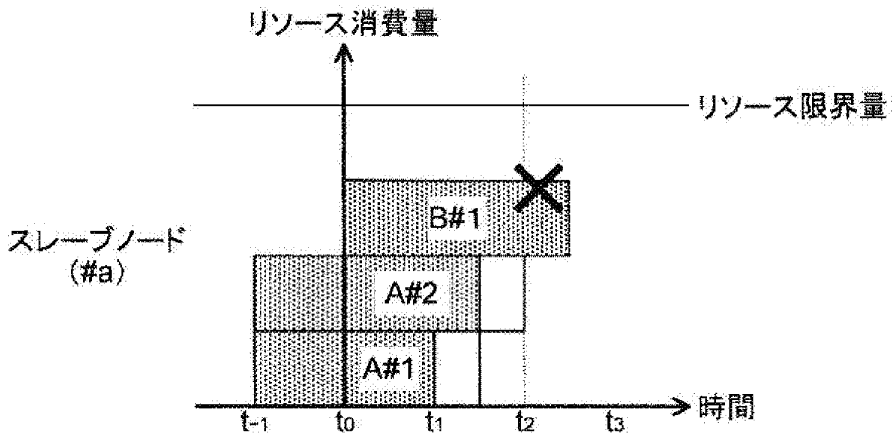

リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#c)
X
時間
t-1
t0
t1
t2
t3

[Fig. 10]

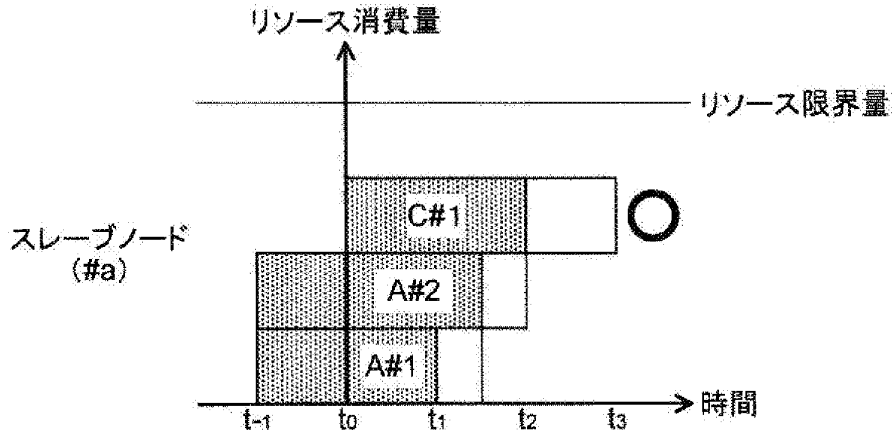

リソース消費量
リソース限界量
スレーブノード
(#a)
A#2
A#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#c)
C#1
時間
t-1
t0
t1
t2
t3

[Fig. 11]

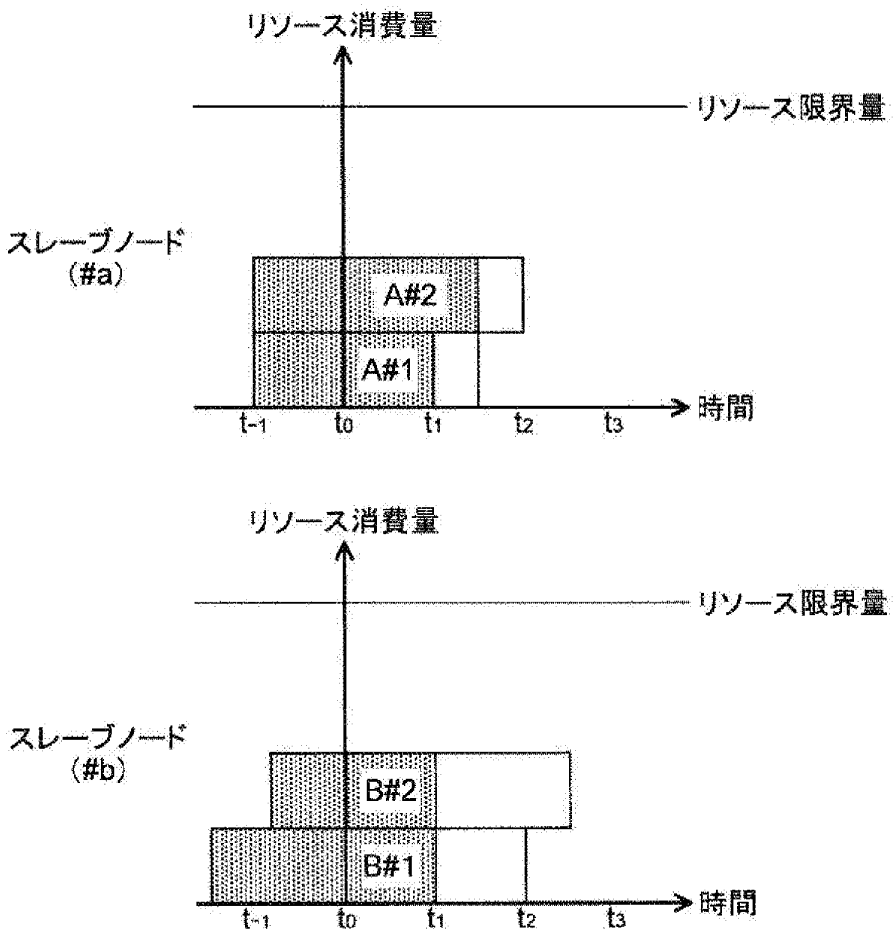
（A）


リソース消費量
リソース限界量
スレーブノード
（#a）
B#1
A#2
A#1
時間
t-1
t0
t1
t2
t3

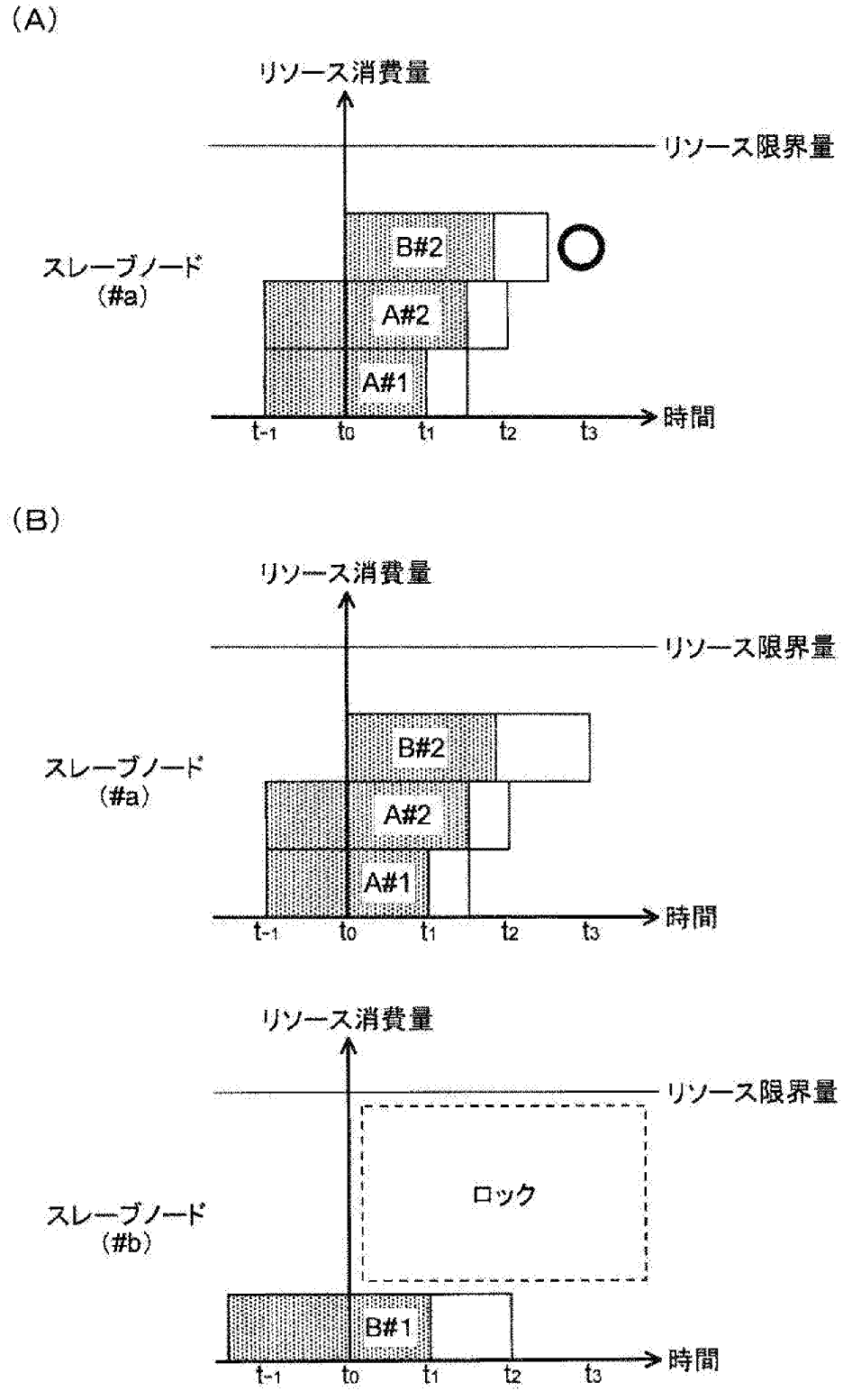
（B）


リソース消費量
リソース限界量
スレーブノード
（#a）
C#1
A#2
A#1
時間
t-1
t0
t1
t2
t3

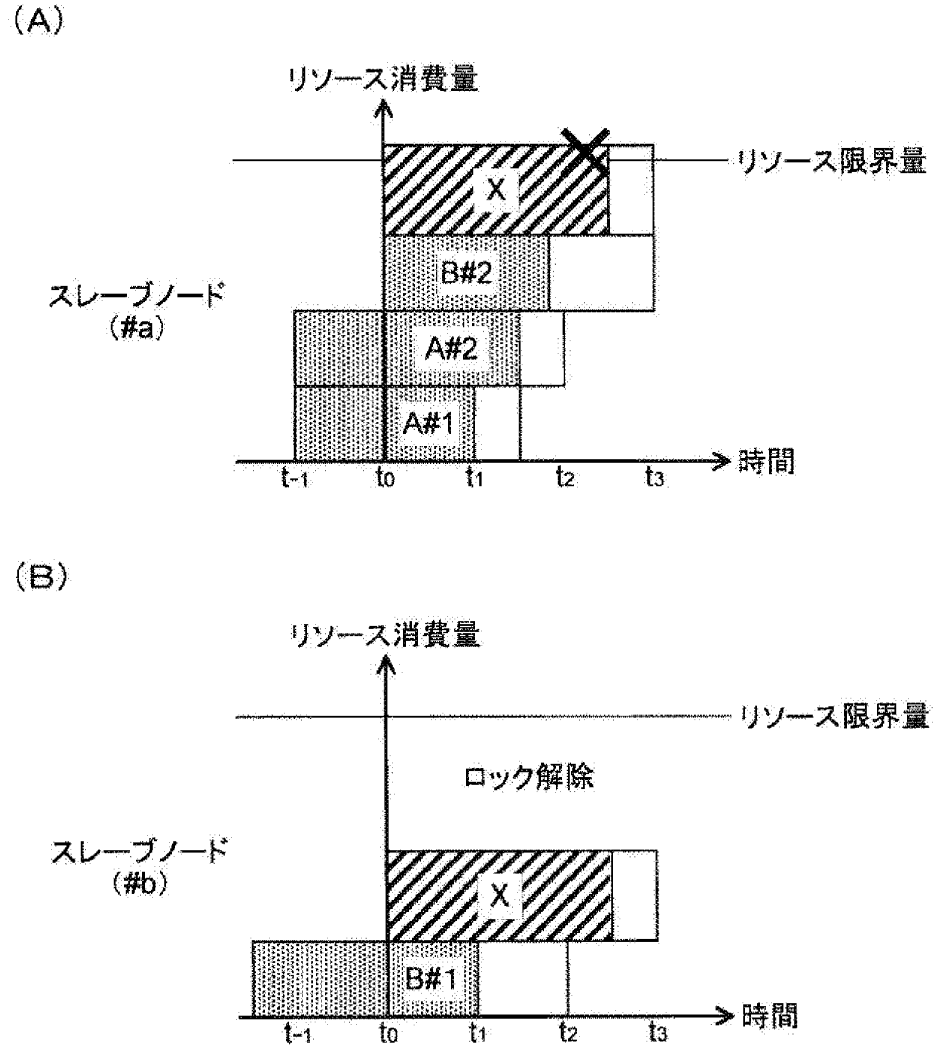
[Fig. 12]


リソース消費量
リソース限界量
スレーブノード
(#a)
A#2
A#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#2
B#1
時間
t-1
t0
t1
t2
t3

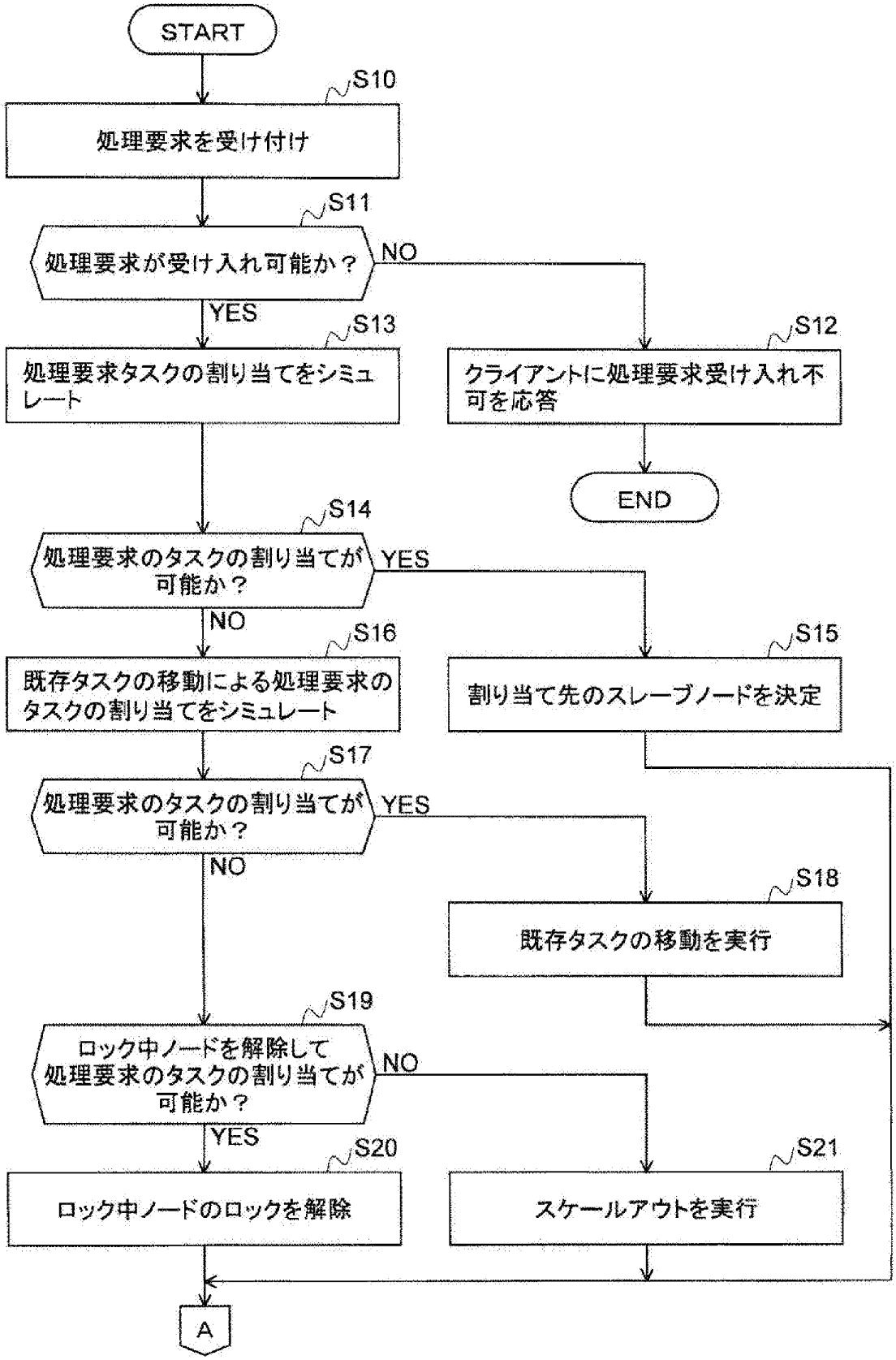
[Fig. 13]


(A)
リソース消費量
リソース限界量
スレーブノード
(#a)
B#2
A#2
A#1
時間
t-1
t0
t1
t2
t3
(B)
リソース消費量
リソース限界量
スレーブノード
(#a)
B#2
A#2
A#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
ロック
スレーブノード
(#b)
B#1
時間
t-1
t0
t1
t2
t3

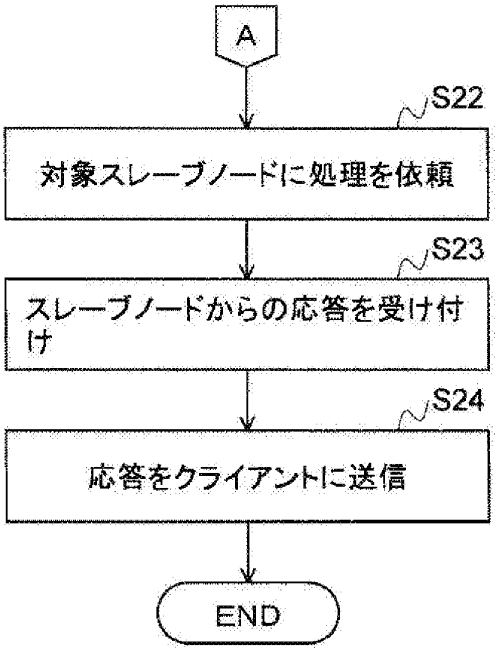
[Fig. 14]


(A)
リソース消費量
リソース限界量
X
B#2
スレーブノード
(#a)
A#2
A#1
時間
t-1
t0
t1
t2
t3
(B)
リソース消費量
リソース限界量
ロック解除
スレーブノード
(#b)
X
B#1
時間
t-1
t0
t1
t2
t3

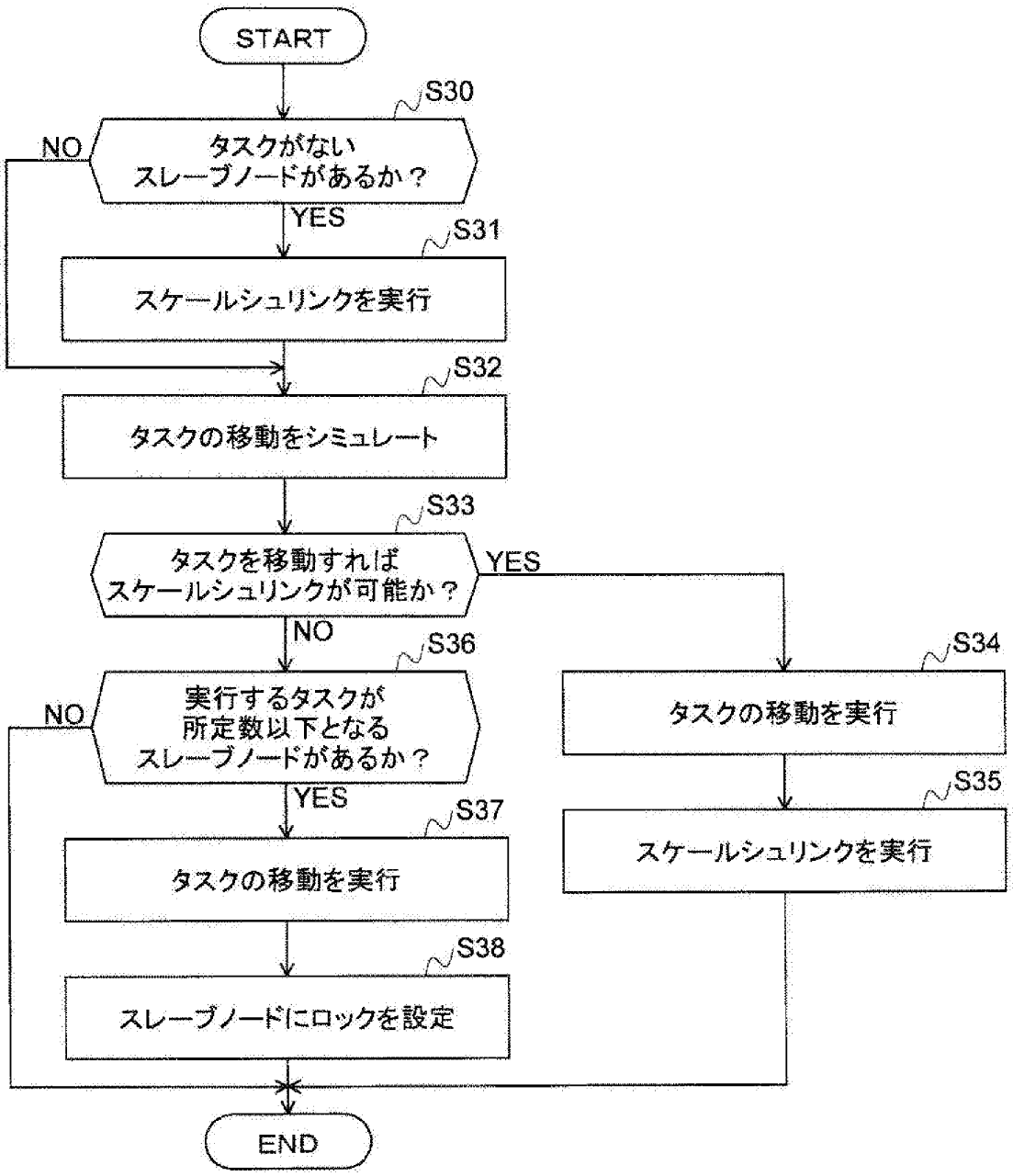
[Fig. 15]


START
S10
処理要求を受け付け
S11
処理要求が受け入れ可能か？
NO
YES
S13
処理要求タスクの割り当てをシミュレート
S12
クライアントに処理要求受け入れ不可を応答
END
S14
処理要求のタスクの割り当てが可能か？
YES
NO
S16
既存タスクの移動による処理要求のタスクの割り当てをシミュレート
S15
割り当て先のスレーブノードを決定
S17
処理要求のタスクの割り当てが可能か？
YES
NO
S18
既存タスクの移動を実行
S19
ロック中ノードを解除して処理要求のタスクの割り当てが可能か？
NO
YES
S20
ロック中ノードのロックを解除
S21
スケールアウトを実行
A

[Fig. 16]


A
S22
対象スレーブノードに処理を依頼
S23
スレーブノードからの応答を受け付け
S24
応答をクライアントに送信
END

[Fig. 17]


START
S30
タスクがない
スレーブノードがあるか？
NO
YES
S31
スケールシュリンクを実行
S32
タスクの移動をシミュレート
S33
タスクを移動すれば
スケールシュリンクが可能か？
YES
NO
S36
実行するタスクが
所定数以下となる
スレーブノードがあるか？
NO
YES
S37
タスクの移動を実行
S38
スレーブノードにロックを設定
S34
タスクの移動を実行
S35
スケールシュリンクを実行
END

drawing open

1 2 3 Four Five 6 7 8 9 Ten ...

Magnify and Rotate

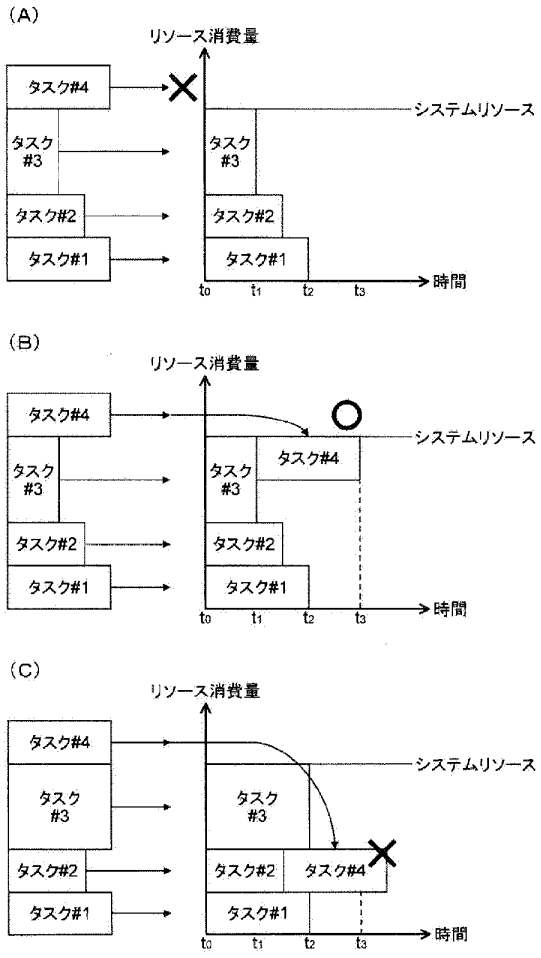


Figure 1

1 / 1 display

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AUTOSCALING METHOD, AUTOSCALING PROGRAM AND COMPUTER NODE

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Abstract of JP2013210683 (A)

PROBLEM TO BE SOLVED: To provide a technology for allowing application of a system with excellent efficiency of charging.SOLUTION: A master node 110 manages tasks to be executed by the respective slave nodes 120. A schedule information storage part 113 stores management information for managing the tasks to be executed by the respective slave nodes 120. A schedule processing part 112 verifies whether or not there is a slave node 120 capable of terminating processing of a task of a processing request in a delivery. In addition, the schedule processing part 112 verifies whether or not a computer node capable of terminating processing of the task of the processing request can be prepared in the delivery when a task whose processing can be terminated even by other computer nodes is moved. As results of verification, when both are negative, a scale out processing part 114 increases the slave nodes 120 by scale out.

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最終頁に続く

(54)【発明の名称】オートスケーリング方法，オートスケーリングプログラムおよびコンピュータノード

(57)【特許請求の範囲】
【請求項１】
要求された処理を複数の仮想化されたコンピュータノードに分散して実行するシステムにおいて，該システムで実行するタスクの管理を行うコンピュータノードが，
納期が指定された処理要求を受け付けた際に，記憶部に記憶された，前記システムが備えるコンピュータノードが実行するタスクを管理する管理情報を参照して，該処理要求のタスクをコンピュータノードに割り当てるシミュレーションを実行し，
前記割り当てのシミュレーションにより，前記処理要求のタスクを納期内に処理終了可能なコンピュータノードがなく，さらに他のコンピュータノードでも納期内に処理終了可能なタスクを移動しても前記処理要求のタスクを納期内に処理終了可能なコンピュータノードを用意できないと判定された場合に，前記システムのコンピュータノードの数を増加する処理を実行する
ことを特徴とするオートスケーリング方法。
【請求項２】
前記タスクの管理を行うコンピュータノードが，さらに，
前記管理情報を参照して，あるコンピュータノードで動作するタスクを，他のコンピュータノードに移動するシミュレーションを実行し，
前記移動のシミュレーションにより，他のコンピュータノードでも納期内に処理終了可能なタスクを移動して，実行するタスクがないコンピュータノードを用意できると判定された場合に，該他のコンピュータノードでも納期内に処理終了可能なタスクを移動し，

実行するタスクがないコンピュータノードを前記システムから削除する処理とを実行する
ことを特徴とする請求項１に記載のオートスケーリング方法。
【請求項３】
前記タスクの管理を行うコンピュータノードが，さらに，
前記移動のシミュレーションにより，他のコンピュータノードでも納期内に処理終了可能なタスクを移動して，実行するタスクの数が所定数以下となるコンピュータノードを用意できると判定された場合に，該他のコンピュータノードでも納期内に処理終了可能なタスクを移動し，
実行するタスクの数が所定数以下のコンピュータノードを処理要求のタスクの割り当て対象外に設定する処理を実行する
ことを特徴する請求項２に記載のオートスケーリング方法。
【請求項４】
前記システムにコンピュータノードを増設する処理では，さらに，前記処理要求のタスクの割り当て対象外に設定されたコンピュータノードの設定を解除しても，前記処理要求のタスクを納期内に処理終了可能なコンピュータノードを用意できないと判定された場合に，前記システムにコンピュータノードを増設する
ことを特徴とする請求項３に記載のオートスケーリング方法。
【請求項５】
要求された処理を複数の仮想化されたコンピュータノードに分散して実行するシステムにおいて，該システムで実行するタスクの管理を行うコンピュータノードに，
納期が指定された処理要求を受け付けた際に，記憶部に記憶された，前記システムが備えるコンピュータノードが実行するタスクを管理する管理情報を参照して，該処理要求のタスクをコンピュータノードに割り当てるシミュレーションを実行し，
前記割り当てのシミュレーションにより，前記処理要求のタスクを納期内に処理終了可能なコンピュータノードがなく，さらに他のコンピュータノードでも納期内に処理終了可能なタスクを移動しても前記処理要求のタスクを納期内に処理終了可能なコンピュータノードを用意できないと判定された場合に，前記システムのコンピュータノードの数を増加する
処理を実行させるためのオートスケーリングプログラム。
【請求項６】
複数の仮想化されたコンピュータノードを備えるシステムにおいて，該システムで実行されるタスクの管理を行うコンピュータノードであって，
前記システムが備えるコンピュータノードが実行するタスクを管理する管理情報の記憶部と，
納期が指定された処理要求を受け付けた際に，前記管理情報を参照して，該処理要求のタスクをコンピュータノードに割り当てるシミュレーションを実行するスケジュール処理部と，
前記スケジュール処理部により，前記処理要求のタスクを納期内に処理終了可能なコンピュータノードがなく，さらに他のコンピュータノードでも納期内に処理終了可能なタスクを移動しても前記処理要求のタスクを納期内に処理終了可能なコンピュータノードを用意できないと判定された場合に，前記システムのコンピュータノードの数を増加する処理を実行するスケールアウト処理部とを備える
ことを特徴とするコンピュータノード。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は，システムが備えるコンピュータノード数を制御するオートスケーリング方法，オートスケーリングプログラムおよびコンピュータノードに関するものである。
【背景技術】

【０００２】
従来のオンプレミスのシステムでは，システムが持つリソース量が固定であったので，そのシステムが持つリソース量を超えて，クライアントからの処理要求を受け付けることができなかった。
【０００３】
これに対して，近年発展しているクラウドコンピューティングを利用したシステムでは，システムが持つリソース量を動的に変更可能である。そのため，クライアントから要求される処理を実行することによってシステムのリソース消費量がシステムが持つリソース量を超えてしまうような場合でも，システムのリソースを動的に増やすことで，クライアントからの要求を受け付け可能となる。
【０００４】
このようなシステムのリソースを増減する技術として，システムにおける仮想化されたコンピュータノードのリソース量を増減するスケールアップ・スケールダウンと呼ばれる技術がある。しかし，仮想化されたコンピュータノードのリソースの増加には，物理マシンのリソース量の限界がある。
【０００５】
システムのリソースを増減する別の技術として，システムにおけるコンピュータノードの数を増減するスケールアウト・スケールシュリンクと呼ばれる技術がある。この技術では，システムのリソース量の増加に，物理マシンのリソース量の限界がない。システムのリソース消費率に応じて自動でスケールアウト・スケールシュリンクを行う，オートスケーリングと呼ばれる技術もある。
【０００６】
なお，分散バッチシステムにおいて，新たなバッチ処理が要求された際に，ある処理サーバで実行中のバッチ処理を他のサーバに移行し，処理可能となったサーバで新しいバッチ処理を実行することで，バッチ処理のデッドラインを管理する技術が知られている。
【先行技術文献】
【特許文献】
【０００７】
【特許文献１】特開２００２－３４２０９８号公報
【発明の概要】
【発明が解決しようとする課題】
【０００８】
しかし，上述のように，システムのリソース消費率に応じてオートスケーリングを行うと，スケールアウトによって無駄なコンピュータノードが増設されたり，誤ったスケールシュリンクによってシステムが実行中の処理が強制的に中断される場合がある。クラウドコンピューティングにおいて，コンピュータノードの数に応じた従量課金が行われる場合には，無駄なスケールアウトによって無駄な課金が発生してしまう場合がある。
【０００９】
一側面では，本発明は，課金の効率がよいシステムの運用が可能となる技術を提供することを目的とする。
【課題を解決するための手段】
【００１０】
１態様では，オートスケーリング方法では，要求された処理を複数の仮想化されたコンピュータノードに分散して実行するシステムにおいて，該システムで実行するタスクの管理を行うコンピュータノードが，納期が指定された処理要求を受け付けた際に，記憶部に記憶されたシステムが備えるコンピュータノードが実行するタスクを管理する管理情報を参照して，該処理要求のタスクをコンピュータノードに割り当てるシミュレーションを実行し，割り当てのシミュレーションにより，処理要求のタスクを納期内に処理終了可能なコンピュータノードがなく，さらに他のコンピュータノードでも納期内に処理終了可能なタスクを移動しても処理要求のタスクを納期内に処理終了可能なコンピュータノードを用

意できないと判定された場合に，システムのコンピュータノードの数を増加する処理を実行する。

【発明の効果】

【００１１】

１態様では，課金の効率がよいシステムの運用が可能となる。

【図面の簡単な説明】

【００１２】

【図１】オンプレミスで実現されるシステムの課題を説明する図である。

【図２】クラウドコンピューティングで実現されるシステムの課題を説明する図である。

【図３】本実施の形態によるシステムの構成例を示す図である。

【図４】本実施の形態による各ノードの機能構成例を示す図である。

【図５】本実施の形態によるノードを実現する仮想マシンシステムの例を示す図である。

【図６】本実施の形態のマスタノードにおけるスケジュール処理部による処理要求のタスクの割り当てシミュレーションの例を説明する図である。

【図７】本実施の形態のマスタノードにおけるスケジュール処理部による処理要求のタスクの割り当てシミュレーションの例を説明する図である。

【図８】本実施の形態のマスタノードにおけるスケジュール処理部による処理要求のタスクの割り当てシミュレーションの例を説明する図である。

【図９】本実施の形態のマスタノードにおけるスケジュール処理部による処理要求のタスクの割り当てシミュレーションの例を説明する図である。

【図１０】本実施の形態のマスタノードにおけるリスケジュール処理部によるタスクの移動シミュレーションの例を説明する図である。

【図１１】本実施の形態のマスタノードにおけるリスケジュール処理部によるタスクの移動シミュレーションの例を説明する図である。

【図１２】本実施の形態のマスタノードにおけるリスケジュール処理部によるスレーブノードにロック設定を行う例を説明する図である。

【図１３】本実施の形態のマスタノードにおけるリスケジュール処理部によるスレーブノードにロック設定を行う例を説明する図である。

【図１４】本実施の形態のマスタノードにおけるスケジュール処理部によるスレーブノードのロック解除を行う例を説明する図である。

【図１５】本実施の形態のマスタノードによる処理要求受け付け時の処理フローチャートである。

【図１６】本実施の形態のマスタノードによる処理要求受け付け時の処理フローチャートである。

【図１７】本実施の形態のマスタノードによるリスケジュールの処理フローチャートである。

【発明を実施するための形態】

【００１３】

以下，本実施の形態について，図を用いて説明する。

【００１４】

図１は，オンプレミスで実現されるシステムの課題を説明する図である。

【００１５】

図１に示す例において，タスクを示す図形の縦の長さは該タスクのリソース消費量を示し，横の長さは該タスクの処理時間を示す。また，図１に示す例において，グラフの縦軸はシステムのリソース消費量を示し，横軸は時間の経過を示す。t_0 ～ t_3 は，等間隔の時刻を示す。

【００１６】

オンプレミスのシステムでは，システムが持つリソースの量は固定となる。すなわち，あらかじめシステムが持つリソース量を超えたリソース消費量の処理を行うことはできない。図１に示す例において，システムリソースのラインは，システムが持つリソースの量

を示す。

【００１７】

例えば，図１（Ａ）において，システムに対して，タスク＃１～タスク＃４の処理要求が，ほぼ同時刻t_0にあったものとする。このとき，システムは，処理要求を受け付けた順，ここではタスク＃１，タスク＃２，タスク＃３，タスク＃４の順に処理を開始する。しかし，図１（Ａ）に示すように，タスク＃３の処理を開始したところで，システムのリソース消費量がシステムが持つリソース量に達してタスク＃４の処理を開始できない状態となり，タスク＃４の処理要求を受け付けられなくなる。

【００１８】

図１（Ｂ）に示す例は，スケジューリングを行うシステムの例である。スケジューリングを行うシステムでは，処理要求を受け付けた時点でタスクの処理時間を見積もり，処理要求が発生した時点でリソースに空きがなくても，実行中の他のタスクの終了後に受け付けた処理要求のタスクを実行するように，タスクのスケジューリングを行う。

【００１９】

例えば，最後に受け付けるタスク＃４の処理の納期が，時刻t_3であるものとする。図１（Ｂ）に示すように，最も処理終了時刻が早いタスク＃３の処理終了時刻がt_1であるので，タスク＃４をタスク＃３の後にスケジュールすれば，タスク＃４の処理終了時刻はt_3となり，納期に間に合う。この場合，タスク＃４の処理要求は，システムで受け付け可能となる。

【００２０】

ところが，図１（Ｃ）に示す例では，最も処理終了時刻が早いタスク＃２の後にタスク＃４をスケジュールすると，タスク＃４の処理終了時刻はt_3を超えてしまい，納期に間に合わない。この場合，タスク＃４の処理要求は，システムで受け付けられない。オンプレミスのシステムでは，スケジューリングを行っても，処理要求を受け付けできない場合がある。

【００２１】

このようなオンプレミスの技術の対極に存在するのが，クラウドコンピューティングの技術である。クラウドコンピューティングによって実現されるシステムのリソース量は，可変となる。

【００２２】

クラウドコンピューティングでは，システムが備える各コンピュータノードが，例えば仮想マシン（ＶＭ：Virtual Machine ）で実現される。なお，以下では，システムが備えるコンピュータノードを，単にノードとも呼ぶ。

【００２３】

クラウドコンピューティングにおいて，システムのリソース量を変更する技術として，例えば，スケールアップ・スケールダウンの技術がある。スケールアップは，ノードのリソース量を増加させる技術である。また，スケールダウンは，ノードのリソース量を減少させる技術である。スケールアップの技術を利用すれば，例えば，現状のリソースでは新たな処理要求のタスクを実行しても納期に間に合わないような場合でも，ノードのリソース量を増加させることで，新たな処理要求のタスクを納期に間に合うように実行できるようになる。

【００２４】

しかし，スケールアップ可能なリソースは，仮想マシンであるノードを実現する物理マシンのリソースが上限となるため，ノードのスケールアップには限界がある。また，通常は１つの物理マシン上に複数の仮想マシンのノードが配置されており，物理マシンのリソースを各ノードに配分しきって余剰がない場合には，他のノードの性能を下げることなく特定のノードの性能を上げることは不可能となる。例えば，マルチテナントの環境では，１つの物理マシン上で複数のテナントの仮想マシンを動作することになり，あるテナントの仮想マシンのリソース量を増やすために，他のテナントのリソース量を減らすといったことは，簡単にはできない。よって，スケールアップの技術を用いても，要求された処理

のタスクをすべて納期を保証して実行できるわけではない。

【００２５】

クラウドコンピューティングにおいて，システムのリソース量を変更する技術として，スケールアップ・スケールダウンの技術以外に，スケールアウト・スケールシュリンクの技術がある。スケールアウトは，システムにノードを増設する技術である。スケールシュリンクは，システムからノードを撤去する技術である。スケールアウトの技術を用いれば，ほぼ確実に要求された処理のタスクをすべて納期を保証して実行できるようになる。

【００２６】

ただし，クラウドコンピューティングの世界では，通常はサービス使用料金が従量制となっており，スケールアウトによってシステムが備えるノードの数が増加するにつれて，サービスの使用料金が増えてしまう。

【００２７】

図２は，クラウドコンピューティングで実現されるシステムの課題を説明する図である。

【００２８】

図２に示す例において，タスクを示す図形の縦の長さは該タスクのリソース消費量を示し，横の長さは該タスクの処理時間を示す。また，図２に示す例において，グラフの縦軸はシステムを構成するノードのリソース消費量の合計を示し，横軸は時間の経過を示す。t_0 ～ t_3 は，等間隔の時刻を示す。図２に示す例において，システムリソースのラインは，システムを構成するノードが持つリソースの量の合計を示す。

【００２９】

図２（Ａ）において，システムは，当初，ＶＭ＃１～ＶＭ＃３の３つのノードを備えているものとする。ここで，システムに対して，タスク＃１～タスク＃４の処理要求が，ほぼ同時刻 t_0 にあったものとする。このとき，システムでは，処理要求を受け付けた順，ここではタスク＃１，タスク＃２，タスク＃３，タスク＃４の順に，ノードにタスクが割り当てられ，処理が開始される。しかし，図２（Ａ）に示すように，ＶＭ＃３のノードにタスク＃３の処理を割り当てたところで，システムのすべてのノードのリソース消費量が上限となり，タスク＃４の処理を割り当て可能なノードがなくなる。

【００３０】

このとき，例えば図２（Ａ）に示すように，システムではスケールアウトが行われ，ＶＭ＃４のノードがシステムに増設される。図２（Ａ）に示すように，スケールアウトによってＶＭ＃４のノードがシステムに増設されることで，要求されたタスク＃４の処理が実行可能となる。例えば，クラウドコンピューティングにおいて，仮想マシンやネットワークなどのインフラをサービスとして提供するＩａａＳ（Infrastructure as a Service）ベンダのサービスとして，システムのリソース消費率が所定以上となったときに自動でスケールアウトを行うサービスがある。クラウドコンピューティングにおいて，自動でシステムの拡張／縮小を行う技術は，オートスケーリングとも呼ばれる。

【００３１】

ここで，タスク＃４の処理の納期が時刻 t_3 であるものとする。図２（Ａ）に示すように，最も処理終了時刻が早いタスク＃３の処理終了時刻が t_1 であるので，タスク＃４をタスク＃３の後にスケジュールすれば，タスク＃４の処理終了時刻は t_3 となり，納期に間に合う。

【００３２】

このように，タスクのスケジューリングを行うことができれば，スケールアウトによりＶＭ＃４のノードを増設しなくても，納期に間に合うようにタスク＃４の処理を実行することが可能であった。しかし，このような判断は，上述のＩａａＳのサービスのようにリソース消費を見ただけではできない。上述したように，クラウドコンピューティングでは，ノードが増えるごとに使用料金が増えるため，ノードを増設しなくても納期に間に合うようにタスクの処理を実行できるのであれば，ノードを増設したくないという要望がある。

【００３３】
また，無駄なノードの使用料金を抑えるために，システムで運用されていないと判断されるノードに対するスケールシュリンクが行われ，該ノードがシステムから撤去される。例えば，クラウドコンピューティングにおいて，ＩａａＳベンダのサービスとして，ノードのＣＰＵ（Central Processing Unit ）使用率が所定以下となったときに，該ノードではタスクの処理が行われておらずＯＳなどのミドルウェアしか動作していないと判断し，自動でスケールシュリンクを行うサービスがある。
【００３４】
だだし，ノードのリソース消費量が少ないからといって，必ずしも要求されたタスクの処理が行われていないとは限らない。たとえば，図２（Ｂ）に示す例において，ＶＭ＃３のノードでは，タスク＃３の処理が終了すると，リソース消費量が極端に減ってしまう。しかし，図２（Ｂ）に示す例において，ＶＭ＃３のノードでは，タスク＃３と並列にリソース消費量が少ないタスク＃４が実行されている。タスク＃３の処理の終了と同時にＶＭ＃３のノードに対するスケールシュリンクが行われると，タスク＃４の処理が強制終了されてしまう。このように，上述のＩａａＳベンダのサービスのようにリソース消費を見ただけでスケールシュリンクを判断すると，例えば，図２（Ｂ）に示すタスク＃４のようにリソース消費量が少ないタスクの処理を実行中であるノードを，誤って撤去してしまう可能性がある。
【００３５】
以下では，このような問題の解決を図った本実施の形態によるオートスケーリングの技術を説明する。
【００３６】
図３は，本実施の形態によるシステムの構成例を示す図である。
【００３７】
本実施の形態において，図３に示すシステム１００は，クラウドコンピューティングにおいて，ＩａａＳ側から提供される仮想マシンのノードから構成されるコンピュータシステムであるものとする。システム１００は，クライアント２００から要求された処理を，複数のノードで分散して実行する。システム１００とクライアント２００とは，ＬＡＮ（Local Area Network）やインターネットなどのネットワーク３００で接続されている。システム１００は，マスタノード１１０，スレーブノード１２０を備える。
【００３８】
マスタノード１１０は，クライアント２００からの処理要求を受け付け，各スレーブノード１２０に対するタスクの割り当てや，システム１００で実行するタスクの管理を行う。なお，本実施の形態によるマスタノード１１０は，スレーブノード１２０のスケールアウトやスケールシュリンクなどのオートスケーリングの処理を行う。なお，マスタノード１１０が，同時にスレーブノード１２０の１つであってもよい。
【００３９】
スレーブノード１２０は，マスタノード１１０から割り当てられた処理要求のタスクを実行するコンピュータノードである。スレーブノード１２０は，複数のタスクの並列処理が可能である。スレーブノード１２０は，オートスケーリングの処理によって，システム１００に増設，またはシステム１００から削除される。例えば，図３において，＃ａのスレーブノード１２０ａと＃ｂのスレーブノード１２０ｂがタスクの処理を実行している場合に，それらのスレーブノード１２０で実行しきれない処理要求があれば，＃ｃのスレーブノード１２０ｃがシステム１００に増設される。また，たとえば，＃ｃのスレーブノード１２０ｃが実行するタスクがなくなれば，＃ｃのスレーブノード１２０ｃがシステム１００から削除される。
【００４０】
クライアント２００は，システム１００に対して，システム１００が提供する処理の実行要求を行う上位アプリケーションを有するコンピュータである。なお，図１に示す例では，クライアント２００がシステム１００外部の装置となっているが，例えばクライアン

ト２００がシステム１００内部のノードであってもよい。

【００４１】

図４は，本実施の形態による各ノードの機能構成例を示す図である。

【００４２】

マスタノード１１０は，クライアント通信部１１１，スケジュール処理部１１２，スケジュール情報記憶部１１３，スケールアウト処理部１１４，スレーブ通信部１１５，リスケジュール処理部１１６，スケールシュリンク処理部１１７を備える。

【００４３】

クライアント通信部１１１は，クライアント２００からの処理要求を受け付ける。クライアント通信部１１１は，受け付けた要求の処理がシステム１００内で実行可能なものであれば，スケジュール処理部１１２に渡す。クライアント通信部１１１は，受け付けた要求の処理がシステム１００内で処理実行不可能なものであれば，その旨をクライアント２００に応答する。システム１００内で処理実行不可能な処理は，例えばスレーブノード１２０にないアプリケーションの処理や，１仮想マシンのスレーブノード１２０では納期までに終了できない大規模な処理などである。大規模な処理を，複数のノードで分散して実行する技術については，本実施の形態による技術の範囲外であるので，ここでは説明を行わない。クライアント通信部１１１は，スレーブノード１２０から受け取った処理結果をクライアント２００に通知する。

【００４４】

スケジュール処理部１１２は，クライアント通信部１１１が納期が指定された処理要求を受け付けた際に，スケジュール情報記憶部１１３に記憶された管理情報を参照して，該処理要求のタスクをスレーブノード１２０に割り当てるシミュレーションを実行する。

【００４５】

スケジュール情報記憶部１１３は，システム１００が備えるスレーブノード１２０が実行するタスクを管理する管理情報の記憶部である。スケジュール情報記憶部１１３に記憶された管理情報には，すべてのスレーブノード１２０で実行するタスクのスケジュールが記録されている。

【００４６】

より具体的には，スケジュール処理部１１２は，まず，現行の状態で，受け付けた処理要求のタスクを，指定された納期内に処理終了可能なスレーブノード１２０の検出を行う。ここでは，スケジュール処理部１１２は，即時に処理実行可能なスレーブノード１２０だけではなく，他のタスクの処理終了後に処理要求のタスクを実行しても，納期内に処理終了可能なスレーブノード１２０も検出する。スケジュール処理部１１２は，ここで検出されたスレーブノード１２０から，処理要求のタスクを割り当てるスレーブノード１２０を選択する。なお，ここでは，ロック中のスレーブノード１２０については，検出の対象外とする。本実施の形態において，ロックは，スレーブノード１２０を，処理要求のタスクの割り当て対象外に設定することをいう。

【００４７】

スケジュール処理部１１２は，現行の状態で処理要求のタスクを納期内に処理終了可能なスレーブノード１２０がなければ，他のスレーブノード１２０に移動しても納期内に処理終了可能なタスクを検出する。スケジュール処理部１１２は，検出されたタスクを移動することで，処理要求のタスクを納期内に処理終了可能なスレーブノード１２０を用意できるかを判定する。タスクを移動することで処理要求のタスクを納期内に処理終了可能なスレーブノード１２０を用意できると判定される場合，スケジュール処理部１１２は，該当タスクを他のスレーブノード１２０に移動する処理を，スレーブ通信部１１５を介して実行する。タスクの移動は，例えば該タスクの処理を移動元のスレーブノード１２０で停止し，移動先のスレーブノード１２０で再起動させる方法でもよいし，移動元のスレーブノード１２０における該タスクの実行中のイメージデータを移動先のスレーブノード１２０に転送する方法でもよい。本実施の形態では，該タスクの処理を移動先のスレーブノード１２０で再起動させる方法でタスクの移動を行うものとする。スケジュール処理部１１

２は，タスクの移動により空きができたスレーブノード１２０を，処理要求のタスクを割り当てる対象のスレーブノード１２０に決定する。

【００４８】

スケジュール処理部１１２は，タスクを移動しても処理要求のタスクを納期内に処理終了可能なスレーブノード１２０を用意できない場合，ロック中のスレーブノード１２０があれば，そのロックを解除すれば，処理要求のタスクを納期内に処理終了可能であるかを判定する。ロック解除により，処理要求のタスクを納期内に処理終了可能となると判定される場合には，スケジュール処理部１１２は，ロック中のスレーブノード１２０のロックを解除する。スケジュール処理部１１２は，ロックを解除したスレーブノード１２０を，処理要求のタスクを割り当てる対象のスレーブノード１２０に決定する。

【００４９】

スケジュール処理部１１２は，ここまでの処理で，処理要求のタスクを割り当てる対象のスレーブノード１２０が見つけられなかった場合，スケールアウトにより，システム１００にスレーブノード１２０を増設すると判断する。

【００５０】

スケールアウト処理部１１４は，スケールアウトによって，システム１００にコンピュータノードを増設する処理を行う。より具体的には，スケールアウト処理部１１４は，ＩａａＳ側で用意しているインタフェースを用いて，ＩａａＳ側の管理コンピュータにアクセスし，自システム１００へのスケールアウトを要求する。

【００５１】

スレーブ通信部１１５は，スレーブノード１２０との通信を行う。例えば，スレーブ通信部１１５は，受け付けた処理要求のタスクを割り当てる対象のスレーブノード１２０に対して，該タスクの処理を依頼する。また，スレーブ通信部１１５は，スレーブノード１２０から，依頼したタスクの処理結果を応答として受け付ける。また，スレーブ通信部１１５は，タスクの移動が行われる際に，移動元のスレーブノード１２０に対して該当タスクの停止を通知し，移動先のスレーブノード１２０に対して該当タスクの実行を通知する。

【００５２】

リスケジュール処理部１１６は，例えば定期的に，スケジュール情報記憶部１１３に記憶された管理情報を参照し，実行するタスクがないスレーブノード１２０を，スケールシュリンクの対象とする。

【００５３】

また，リスケジュール処理部１１６は，スケジュール情報記憶部１１３に記憶された管理情報を参照して，あるスレーブノード１２０で動作するタスクを，他のスレーブノード１２０に移動するシミュレーションを実行する。リスケジュール処理部１１６は，他のスレーブノード１２０に移動しても納期内に処理終了可能なタスクを検出する。

【００５４】

リスケジュール処理部１１６は，検出されたタスクを移動することで，実行するタスクがないスレーブノード１２０を用意できるかを判定する。タスクを移動することで実行するタスクがないスレーブノード１２０を用意できると判定される場合，リスケジュール処理部１１６は，該当タスクを他のスレーブノード１２０に移動する処理を，スレーブ通信部１１５を介して実行する。タスクの移動については，上述のスケジュール処理部１１２の場合と同様である。リスケジュール処理部１１６は，タスクの移動により実行するタスクがなくなったスレーブノード１２０を，スケールシュリンクの対象とする。

【００５５】

また，リスケジュール処理部１１６は，検出されたタスクを移動することで，実行するタスクの数が所定数以下となるスレーブノード１２０を用意できるかを判定する。タスクの移動により実行するタスクの数が所定数以下となるスレーブノード１２０を用意できると判定される場合，リスケジュール処理部１１６は，該当タスクを他のスレーブノード１２０に移動する処理を，スレーブ通信部１１５を介して実行する。リスケジュール処理部

１１６は，タスクの移動により実行するタスクの数が所定数以下となるスレーブノード１２０にロックを設定する。ロック中のスレーブノード１２０には，原則として新たな処理要求のタスクが割り当てられないので，残ったタスクの処理が終了した後で，スケールシュリンクの対象となる。

【００５６】

スケールシュリンク処理部１１７は，スケールシュリンクによって，対象のスレーブノード１２０をシステム１００から削除する処理を行う。より具体的には，スケールシュリンク処理部１１７は，ＩａａＳ側で用意しているインタフェースを用いて，ＩａａＳ側の管理コンピュータにアクセスし，対象スレーブノード１２０のスケールシュリンクを要求する。

【００５７】

スレーブノード１２０は，マスタ通信部１２１，アプリケーション１２２を備える。図４に示すように，スレーブノード１２０では，複数種類のアプリケーション１２２ａ，ｂ，... を稼働することが可能である。処理要求のタスクが割り当てられた際には，該処理要求に対応するアプリケーション１２２によって，タスクの処理が実行される。

【００５８】

マスタ通信部１２１は，マスタノード１１０との通信を行う。例えば，マスタ通信部１２１は，マスタノード１１０からタスクの実行要求や停止要求を受け付け，タスクの実行開始または実行停止の処理を行う。また，タスクの処理が終了した場合には，マスタ通信部１２１は，マスタノード１１０に処理結果の応答を返す。

【００５９】

図５は，本実施の形態によるノードを実現する仮想マシンシステムの例を示す図である。

【００６０】

図５に示す仮想マシンシステムは，例えば，１台の物理マシン上で１または複数台の仮想マシンが動作するシステムである。図５に示す仮想マシンシステムの例では，ＣＰＵ１１やメモリ１２などの，物理マシンであるコンピュータ１０の資源を利用して，マスタノード１１０やスレーブノード１２０を含む複数の仮想マシン３０が動作している。なお，図５に示す仮想マシンシステムでは，マスタノード１１０とスレーブノード１２０とが同じ物理マシンで実現されているが，クラウドコンピューティングの環境では，マスタノード１１０や，各スレーブノード１２０が，それぞれ異なる物理マシンで実現されることも多い。

【００６１】

図５に示す仮想マシンシステムにおいて，ハイパーバイザ２０は，コンピュータ１０を利用した仮想化環境を実現するソフトウェアである。マスタノード１１０やスレーブノード１２０を含む仮想マシン３０は，ハイパーバイザ２０上に構築可能である。

【００６２】

図４に示すマスタノード１１０，スレーブノード１２０を仮想マシンで実現するコンピュータ１０は，例えば，ＣＰＵ１１，主記憶となるメモリ１２，記憶装置１３，通信装置１４，媒体読取・書込装置１５，入力装置１６，出力装置１７等のハードウェアを備える。記憶装置１３は，例えばＨＤＤ（Hard Disk Drive ）等の外部記憶装置や，補助記憶装置などである。媒体読取・書込装置１５は，例えばＣＤ－Ｒ（Compact Disc Recordable ）ドライブやＤＶＤ－Ｒ（Digital Versatile Disc Recordable ）ドライブなどである。入力装置１６は，例えばキーボード・マウスなどである。出力装置１７は，例えばディスプレイ等の表示装置などである。なお，コンピュータ１０のハードウェア構成は，必要に応じて任意の設計が可能である。

【００６３】

図４に示すマスタノード１１０，スレーブノード１２０および各ノードが備える機能部は，コンピュータ１０が備えるＣＰＵ１１，メモリ１２等のハードウェアと，ソフトウェアプログラムとによって実現することが可能である。コンピュータ１０が実行可能なプロ

グラムは，例えば，記憶装置１３に記憶され，その実行時にメモリ１２に読み出され，ＣＰＵ１１により実行される。

【００６４】

コンピュータ１０は，可搬型記録媒体から直接プログラムを読み取り，そのプログラムに従った処理を実行することもできる。また，コンピュータ１０は，サーバコンピュータからプログラムが転送されるごとに，逐次，受け取ったプログラムに従った処理を実行することもできる。さらに，このプログラムは，コンピュータで読み取り可能な記録媒体に記録しておくことができる。

【００６５】

以下，本実施の形態によるマスタノード１１０による処理について，より具体的な例を用いて説明する。

【００６６】

図６～図９は，本実施の形態のマスタノードにおけるスケジュール処理部による処理要求のタスクの割り当てシミュレーションの例を説明する図である。

【００６７】

図６（Ａ）は，タスクの表記の例を示す。図６（Ａ）において，塗り潰しされた図形が，タスクの処理を表す。タスクの処理を示す図形の縦の長さは該タスクのリソース消費量を示し，横の長さは該タスクの処理時間を示す。また，図６（Ａ）において，白抜き図形の右端は，該タスクの納期を示す。納期は，クライアント２００に指定されたタスクの処理を終了する期限である。以下の説明において，タスクについてはすべて図６（Ａ）に示す通りの表記が行われる。

【００６８】

図６（Ｂ）は，クライアント２００から時刻t_0に処理要求を受け付けた時点における，システム１００が備える各スレーブノード１２０ａ，ｂが実行するタスクのスケジュールを示す。図６（Ｂ）に示すように，この時点でシステム１００が備えるスレーブノード１２０は，＃ａのスレーブノード１２０ａと＃ｂのスレーブノード１２０ｂの２つである。なお，スケジュール情報記憶部１１３には，例えば図６（Ｂ）のグラフに示すようなシステム１００が備えるスレーブノード１２０が実行するタスクのスケジュールをデータ化した管理情報が記憶されている。図６（Ｂ）において，グラフの縦軸はスレーブノードのリソース消費量を示し，横軸は時間の経過を示す。t_{-1}～t_3は，等間隔の時刻を示す。

【００６９】

図６（Ｃ）は，時刻t_0の時点でクライアント２００から受け付けた処理要求のタスクＸを示す図形である。図６（Ｃ）に示すように，処理要求のタスクＸの処理については，他のタスクと区別がつくように，ハッチングで表されている。図６（Ｃ）に示すように，処理要求のタスクＸについては，時刻t_3の納期が指定されている。

【００７０】

なお，タスクの処理時間やリソース消費量の推定については，過去の実績から求める方法や理論的に求める方法などで多数の周知技術が存在するので，ここでは詳細な説明を省略する。タスクの処理時間の推定は，タスクが対象とする処理によって異なる。例えば画像の処理の処理時間については，画像ファイルサイズの影響を受ける。データベースを用いた処理では，データベースへのアクセス回数の影響を受ける。また，タスクのリソース消費量については，例えば，タスクの処理を行うアプリケーション１２２ごとに値が決まっている場合にはその値を用いることができる。スレーブノード１２０にリソース消費量を問い合わせるようにしてもよい。その他，様々な周知技術の利用が可能である。

【００７１】

マスタノード１１０において，スケジュール処理部１１２は，処理要求を受け付けると，まず，現状で，処理要求のタスクをスレーブノード１２０に割り当て可能であるかを検証する。

【００７２】

図７（Ａ）は，処理要求のタスクＸを，時刻t_0に処理実行を開始するように，＃ａの

スレーブノード１２０ａに対して割り当てした検証の例を示す。また，図７（Ｂ）は，処理要求のタスクＸを，時刻t_0に処理実行を開始するように，＃ｂのスレーブノード１２０ｂに対して割り当てした検証の例を示す。いずれも，ノードのリソース消費量が，ノードのリソース限界量を超えてしまうため，検証結果はＮＧとなる。

【００７３】

図７（Ｃ）は，最も早く処理が終了する，＃ａのスレーブノード１２０ａが実行するタスクＡ＃１の処理終了後に，処理要求のタスクＸをスケジュールした検証の例を示す。この場合，処理要求のタスクＸの処理終了時刻が納期t_3を超えてしまうため，検証結果はＮＧとなる。

【００７４】

次に，スケジュール処理部１１２は，他のタスクで再起動しても納期までに処理終了可能なタスクを移動する検証を行う。図８（Ａ）に示すように，＃ｂのスレーブノード１２０ｂが実行するタスクＢ＃３は，リソース消費量の面でも＃ａのスレーブノード１２０ａに移動可能であり，＃ａのスレーブノード１２０ａで再起動しても納期までに処理終了可能である。図８（Ｂ）は，図８（Ａ）に示すタスクの移動によってリソース消費量が減った＃ｂのスレーブノード１２０ｂに対して，処理要求のタスクＸを割り当てした検証の例を示す。タスクの移動を行っても，ノードのリソース消費量が，ノードのリソース限界量を超えてしまうため，検証結果はＮＧとなる。

【００７５】

他にロック中のスレーブノード１２０が存在しないので，スケジュール処理部１１２は，スケールアウト処理部１１４によるスケールアウトの処理でスレーブノード１２０を増設すると判断する。図９は，スケールアウト処理部１１４によって増設された＃ｃのスレーブノード１２０ｃに，処理要求のタスクＸが割り当てられた状態を示す。

【００７６】

このように，本実施の形態によるマスタノード１１０は，現状のスレーブノード１２０の状態でスケジューリングを含めた検証を行っても，さらにタスクの移動を行う検証を行っても，納期内に処理が終了するように処理要求のタスクを割り当てできない場合にのみ，スケールアウトを実行する。これにより，無駄なスケールアウトを抑制できるので，無駄な課金が発生しない，効率がよいシステム１００の運用が可能となる。

【００７７】

図１０，図１１は，本実施の形態のマスタノードにおけるリスケジュール処理部によるタスクの移動シミュレーションの例を説明する図である。

【００７８】

図１０は，時刻t_0の時点での，システム１００が備える各スレーブノード１２０ａ，ｂ，ｃが実行するタスクのスケジュールを示す。図１０に示すように，この時点でシステム１００が備えるスレーブノード１２０は，＃ａのスレーブノード１２０ａと，＃ｂのスレーブノード１２０ｂと，＃ｃのスレーブノード１２０ｃの３つである。

【００７９】

まず，マスタノード１１０において，リスケジュール処理部１１６は，定期的にスケジュール情報記憶部１１３を参照して，実行するタスクがないスレーブノード１２０があるかをチェックする。図１０に示すように，この時点では，すべてのスレーブノード１２０が処理を実行しているので，実行するタスクがないスレーブノード１２０はない。このとき，リスケジュール処理部１１６は，現状のままでスケールシュリンクできるスレーブノード１２０はないと判断する。

【００８０】

次に，リスケジュール処理部１１６は，他のタスクで再起動しても納期までに処理終了可能なタスクを移動する検証を行う。

【００８１】

図１１（Ａ）は，＃ｂのスレーブノード１２０ｂが実行するタスクＢ＃１を，＃ａのスレーブノード１２０ａで再起動する検証の例を示す。図１１（Ａ）に示すように，タスク

Ｂ＃１を他のスレーブノード１２０で再起動すると，処理の終了時刻が納期t_2を超えてしまうため，検証結果はＮＧとなる。リスケジュール処理部１１６は，タスクを移動して＃ｂのスレーブノード１２０ｂに対してスケールシュリンクを行うことはできないと判断する。

【００８２】

図１１（Ｂ）は，＃ｃのスレーブノード１２０ｃが実行するタスクＣ＃１を，＃ａのスレーブノード１２０ａで再起動する検証の例を示す。図１１（Ｂ）に示すように，タスクＣ＃１は，＃ａのスレーブノード１２０ａで再起動しても納期t_3までに処理終了可能である。さらに，タスクＣ＃１を＃ａのスレーブノード１２０ａに移動すると，＃Ｃのスレーブノード１２０ｃが実行するタスクがなくなるため，＃Ｃのスレーブノード１２０ｃに対してスケールシュリンクを行うことが可能である。

【００８３】

リスケジュール処理部１１６は，スレーブ通信部１１５を介して，＃Ｃのスレーブノード１２０ｃにタスクＣ＃１の停止を指示し，＃Ａのスレーブノード１２０ａにタスクＣ＃１の実行を指示する。＃Ｃのスレーブノード１２０ｃが実行するタスクがなくなるので，リスケジュール処理部１１６は，＃Ｃのスレーブノード１２０ｃをスケールシュリンクの対象とする。スケールシュリンク処理部１１７は，＃Ｃのスレーブノード１２０ｃに対するスケールシュリンクの処理を実行する。

【００８４】

このように，本実施の形態によるマスタノード１１０は，他のスレーブノード１２０にタスクを移動することで，実行するタスクがないスレーブノード１２０を積極的に作り，スケールシュリンクを実行する。これにより，無駄なスレーブノード１２０を積極的に削除することが可能となるので，無駄な課金が発生しない効率がよいシステム１００の運用が可能となる。

【００８５】

図１２，図１３は，本実施の形態のマスタノードにおけるリスケジュール処理部によるスレーブノードにロック設定を行う例を説明する図である。

【００８６】

図１２は，時刻t_0の時点での，システム１００が備える各スレーブノード１２０ａ，ｂが実行するタスクのスケジュールを示す。図１２に示すように，この時点でシステム１００が備えるスレーブノード１２０は，＃ａのスレーブノード１２０ａと＃ｂのスレーブノード１２０ｂの２つである。

【００８７】

マスタノード１１０において，リスケジュール処理部１１６は，タスクを移動しても実行するタスクがないスレーブノード１２０が用意できない場合に，タスクを移動することで実行するタスクの数が所定数以下となるスレーブノード１２０を用意できるかを検証する。例えば，ここでは，所定数を１とする。

【００８８】

図１３（Ａ）は，＃ｂのスレーブノード１２０ｂが実行するタスクＢ＃２を，＃ａのスレーブノード１２０ａで再起動する検証の例を示す。図１３（Ａ）に示すように，タスクＢ＃２は，＃ａのスレーブノード１２０ａで再起動しても納期t_3までに処理終了可能である。なお，＃ｂのスレーブノード１２０ｂが実行するタスクＢ＃１を，＃ａのスレーブノード１２０ａで再起動しようとしても，処理の終了時刻が納期t_2を超えてしまうため，タスクＢ＃１は移動できない。

【００８９】

タスクＢ＃２を＃ａのスレーブノード１２０ａに移動したとすると，図１３（Ｂ）に示すように，＃ｂのスレーブノード１２０ｂは，実行するタスクの数が所定数１以下となる。このとき，リスケジュール処理部１１６は，スレーブ通信部１１５を介して，＃Ｂのスレーブノード１２０ｂにタスクＢ＃２の停止を指示し，＃Ａのスレーブノード１２０ａにタスクＢ＃２の実行を指示する。

【００９０】
また，図１３（Ｂ）に示すように，実行するタスクがＢ＃１のみとなった＃ｂのスレーブノード１２０ｂに，ロックを設定する。なお，ロックを設定したスレーブノード１２０の情報は，スケジュール情報記憶部１１３など，スケジュール処理部１１２がアクセス可能な記憶部に記録しておく。これで，＃ｂのスレーブノード１２０ｂには，原則として，新規の処理要求のタスクが割り当てされないので，残っている＃Ｂ１のタスクの終了後に，スケールシュリンク処理部１１７によって，＃ｂのスレーブノード１２０ｂを削除することができる。
【００９１】
このように，本実施の形態によるマスタノード１１０は，他のスレーブノード１２０にタスクを移動して，実行するタスクが少ないスレーブノード１２０を積極的に作り，そのスレーブノード１２０に対する新規の処理要求のタスクの割り当てを抑制する。これにより，システム１００の環境が，実行するタスクがないスレーブノード１２０ができやすい環境となり，無駄なスレーブノード１２０を積極的に削除することが可能となるので，無駄な課金が発生しない効率がよいシステム１００の運用が可能となる。
【００９２】
図１４は，本実施の形態のマスタノードにおけるスケジュール処理部によるスレーブノードのロック解除を行う例を説明する図である。
【００９３】
ここで，システム１００が，図１３（Ｂ）に示す状態で，クライアント２００から，図６（Ｃ）に示すタスクＸの処理要求を受けたものとする。このとき，スケジュール処理部１１２は，処理要求のタスクＸを，図１４（Ａ）に示すようにロックされていない＃ａのスレーブノード１２０ａに割り当てしようとするが，ノードのリソース消費量がノードのリソース限界量を超えてしまうため，割り当てできない。さらに，他にタスクを移動できる相手先のスレーブノード１２０もない。
【００９４】
このとき，スケジュール処理部１１２は，ロック中の＃ｂのスレーブノード１２０ｂのロックを解除すれば，＃ｂのスレーブノード１２０ｂで処理要求のタスクＸが納期までに処理終了可能かを検証する。図１４（Ｂ）に示すように，＃ｂのスレーブノード１２０ｂで処理要求のタスクＸが納期までに処理終了可能であるので，スケジュール処理部１１２は，ロック中の＃ｂのスレーブノード１２０ｂのロックを解除し，＃ｂのスレーブノード１２０ｂに処理要求のタスクＸを割り当てる。
【００９５】
このように，ロック中のスレーブノード１２０には，他のスレーブノード１２０に処理要求のタスクを割り当てできない場合にのみ，処理要求のタスクの割り当てが行われる。これにより，スケールシュリンクを実行しやすい環境をギリギリまで維持しながら，スケールアウトの発生を抑制できるので，無駄な課金が発生しない効率がよいシステム１００の運用が可能となる。
【００９６】
なお，本実施の形態によるマスタノード１１０は，納期内にタスクの処理が終了することを最優先としているので，システム１００では常に最低限の処理性能が維持されている。
【００９７】
図１５，図１６は，本実施の形態のマスタノードによる処理要求受け付け時の処理フローチャートである。
【００９８】
マスタノード１１０において，クライアント通信部１１１は，クライアントから処理要求を受け付ける（ステップＳ１０）。ここで受け付ける処理要求には，納期が指定されている。クライアント通信部１１１は，処理要求が受け入れ可能かを判定する（ステップＳ１１）。処理要求が受け入れ可能でなければ（ステップＳ１１のＮＯ），クライアント通

信部１１１は，クライアントに処理要求の受け入れが不可能である旨を応答し（ステップＳ１２），処理を終了する。

【００９９】

処理要求が受け入れ可能であれば（ステップＳ１１のＹＥＳ），スケジュール処理部１１２は，スケジュール情報記憶部１１３の管理情報を参照し，現状のスレーブノード１２０に処理要求のタスクを割り当てるシミュレーションを行う（ステップＳ１３）。ここでは，例えば，図７に示すようにスケジューリングを含めた検証が行われる。

【０１００】

スケジュール処理部１１２は，現状のスレーブノード１２０に対する処理要求のタスクの割り当てが可能かを判定する（ステップＳ１４）。処理要求のタスクの割り当てが可能であれば（ステップＳ１４のＹＥＳ），スケジュール処理部１１２は，処理要求のタスクを割り当てる先のスレーブノード１２０を決定する（ステップＳ１５）。スレーブ通信部１１５は，決定されたスレーブノード１２０に処理要求のタスクの処理を依頼する（ステップＳ２２）。

【０１０１】

処理要求のタスクの割り当てが可能でなければ（ステップＳ１４のＮＯ），スケジュール処理部１１２は，スケジュール情報記憶部１１３の管理情報を参照し，既存のタスクを移動して，処理要求のタスクを割り当てるシミュレーションを行う（ステップＳ１６）。ここでは，例えば，図８に示すように，他のスレーブノード１２０に移動して再実行しても納期内に処理を終了可能な既存のタスクがある場合に，その既存タスクを移動してリソースに空きができたスレーブノード１２０に処理要求のタスクを割り当てることができるかが検証される。

【０１０２】

スケジュール処理部１１２は，既存タスクを移動して処理要求のタスクの割り当てが可能となるかを判定する（ステップＳ１７）。処理要求のタスクの割り当てが可能となれば（ステップＳ１７のＹＥＳ），スケジュール処理部１１２は，該当既存タスクの移動を実行する（ステップＳ１８）。より具体的には，スケジュール処理部１１２は，スレーブ通信部１１５を介して，既存タスクの移動元のスレーブノード１２０に該タスクの停止を依頼する。また，スケジュール処理部１１２は，スレーブ通信部１１５を介して，既存タスクの移動先のスレーブノード１２０に該タスクの実行を依頼する。スレーブ通信部１１５は，既存タスクの移動によりリソースに空きができたスレーブノード１２０に処理要求のタスクの処理を依頼する（ステップＳ２２）。

【０１０３】

処理要求のタスクの割り当てが可能とならなければ（ステップＳ１７のＮＯ），スケジュール処理部１１２は，ロック中のスレーブノード１２０が存在して，該スレーブノード１２０のロックを解除すれば，処理要求のタスクの割り当てが可能となるかを判定する（ステップＳ１９）。ロックを解除して処理要求のタスクの割り当てが可能となれば（ステップＳ１９のＹＥＳ），スケジュール処理部１１２は，ロック中のスレーブノード１２０のロックを解除する（ステップＳ２０）。スレーブ通信部１１５は，ロックが解除されたスレーブノード１２０に処理要求のタスクの処理を依頼する（ステップＳ２２）。このケースは，図１４の例に示されるケースである。

【０１０４】

ロック中のスレーブノード１２０がないか，ロックを解除しても処理要求のタスクの割り当てが可能とならなければ（ステップＳ１９のＮＯ），スケールアウト処理部１１４は，スケールアウトの処理を実行する（ステップＳ２１）。スケールアウトにより，システム１００にスレーブノード１２０が増設される。スレーブ通信部１１５は，増設されたスレーブノード１２０に処理要求のタスクの処理を依頼する（ステップＳ２２）。このケースは，図９の例に示されるケースである。

【０１０５】

スレーブ通信部１１５が，スレーブノード１２０から処理要求に対する処理結果の応答

を受け付けると（ステップＳ２３），クライアント通信部１１１は，その応答をクライアントに送信する（ステップＳ２４）。

【０１０６】

図１７は，本実施の形態のマスタノードによるリスケジュールの処理フローチャートである。

【０１０７】

マスタノード１１０において，リスケジュール処理部１１６は，所定のタイミングで本処理を開始する。

【０１０８】

リスケジュール処理部１１６は，スケジュール情報記憶部１１３の管理情報を参照し，現状で実行するタスクがないスレーブノード１２０があるかを判定する（ステップＳ３０）。実行するタスクがないスレーブノード１２０があれば（ステップＳ３０のＹＥＳ），スケールシュリンク処理部１１７は，該当スレーブノード１２０に対するスケールシュリンクの処理を実行する（ステップＳ３１）。スケールシュリンクにより，システム１００からスレーブノード１２０が削除される。

【０１０９】

リスケジュール処理部１１６は，スケジュール情報記憶部１１３の管理情報を参照し，タスクを移動するシミュレーションを行う（ステップＳ３２）。ここでは，例えば図１１に示すように，他のスレーブノード１２０に移動して再実行しても納期内に処理を終了可能なタスクがある場合に，そのタスクを移動して実行するタスクがないスレーブノード１２０を生成できるかが検証される。また，例えば図１３に示すように，他のスレーブノード１２０に移動して再実行しても納期内に処理を終了可能なタスクがある場合に，そのタスクを移動して実行するタスクが所定数以下となるスレーブノード１２０を生成できるかが検証される。

【０１１０】

リスケジュール処理部１１６は，タスクを移動して実行するタスクがないスレーブノード１２０を生成できるか，すなわちタスクを移動してスケールシュリンクが可能となるかを判定する（ステップＳ３３）。タスクを移動してスケールシュリンクが可能となれば（ステップＳ３３のＹＥＳ），リスケジュール処理部１１６は，該当タスクの移動を実行する（ステップＳ３４）。より具体的には，リスケジュール処理部１１６は，スレーブ通信部１１５を介して，タスクの移動元のスレーブノード１２０に該タスクの停止を依頼する。また，リスケジュール処理部１１６は，スレーブ通信部１１５を介して，タスクの移動先のスレーブノード１２０に該タスクの実行を依頼する。スケールシュリンク処理部１１７は，タスクの移動により実行するタスクがなくなったスレーブノード１２０に対するスケールシュリンクの処理を実行する（ステップＳ３５）。スケールシュリンクにより，システム１００からスレーブノード１２０が削除される。

【０１１１】

タスクを移動してもスケールシュリンクが可能とならなければ（ステップＳ３３のＮＯ），リスケジュール処理部１１６は，タスクを移動して実行するタスクが所定数以下となるスレーブノード１２０があるかを判定する（ステップＳ３６）。タスクを移動しても実行するタスクが所定数以下となるスレーブノード１２０がなければ（ステップＳ３６のＮＯ），リスケジュール処理部１１６は，処理を終了する。

【０１１２】

タスクを移動して実行するタスクが所定数以下となるスレーブノード１２０があれば（ステップＳ３６のＹＥＳ），リスケジュール処理部１１６は，該当タスクの移動を実行する（ステップＳ３７）。より具体的には，リスケジュール処理部１１６は，スレーブ通信部１１５を介して，タスクの移動元のスレーブノード１２０に該タスクの停止を依頼する。また，リスケジュール処理部１１６は，スレーブ通信部１１５を介して，タスクの移動先のスレーブノード１２０に該タスクの実行を依頼する。リスケジュール処理部１１６は，タスクを移動して実行するタスクが所定数以下となったスレーブノード１２０にロック

を設定する（ステップＳ３８）。このまま，ロックが解除されずに残ったタスクの処理がすべて終了すれば，ロックが設定されたスレーブノード１２０は，その後のステップＳ３０，Ｓ３１の処理でスケールシュリンクの対象となる。

【０１１３】

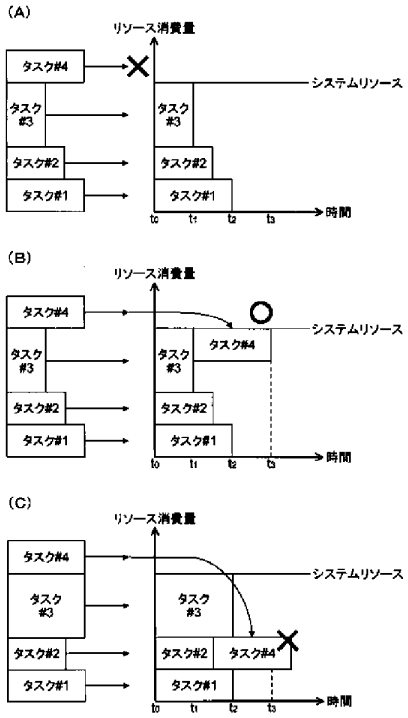
以上，本実施の形態について説明したが，本発明はその主旨の範囲において種々の変形が可能であることは当然である。

【符号の説明】

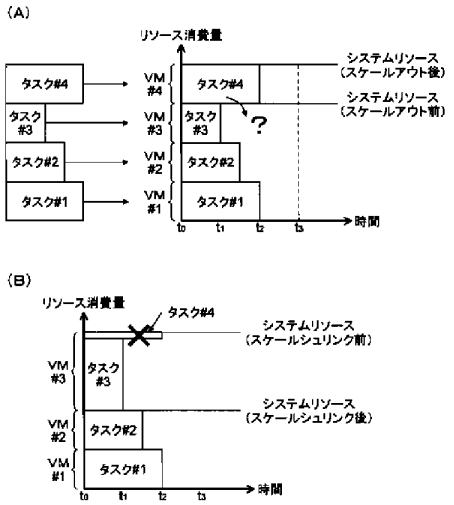
【０１１４】

１００　システム
１１０　マスタノード
１１１　クライアント通信部
１１２　スケジュール処理部
１１３　スケジュール情報記憶部
１１４　スケールアウト処理部
１１５　スレーブ通信部
１１６　リスケジュール処理部
１１７　スケールシュリンク処理部
１２０　スレーブノード
１２１　マスタ通信部
１２２　アプリケーション
２００　クライアント
３００　ネットワーク

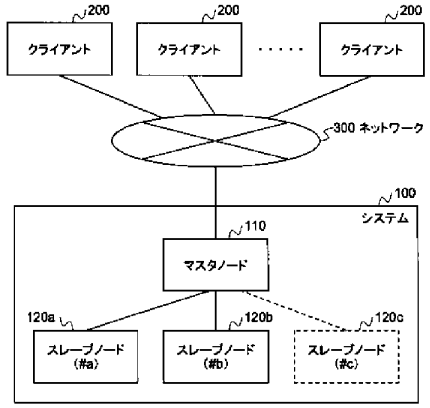
【図１】



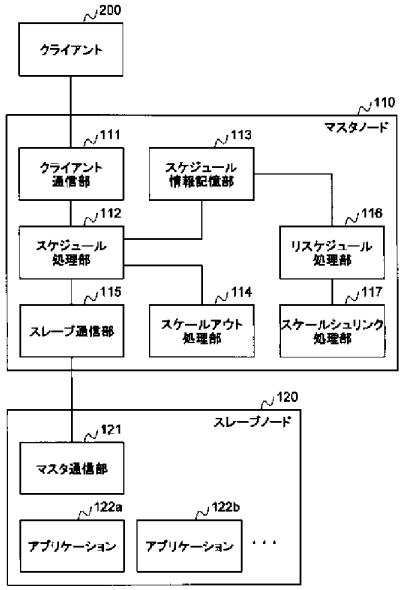
【図２】



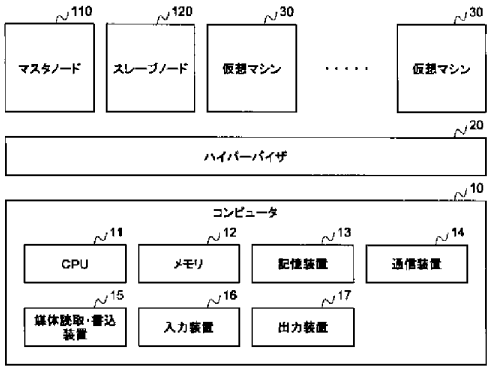
【図３】


200
クライアント
200
クライアント
200
クライアント
300 ネットワーク
100
システム
110
マスタノード
120a
スレーブノード
(#a)
120b
スレーブノード
(#b)
120c
スレーブノード
(#c)

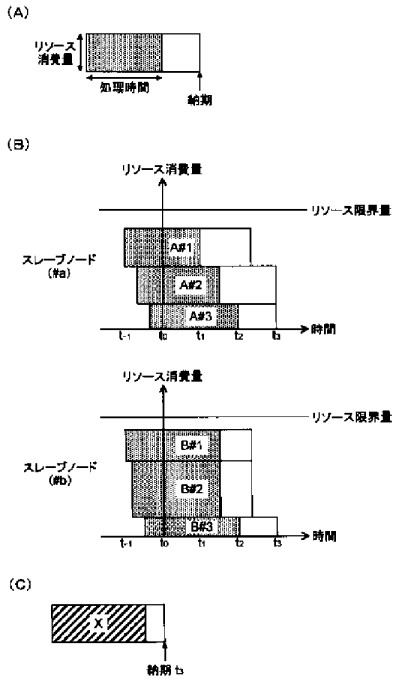
【図４】


200
クライアント
110
マスタノード
111
クライアント
通信部
113
スケジュール
情報記憶部
112
スケジュール
処理部
116
リスケジュール
処理部
115
スレーブ通信部
114
スケールアウト
処理部
117
スケールシュリンク
処理部
120
スレーブノード
121
マスタ通信部
122a
アプリケーション
122b
アプリケーション

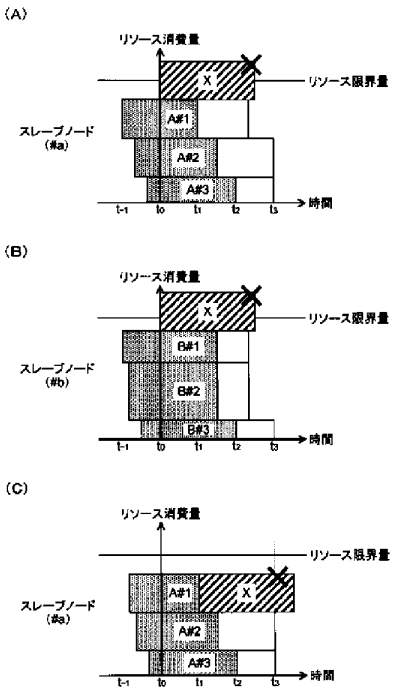
【図５】


110
マスタノード
120
スレーブノード
30
仮想マシン
30
仮想マシン
20
ハイパーバイザ
10
コンピュータ
11
CPU
12
メモリ
13
記憶装置
14
通信装置
15
媒体読取・書込
装置
16
入力装置
17
出力装置

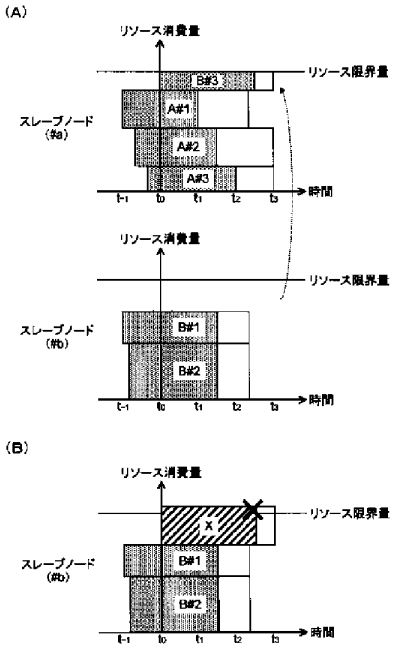
【図６】


(A)
リソース
消費量
処理時間
納期
(B)
リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
(C)
X
納期 b

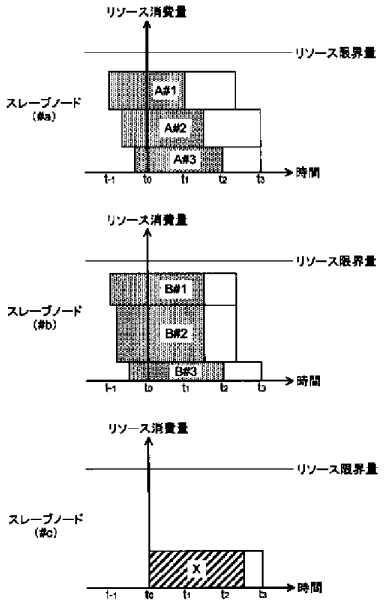
【図７】


(A)
リソース消費量
リソース限界量
X
スレーブノード
(#a)
A#1
A#2
A#3
時間
(B)
リソース消費量
リソース限界量
X
スレーブノード
(#b)
B#1
B#2
B#3
時間
(C)
リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
X
A#2
A#3
時間

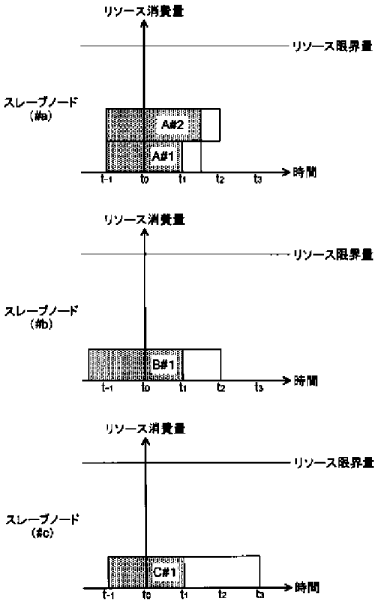
【図８】


(A)
リソース消費量
リソース限界量
B#3
スレーブノード
(#a)
A#1
A#2
A#3
時間
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
時間
(B)
リソース消費量
リソース限界量
X
スレーブノード
(#b)
B#1
B#2
時間

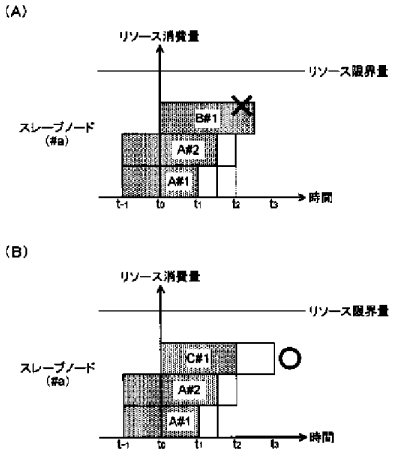
【図９】


リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
リソース消費量
リソース限界量
スレーブノード
(#c)
X
時間

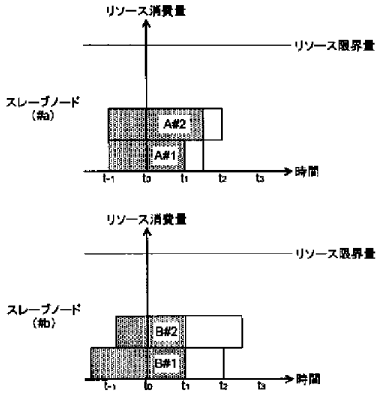
【図１０】


リソース消費量
リソース限界量
スレーブノード
(#a)
A#2
A#1
時間
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
時間
リソース消費量
リソース限界量
スレーブノード
(#c)
C#1
時間

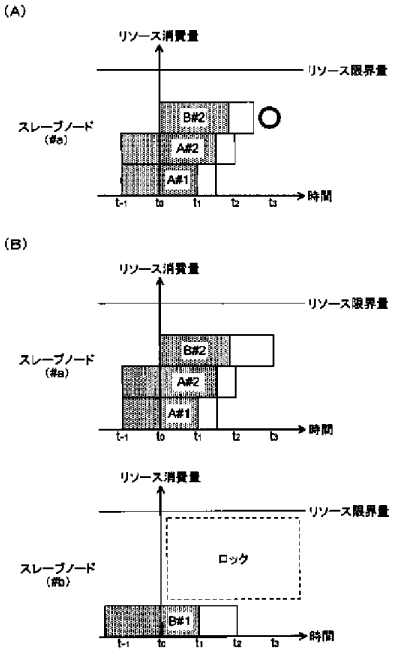
【図１１】



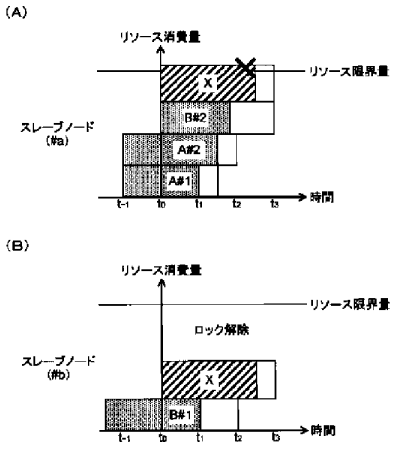
【図１２】



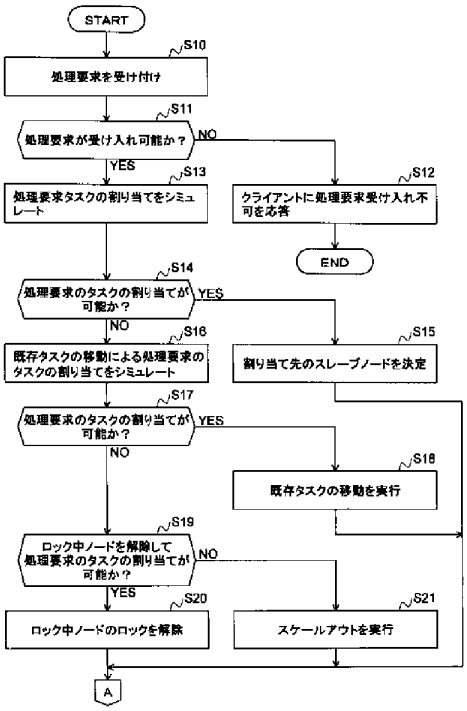
【図１３】



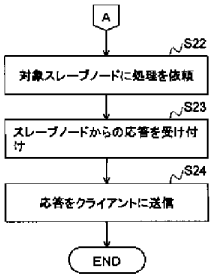
【図１４】



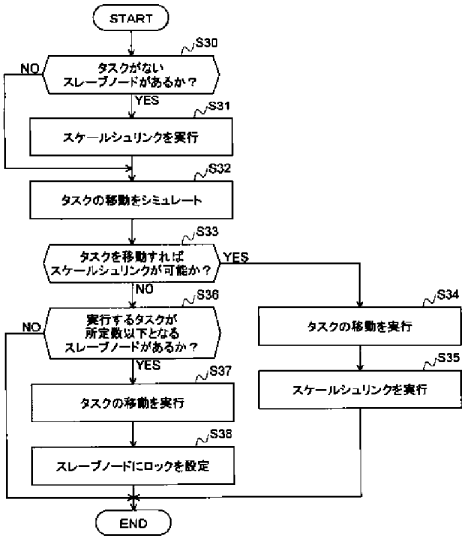
【図１５】


START
S10
処理要求を受け付け
S11
処理要求が受け入れ可能か？
NO
YES
S12
クライアントに処理要求受け入れ不可を応答
END
S13
処理要求タスクの割り当てをシミュレート
S14
処理要求のタスクの割り当てが可能か？
YES
NO
S15
割り当て先のスレーブノードを決定
S16
既存タスクの移動による処理要求のタスクの割り当てをシミュレート
S17
処理要求のタスクの割り当てが可能か？
YES
NO
S18
既存タスクの移動を実行
S19
ロック中ノードを解除して処理要求のタスクの割り当てが可能か？
NO
YES
S20
ロック中ノードのロックを解除
S21
スケールアウトを実行
A

【図１６】


A
S22
対象スレーブノードに処理を依頼
S23
スレーブノードからの応答を受け付け
S24
応答をクライアントに送信
END

【図１７】


START
S30
タスクがないスレーブノードがあるか？
NO
YES
S31
スケールシュリンクを実行
S32
タスクの移動をシミュレート
S33
タスクを移動すればスケールシュリンクが可能か？
YES
NO
S34
タスクの移動を実行
S35
スケールシュリンクを実行
S36
実行するタスクが所定数以下となるスレーブノードがあるか？
NO
YES
S37
タスクの移動を実行
S38
スレーブノードにロックを設定
END

フロントページの続き

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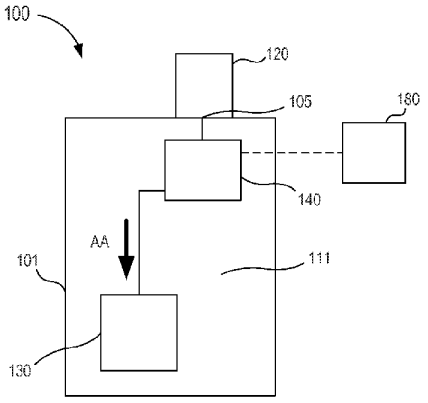


FIG. 1

(57) Abstract: An apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing includes an inlet port removably coupled to the cannula assembly and defines an inner volume. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a volume of bodily fluid from a patient. The flow control mechanism is at least partially disposed in the inner volume. The actuator is operably coupled to the flow control mechanism and is configured to move the flow control mechanism between a first configuration, in which bodily fluid can flow, via a fluid flow path defined by the flow control mechanism, from the cannula assembly, through the inlet port and into the fluid reservoir, to a second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

WO 2014/058945 A1

SYSTEMS AND METHODS FOR DELIVERING A FLUID TO A PATIENT WITH REDUCED CONTAMINATION

Cross-Reference to Related Applications

[1001] This application claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 61/712,468, filed October 11, 2012, entitled, "Systems and Methods for Delivering a Fluid to a Patient with Reduced Contamination," the disclosure of which is incorporated herein by reference in its entirety.

Background

[1002] Embodiments described herein relate generally to delivering a fluid to a patient, and more particularly to devices and methods for delivering a parenteral fluid to a patient with reduced contamination from microbes or other contaminants exterior to the body and/or the fluid source, such as dermally residing microbes.

[1003] Human skin is normally habituated in variable small amounts by certain bacteria such as coagulase-negative Staphylococcus species, Proprionobacterium acnes, Micrococcus species, Streptococci Viridans group, Corynebacterium species, and Bacillus species. These bacteria for the most part live in a symbiotic relationship with human skin but in some circumstances can give rise to serious infections in the blood stream known as septicemia. Septicemia due to these skin residing organisms is most often associated with an internal nidus of bacterial growth at the site of injured tissue, for example a damaged, scarred heart valve, or a foreign body (often an artificial joint, vessel, or valve). Furthermore, there are predisposing factors to these infections such as malignancy, immunosuppression, diabetes mellitus, obesity, rheumatoid arthritis, psoriasis, and advanced age. In some instances, these infections can cause serious illness and/or death. Moreover, these infections can be very expensive and difficult to treat and often can be associated with medical related legal issues.

[1004] In general medical practice, blood is drawn from veins (phlebotomy) for two main purposes; (1) donor blood in volumes of approximately 500mL is obtained for the treatment of anemia, deficient blood clotting factors including platelets and other medical conditions; and (2) smaller volumes (e.g., from a few drops to 10mL or more) of blood are obtained for testing purposes. In each case, whether for donor or testing specimens, a fluid communicator (e.g., catheter, cannula, needle, etc.) is used to penetrate and enter a vein (known as venipuncture) enabling withdrawing of blood into a tube or vessel apparatus in the desired

amounts for handling, transport, storage and/or other purposes. The site of venipuncture, most commonly the antecubital fossa, is prepared by cleansing with antiseptics to prevent the growth of skin residing bacteria in blood withdrawn from the vein. It has been shown venipuncture needles dislodge fragments of skin including hair and sweat gland structures as well as subcutaneous fat and other adnexal structures not completely sterilized by skin surface antisepsis. These skin fragments can cause septicemia in recipients of donor blood products, false positive blood culture tests and other undesirable outcomes. Furthermore, methods, procedures and devices are in use, which divert the initial portion of venipuncture blood enabling exclusion of these skin fragments from the venipuncture specimen in order to prevent septicemia in recipients of donor blood products, false positive blood culture tests and other undesirable outcomes.

[1005] Venipuncture is also the most common method of accessing the blood stream of a patient to deliver parenteral fluids into the blood stream of patients needing this type of medical treatment. Fluids in containers are allowed to flow into the patient's blood stream through tubing connected to the venipuncture needle or through a catheter that is placed into a patient's vasculature (e.g. peripheral IV, central line, etc.). During this process, fragments of incompletely sterilized skin can be delivered into the blood stream with the flow of parenteral fluids and/or at the time of venipuncture for introduction and insertion of a peripheral catheter. These fragments are undesirable in the blood stream and their introduction into the blood stream of patients (whether due to dislodging of fragments by venipuncture needle when inserting a catheter or delivered through tubing attached to needle or catheter) is contrary to common practices of antisepsis. Further, these microbes can be associated with a well-known phenomenon of colonization by skin residing organisms of the tubing and tubing connectors utilized to deliver parenteral fluids. The colonization is not typically indicative of a true infection but can give rise to false positive blood culture tests, which may result in unnecessary antibiotic treatment, laboratory tests, and replacement of the tubing apparatus with attendant patient risks and expenses. Furthermore, the risk of clinically significant serious infection due to skin residing organisms is increased.

[1006] As such, a need exists for improved fluid transfer devices, catheter introduction techniques and devices, as well as methods for delivering a parenteral fluid to a patient that reduce microbial contamination and inadvertent injection of undesirable external microbes into a patient's blood stream.

Summary

[1007] Devices and methods for delivering a fluid to a patient and/or introducing a peripheral catheter with reduced contamination from dermally residing microbes or other contaminants exterior to the body and/or an external fluid source are described herein. In some embodiments, an apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes an inlet port removably coupled to the cannula assembly. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient. The flow control mechanism is at least partially disposed in the inner volume and is configured to move relative to the housing between a first configuration and a second configuration. The flow control mechanism defines a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration. The actuator is operably coupled to the flow control mechanism to move the flow control mechanism from the first configuration, in which the inlet port is placed in fluid communication the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

Brief Description of the Drawings

[1008] FIGS. 1 and 2 are schematic illustrations of a fluid transfer device according to an embodiment.

[1009] FIG. 3 is a schematic illustration of a fluid transfer device according to an embodiment.

[1010] FIG. 4 is a perspective view of a fluid transfer device according to an embodiment.

[1011] FIG. 5 is an exploded view of the fluid transfer device of FIG. 4.

[1012] FIG. 6 is a cross-sectional view of the fluid transfer device taken along the line X_1-X_1 in FIG. 4, in a first configuration.

[1013] FIG. 7 is an enlarged view of a portion of the fluid transfer device labeled as region **A** in FIG. 6.

[1014] FIGS. 8 and 9 are cross-sectional views of the fluid transfer device taken along the line X_1-X_1 in FIG. 4, in a second and third configuration, respectively.

[1015] FIG. 10 is a side view of the fluid transfer device of FIG. 4 in a fourth configuration.

[1016] FIG. 11 is a perspective view of a fluid transfer device according to an embodiment.

[1017] FIG. 12 is an exploded view of the fluid transfer device of FIG. 11.

[1018] FIGS. 13 and 14 are cross-sectional views of the fluid transfer device taken along the line X_2-X_2 in FIG. 11, in a first and second configuration, respectively.

[1019] FIG. 15 is a side view of the fluid transfer device of FIG. 11 in a third configuration.

[1020] FIG. 16 is a perspective view of a fluid transfer device according to an embodiment.

[1021] FIG. 17 is an exploded view of the fluid transfer device of FIG. 16.

[1022] FIG. 18 is a cross-sectional perspective view of a housing included in the fluid transfer device taken along the line X_4-X_4 in FIG. 17.

[1023] FIG. 19 is a cross-sectional perspective view of a portion of a flow control mechanism included in the fluid transfer device taken along the line X_5-X_5 in FIG. 17.

[1024] FIG. 20 is a cross-sectional view of the fluid transfer device taken along the line X_3-X_3 in FIG. 16, in a first configuration.

[1025] FIG. 21 is a front view of the fluid transfer device of FIG. 16 in a second configuration.

[1026] FIG. 22 is a cross-sectional view of the fluid transfer device taken along the line X_3-X_3 in FIG. 16, in the second configuration.

[1027] FIG. 23 is a side view of the fluid transfer device of FIG. 16 in a third configuration.

[1028] FIG. 24 is a perspective view of a fluid transfer device according to an embodiment.

[1029] FIG. 25 is an exploded view of the fluid transfer device of FIG. 24.

[1030] FIG. 26 is a cross-sectional perspective view of a fluid reservoir included in the fluid transfer device taken along the line X_7-X_7 in FIG. 25.

[1031] FIG. 27 is a cross-sectional perspective view of a flow control mechanism included in the fluid transfer device taken along the line X_8-X_8 in FIG. 25.

[1032] FIGS. 28-30 are cross-sectional views of the fluid transfer device taken along the line X_6-X_6 in FIG. 24, in a first, second, and third configuration, respectively.

[1033] FIG. 31 is a perspective view of a fluid transfer device according to an embodiment.

[1034] FIG. 32 is an exploded view of the fluid transfer device of FIG. 31.

[1035] FIGS. 33 and 34 are cross-sectional views of the fluid transfer device taken along the line X_9-X_9 in FIG. 31, in a first configuration and a second configuration, respectively.

[1036] FIG. 35 is a perspective view of a fluid transfer device according to an embodiment.

[1037] FIG. 36 is an exploded view of the fluid transfer device of FIG. 35.

[1038] FIG. 37 is a cross-sectional view of the fluid transfer device taken along the line X_{10}-X_{10} in FIG. 35, in a first configuration.

[1039] FIG. 38 is a front view of the fluid transfer device of FIG. 35 in a second configuration.

[1040] FIG. 39 is a cross-sectional view of the fluid transfer device taken along the line X_{10}-X_{10} in FIG. 35, in the second configuration.

[1041] FIG. 40 is a flowchart illustrating a method of delivering a fluid to a patient using a fluid transfer device according to an embodiment.

Detailed Description

[1042] Devices and methods for delivering a fluid to a patient with reduced contamination from dermally residing microbes or other contaminants exterior to the body are described herein. In some embodiments, an apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes an inlet port configured to be removably coupled to the cannula assembly. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient. The flow control mechanism is at least partially disposed in the inner volume and is configured to move relative to the housing between a first configuration and a second configuration. The flow control mechanism defines a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration. The actuator is operably coupled to the flow control mechanism to move the flow control mechanism from the first configuration, in which the inlet port is placed in fluid communication the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

[1043] In some embodiments, a device for delivering a fluid to a patient with reduced contamination includes a housing, a fluid reservoir, and a flow control mechanism. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes a first port configured to be removably coupled to a cannula assembly, and a second port configured to be fluidically coupled to a fluid source. The fluid reservoir is fluidically coupleable to the cannula assembly and configured to receive and isolate a predetermined volume of bodily fluid withdrawn from the patient. The flow control mechanism is at least partially disposed in the inner volume of the housing and is configured to move between a first configuration and a second configuration. When in the first configuration, the first port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the first port and to the fluid reservoir. When in the second configuration, the fluid reservoir is fluidically isolated

from the cannula assembly and fluid can flow from the fluid source, in the second port, through the flow control mechanism, out the first port and to the cannula assembly.

[1044] In some embodiments, a method of delivering a fluid to a patient using a fluid transfer device includes establishing fluid communication between the patient and the fluid transfer device. Once in fluid communication, a predetermined volume of a bodily fluid is withdrawn from the patient. The predetermined volume of bodily fluid is transferred to a fluid reservoir. The fluid transfer device is fluidically isolated from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir. The method further includes establishing fluid communication between the patient and a fluid source with the fluid transfer device.

[1045] In some embodiments, an apparatus includes a housing, a cannula assembly, a flow control mechanism, and a fluid reservoir. The flow control mechanism is configured to move relative to the housing between a first configuration and a second configuration. The cannula assembly is coupled to the housing and fluidically coupled to the fluid reservoir when the flow control mechanism is in the first configuration. The fluid reservoir is fluidically isolated from the cannula assembly when the flow control mechanism is in a second configuration such that the cannula assembly can be fluidically coupled to an external fluid reservoir and/or an external fluid source.

[1046] As referred to herein, "bodily fluid" can include any fluid obtained from a body of a patient, including, but not limited to, blood, cerebrospinal fluid, urine, bile, lymph, saliva, synovial fluid, serous fluid, pleural fluid, amniotic fluid, and the like, or any combination thereof.

[1047] As used herein, the term "set" can refer to multiple features or a singular feature with multiple parts. For example, when referring to set of walls, the set of walls can be considered as one wall with distinct portions, or the set of walls can be considered as multiple walls. Similarly stated, a monolithically constructed item can include a set of walls. Such a set of walls can include, for example, multiple portions that are in discontinuous from each other. A set of walls can also be fabricated from multiple items that are produced separately and are later joined together (e.g., via a weld, an adhesive or any suitable method).

[1048] As used in this specification, the words "proximal" and "distal" refer to the direction closer to and away from, respectively, a user who would place the device into

contact with a patient. Thus, for example, the end of a device first touching the body of the patient would be the distal end, while the opposite end of the device (e.g., the end of the device being manipulated by the user) would be the proximal end of the device.

[1049] FIGS. 1 and 2 are schematic illustrations of a fluid transfer device 100 according to an embodiment, in a first and second configuration, respectively. Generally, the fluid transfer device 100 (also referred to herein as "transfer device") is configured to facilitate the insertion of a piercing member (e.g., a needle, a trocar, a cannula, or the like) into a patient to withdrawal and isolate a predetermined amount of bodily fluid from the patient containing, for example, dermally residing microbes. The fluid transfer device 100 is further configured to facilitate the delivery of parenteral fluid to the patient that does not substantially contain, for example, the dermally residing microbes. In other words, the transfer device 100 is configured to transfer and fluidically isolate the predetermined amount of bodily fluid, including dermally residing microbes dislodged from a venipuncture, within a collection reservoir and deliver parenteral fluids to the patient that are substantially free from the dislodged dermally residing microbes and/or other undesirable external contaminants.

[1050] The transfer device 100 includes a housing 101, a cannula assembly 120, a fluid reservoir 130, a flow control mechanism 140, and an actuator 180. The housing 101 can be any suitable shape, size, or configuration and is described in further detail herein with respect to specific embodiments. As shown in FIG. 1, the housing 101 defines an inner volume 111 that can movably receive and/or movably house at least a portion of the flow control mechanism 140, as described in further detail herein. A portion of the housing 101 can be, at least temporarily, physically and fluidically coupled to the cannula assembly 120. For example, in some embodiments, a distal end portion of the housing 101 can include an inlet port 105 or the like configured to physically and fluidically couple to a lock mechanism (not shown in FIGS. 1 and 2) included in the cannula assembly 120. In such embodiments, the lock mechanism can be, for example, a Luer-Lok® or the like that can engage the port. In some embodiments, the housing 101 can be monolithically formed with at least a portion of the cannula assembly 120. In other words, in some embodiments, the inlet port 105 can be monolithically formed with a portion of the cannula assembly 120 to define a fluid flow path between a portion of the housing 101 the cannula assembly 120. In this manner, a portion of the housing 101 can receive a bodily fluid from and/or deliver a parenteral fluid to a patient via a cannula included in the cannula assembly 120, as described in further detail herein.

[1051] The cannula assembly 120 can be any suitable configuration. For example, in some embodiments, the cannula assembly 120 includes an engagement portion and a cannula portion (not shown in FIGS. 1 and 2). In such embodiments, the engagement portion can physically and fluidically couple the cannula assembly 120 to the housing 101 (e.g., it can be the lock mechanism physically and fluidically coupled to the inlet port 105 as described above). The cannula portion can be configured to be inserted into a portion of a patient to deliver a fluid to or receive a fluid from the patient. For example, in some embodiments, the cannula portion can include a distal end with a sharp point configured to pierce a portion of the patient to dispose the cannula portion, at least in part, within a vein of the patient. In other embodiments, a piercing member (e.g., a lumen defining needle) can be movably disposed within the cannula assembly 120 to facilitate the insertion of the cannula portion 120 into the portion of the patient.

[1052] As shown in FIG. 1, the housing 101 can house and/or define the fluid reservoir 130. Similarly stated, in some embodiments, the fluid reservoir 130 can be disposed within and/or at least partially defined by the inner volume 111 of the housing 101. The fluid reservoir 130 can be configured to receive a predetermined amount of the bodily fluid and fluidically isolate the bodily fluid from a volume outside the fluid reservoir 130, as described in further detail herein. While shown in FIGS. 1 and 2 as being disposed within the inner volume 111 of the housing 101, in some embodiments, the fluid reservoir 130 can be disposed substantially outside the housing 101. In such embodiments, the fluid reservoir 130 can be physically and fluidically coupled to a portion of the housing 101. For example, in some embodiments, the fluid reservoir 130 can be coupled to an outlet port (not shown in FIGS. 1 and 2). In other embodiments, the fluid reservoir 130 can be operably coupled to the housing 101 via an intervening structure, such as, for example, a Luer-Lok® and/or flexible sterile tubing. In still other embodiments, the fluid reservoir 130 can be monolithically formed with at least a portion of the housing 101.

[1053] The flow control mechanism 140 included in the transfer device 100 is disposed, at least partially, within the inner volume 111 of the housing 101 and can be moved between a first configuration (FIG. 1) and a second configuration (FIG. 2). The flow control mechanism 140 can be any suitable mechanism configured to control or direct a flow of a fluid. For example, in some embodiments, the flow control mechanism 140 can include a valve (e.g., a check valve or the like) that allows a flow of a fluid in a single direction. In

other embodiments, a valve can selectively control a flow of a fluid in multiple directions. In still other embodiments, the flow control mechanism 140 can define one or more lumens configured to selectively receive a flow of a fluid. In such embodiments, the flow control mechanism 140 can be moved relative to the housing 101 to selectively place a lumen in fluid communication with a portion of the transfer device 100 (e.g., the housing 101, the cannula assembly 120, and/or the fluid reservoir 130). For example, in some embodiments, a portion of the flow control mechanism 140 can be movably disposed, at least temporarily, within the cannula assembly 120 to selectively place the fluid reservoir 130 in fluid communication with the cannula assembly 120. In some embodiments, the portion of the flow control mechanism 140 can include a piercing member such as, for example, a needle configured to extend beyond a distal end of the cannula assembly 120 (not shown in FIGS. 1 and 2) to pierce the skin of a patient and facilitate the insertion of the cannula assembly 120 into a vein of the patient.

[1054] In some embodiments, the transfer device 100 can include an actuator 180 operably coupled to the flow control mechanism 140 and configured to move the flow control mechanism 140 between the first and the second configuration. For example, in some embodiments, the actuator 180 can be a push button, a slider, a toggle, a pull-tab, a handle, a dial, a lever, an electronic switch, or any other suitable actuator. In this manner, the actuator 180 can be movable between a first position corresponding to the first configuration of the flow control mechanism 140, and a second position, different from the first position, corresponding to the second configuration of the flow control mechanism 140. In some embodiments, the actuator 180 can be configured for uni-directional movement. For example, the actuator 180 can be moved from its first position to its second position, but cannot be moved from its second position back to its first position. In this manner, the flow control mechanism 140 is prevented from being moved to its second configuration before its first configuration, as described in further detail herein.

[1055] In use, the flow control mechanism 140 can be in the first configuration to place the fluid reservoir 130 in fluid communication with the cannula assembly 120, as indicated by the arrow AA in FIG. 1. In this manner, the fluid reservoir 130 can receive a flow of bodily fluid that can include dermally residing microbes dislodged during a venipuncture event (e.g., when the cannula assembly 120 and/or the flow control mechanism 140 pierces the skin of the patient). In some embodiments, the fluid reservoir 130 can be configured to

receive a predetermined volume of the bodily fluid. With a desired amount of bodily fluid transferred to the fluid reservoir 130, a user (e.g., a doctor, physician, nurse, technician, phlebotomist, etc.) can manipulate the actuator 180 to move the flow control mechanism 140 from the first configuration to the second configuration. For example, the flow control mechanism 140 can be in the first configuration when the flow control mechanism 140 is in a distal position relative to the housing 101 (FIG. 1) and the actuator 180 can move the flow control mechanism 140 in a proximal direction relative to the housing 101 to place the flow control mechanism in the second configuration, as indicated by the arrow BB in FIG. 2. Moreover, when in the second configuration, the flow control mechanism 140 no longer facilitates the fluidic coupling of the fluid reservoir 130 to the cannula assembly 120. Thus, the fluid reservoir 130 is fluidically isolated from the cannula assembly 120.

[1056] While shown in FIGS. 1 and 2 as being moved in the proximal direction (e.g., in the direction of the arrow BB), in other embodiments, the actuator 180 can move the flow control mechanism 140 between the first configuration and the second configuration in any suitable manner or direction. For example, in some embodiments, the flow control mechanism 140 can be moved in a rotational motion between the first configuration and the second configuration. In other embodiments, the flow control mechanism 140 can be moved in a transverse motion (e.g., substantially perpendicular to the direction of the arrow BB). In such embodiments, the rotational or transverse motion can be such that the flow control mechanism 140 selectively defines one or more fluid flow paths configured to receive a fluid from a patient or to deliver a fluid to the patient, as described in further detail herein.

[1057] In some embodiments, the movement of the flow control mechanism 140 to the second configuration can substantially correspond to a physical and fluidic decoupling of at least a portion of the housing 101 from the cannula assembly 120 such that an external fluid reservoir 199 (e.g., also referred to herein as "fluid source") can be physically and fluidically coupled to the cannula assembly 120. For example, as shown in FIG. 2, in some embodiments, the housing 101 can be moved in the proximal direction (e.g., in the direction of the arrow BB) to be physically and fluidically decoupled from the cannula assembly 120. In some embodiments, the proximal movement of the flow control mechanism 140 urges the housing 101 to move in the proximal direction. In other embodiments, a user (e.g., a physician, phlebotomist, or nurse) can move the housing 101 in the proximal direction. In this manner, the external fluid reservoir 199 can be fluidically coupled to the cannula

assembly 120. Expanding further, with the predetermined amount of bodily fluid transferred to the fluid reservoir 130, the external fluid reservoir 199 can be fluidically coupled to the cannula assembly 120 to deliver a flow of a parenteral fluid that is substantially free from dermally residing microbes dislodged during the venipuncture event, as indicated by the arrow CC in FIG. 2. Similarly stated, the dermally residing microbes that are dislodged during the venipuncture event can be entrained in the flow of the bodily fluid delivered to the fluid reservoir 130. Thus, when the flow control mechanism 140 is moved to the second configuration and the fluid reservoir 130 is fluidically isolated from the cannula assembly 120, the external fluid reservoir 199 can deliver the flow of parenteral fluid substantially free from dermally residing microbes.

[1058] While the housing 101 is shown in FIG. 2 as being moved in the proximal direction such that the external fluid reservoir 199 can be physically and fluidically coupled to the cannula assembly 120, in other embodiments, a housing need not be decoupled from a cannula assembly. For example, FIG. 3 is a schematic illustration of a transfer device 200 according to an embodiment. The transfer device 200 includes a housing 201, a cannula assembly 220, a fluid reservoir 230, and a flow control mechanism 240.

[1059] As shown in FIG. 3, the housing 201 includes a proximal end portion 202 and a distal end portion 203 and defines an inner volume 211 therebetween. The distal end portion 203 can be physically and fluidically coupled to the cannula assembly 220, as described above in reference to FIG. 1. For example, in some embodiments, the distal end portion 203 can include an inlet port 205 (also referred to herein as "first port") or the like that can be physically and fluidically coupled to the cannula assembly 220. The proximal end portion 202 includes an outlet port 206 (also referred to herein as "second port") that can be physically and fluidically coupled to an external fluid reservoir 299. The external fluid reservoir 299 can be any suitable fluid reservoir and can be coupled to the second port 206 via an adhesive, a resistance fit, a mechanical fastener, any number of mating recesses, a threaded coupling, and/or any other suitable coupling or combination thereof. For example, in some embodiments, the external fluid reservoir 299 can be substantially similar to known fluid reservoirs configured to deliver a parenteral fluid (e.g., a fluid source). In some embodiments, the external fluid reservoir 299 is monolithically formed with the second port 206. In still other embodiments, the external fluid reservoir 299 can be operably coupled to the second port 206 via an intervening structure (not shown in FIG. 3), such as, for example,

a flexible sterile tubing. More particularly, the intervening structure can define a lumen configured to place the external fluid reservoir 299 in fluid communication with the second port 206.

[1060] The housing 201 can house or define at least a portion of the fluid reservoir 230. Similarly stated, the fluid reservoir 230 can be at least partially disposed within the inner volume 211 of the housing 201. The fluid reservoir 230 can receive and fluidically isolate a predetermined amount of the bodily fluid, as described above in reference to FIGS. 1 and 2. Similarly, the flow control mechanism 240 is at least partially disposed within the inner volume 211 of the housing 201 and can be moved between a first configuration and a second configuration. More specifically, the flow control mechanism 240 defines a first lumen 246 that fluidically couples the cannula assembly 220 to the fluid reservoir 230 when the flow control mechanism 240 is in the first configuration and a second lumen 247 that fluidically couples the cannula assembly 220 to the external fluid reservoir 299 when the flow control mechanism 240 is in the second configuration.

[1061] In use, the flow control mechanism 240 can be placed in the first configuration to fluidically couple the cannula assembly 220 to the fluid reservoir 230 via the first lumen 246. In this manner, a flow of a bodily fluid can be delivered to the fluid reservoir 230, as indicated by the arrow DD in FIG. 3. More specifically, the bodily fluid can flow from the cannula assembly 220, through the first port 205 (e.g., the inlet port) and into the fluid reservoir 230. As described above in the previous embodiment, the flow of the bodily fluid can contain dermally residing microbes dislodged by a venipuncture event (e.g., the insertion of a portion of the cannula assembly 220 into a vein of the patient).

[1062] With a predetermined amount of bodily fluid disposed within the fluid reservoir 230, the flow control mechanism 240 can be moved (e.g., by an actuator and/or manual intervention from the user) to the second configuration to fluidically isolate the fluid reservoir 230 from the cannula assembly 220. More specifically, the flow control mechanism 240 can be moved from the first configuration to fluidically isolate the first lumen 246 from the cannula assembly 220 and/or the fluid reservoir 230, thereby fluidically isolating the fluid reservoir 230 from the cannula assembly 220. In addition, the movement of the flow control mechanism 240 to the second configuration can place the second lumen 247 in fluid communication with the cannula assembly 220 and the outlet port 206 (e.g., the second port) disposed at the proximal end portion 202 of the housing 201. Thus, the external fluid

reservoir 299 can be fluidically coupled (as described above) to the second port 206 to deliver a flow of parenteral fluid to the patient via the second lumen 247 and the cannula assembly 220, as indicated by the arrow EE. For example, the flow of parenteral fluid can flow from the external fluid reservoir 299 (e.g., a fluid source), in the second port 206, through the second lumen 247 defined by the flow control mechanism 240, out the first port 205 and to the cannula assembly 220 to be delivered to the patient. Moreover, the flow of the parenteral fluid is substantially free from dermally residing microbes and/or other undesirable external contaminants.

[1063] In some embodiments, the transfer device 200 can be configured such that the first amount of bodily fluid needs to be conveyed to the fluid reservoir 230 before the transfer device 200 will permit the flow of the parenteral fluid to be conveyed through the transfer device 200 to the patient. In this manner, the transfer device 200 can be characterized as requiring compliance by a health care practitioner regarding the collection of the predetermined amount of bodily fluid prior to the delivery of the parenteral fluid. Similarly stated, the transfer device 200 can be configured to prevent a health care practitioner from delivering the parenteral fluid to the patient without first diverting or transferring the predetermined amount of bodily fluid to the fluid reservoir 230. In this manner, the health care practitioner is substantially prevented from introducing (whether intentionally or unintentionally) bodily surface microbes and/or other undesirable external contaminants into, for example, the flow of the parenteral fluid and/or the blood stream of the patient. In other embodiments, the fluid transfer device 200 need not include a forced-compliance feature or component.

[1064] FIGS. 4-10 illustrate a transfer device 300 according to an embodiment. The transfer device 300 includes a housing 301, a cannula assembly 320, a fluid reservoir 330, a flow control mechanism 340, and an actuator 380. The transfer device 300 can be any suitable shape, size, or configuration. For example, while shown in FIG. 4 as being substantially cylindrical, the transfer device 300 can be square, rectangular, polygonal, and/or any other non-cylindrical shape. Moreover, any portion of the transfer device 300 can include any feature or finish configured to enhance the ergonomics of the transfer device 300. For example, the housing 301 can include a portion configured to form a grip configured to be engaged by a user's hand.

[1065] The housing 301 includes a proximal end portion 302 and a distal end portion 303 and defines an inner volume 311 therebetween (see e.g., FIG. 6). As shown in FIG. 5, the proximal end portion 302 of the housing 301 includes a protrusion 304 that selectively engages a portion of the fluid reservoir 330, as described in further detail herein. The distal end portion 303 of the housing 301 is coupled to a port 305. More specifically, the port 305 can be coupled to the distal end portion 303 in any suitable manner such as, for example, via a friction fit, a threaded coupling, a mechanical fastener, an adhesive, any number of mating recesses, and/or any combination thereof. In other embodiments, the port 305 can be monolithically formed with the housing 301. Moreover, the port 305 can be coupled to the distal end portion 303 of the housing 301 such that a seal member 316 is disposed between the port 305 and a distal wall 308 of the housing 301. In this manner, when the port 305 is coupled to the housing 301, the seal member 316 can engage the distal wall 308 of the housing 301 and the port 305 to selectively form a substantially fluid tight seal, as described in further detail herein.

[1066] As shown in FIG. 6, the port 305 is removably coupled to a lock mechanism 321 of the cannula assembly 320. The lock mechanism 321 of the cannula assembly 320 can be, at least temporarily, coupled to the port 305 to selectively place the housing 301 in fluid communication with the cannula assembly 320. For example, in some embodiments, the lock mechanism 321 can be a Luer-Lok® that receives a portion of the port 305 to physically and fluidically couple the cannula assembly 320 to the housing 301. In other embodiments, the lock mechanism 321 and the port 305 can be removably coupled in any suitable manner.

[1067] As shown in FIGS. 5 and 6, the fluid reservoir 330 defines an inner volume 333 between a proximal end portion 331 and a distal end portion 332. More specifically, the inner volume 333 is closed at the proximal end portion 331 of the fluid reservoir 330 such that at the proximal end, the inner volume 333 is fluidically isolated from a volume outside the fluid reservoir 330. Conversely, the distal end portion 332 of the fluid reservoir 330 is open such that at the distal end, the inner volume 333 can be in fluid communication with a volume outside the fluid reservoir 330. The distal end portion 332 of the fluid reservoir 330 is movably disposed about the proximal end portion 302 of the housing 301, as shown in FIG. 6. Similarly stated, the proximal end portion 302 of the housing 301 is movably disposed within the inner volume 333 defined by the fluid reservoir 330 such that the inner volume 311 defined by the housing 301 is in fluid communication with the inner volume 333 of the fluid

reservoir 330. Moreover, the distal end portion 332 of the fluid reservoir 330 includes a protrusion 335 that can be placed in contact with the protrusion 304 disposed at the proximal end portion 302 of the housing 301 to substantially limit the movement of the fluid reservoir 330 relative to the housing 301, as described in further detail herein.

[1068] The flow control mechanism 340 included in the transfer device 300 is at least partially disposed within the inner volume 311 of the housing 301 and is configured to be moved between a first configuration and a second configuration. Expanding further, the flow control mechanism 340 is in the first configuration when disposed in a distal position relative to the housing 301 (see e.g., FIG. 6) and is in the second configuration when disposed in a proximal position relative to the housing 301 (see e.g., FIG. 9). As shown in FIGS. 6 and 7, the flow control mechanism 340 includes a first member 341 and a second member 360. The first member 341 includes a proximal end portion 342 and a distal end portion 343 and defines a lumen 346 therethrough. The first member 341 can be any suitable shape, size, or configuration. For example, as shown in FIG. 5, the first member 341 can be substantially cylindrical and can have a diameter substantially corresponding to the diameter of the inner volume 311 of the housing 301.

[1069] The second member 360 of the flow control mechanism 340 includes a proximal end portion 361 and a distal end portion 362 and defines a lumen 363 therethrough. As shown in FIG. 6, at least a portion of the second member 360 is movably disposed within the cannula assembly 320. More specifically, the second member 360 can be substantially cylindrical and can have a diameter substantially corresponding to the inner diameter of the cannula 324 included in the cannula assembly 320. As shown in the enlarged view of FIG. 7, the proximal end portion 361 of the second member 360 is configured to extend through the port 305 and the seal member 316 (described above), and through an opening 309 defined in the distal wall 308 to allow the second member 360 to be coupled to the first member 341. Expanding further, the proximal end portion 361 of the second member 360 is disposed within the lumen 346 defined by the first member 341. In some embodiments, the proximal end portion 361 of the second member 360 can form a friction fit with the walls of the first member 341 that define the lumen 346, thereby coupling the second member 360 to the first member 341. In other embodiments, the second member 360 can be coupled to the first member 341 via an adhesive or the like.

[1070] The distal end portion 362 of the second member 360 is configured to extend beyond a distal end of the cannula 324 included in the cannula assembly 320, when the flow control mechanism 340 is in the first configuration. Furthermore, the distal end portion 362 of the second member 360 can include a sharp point that can facilitate the insertion of the transfer device 300 (e.g., the flow control mechanism 340 and the cannula assembly 320) into a portion of a patient. For example, the distal end portion 362 of the second member 360 can be used to access a vein of the patient and facilitate the introduction of the cannula 324 into the vein. Moreover, with the cannula 324 and the distal end portion 362 of the second member 360 disposed within the vein of the patient the transfer device 300 can be configured to transfer a portion of a bodily fluid from the patient to the fluid reservoir 330 to prevent injection of dislodged dermally residing microbes that have been incompletely sterilized by surface antisepsis and/or other undesirable external contaminants.

[1071] As shown in FIG. 8, the transfer device 300 can be moved to a second configuration to begin a flow of bodily fluid (e.g., blood) from the patient to the transfer device 300. More specifically, the fluid reservoir 330 can be moved in the proximal direction relative to the housing 301 to place the transfer device 300 in the second configuration, as indicated by the arrow FF. The arrangement of the fluid reservoir 330 and the housing 301 is such that the proximal motion of the fluid reservoir 330, relative to the housing 301, increases the inner volume 333 defined by the fluid reservoir 330. Expanding further, the proximal end portion 302 of the housing 301 can be disposed within the inner volume 333 of the fluid reservoir 330 such that the protrusion 304 engages an inner surface of the fluid reservoir 330 to define a substantially fluid tight seal. In addition, the protrusion 335 of the fluid reservoir 330 can be placed in contact with the protrusion 304 of the housing 301 to limit the proximal motion of the fluid reservoir 330 relative to the housing 301. In this manner, the proximal motion of the fluid reservoir 330 relative to the housing 301 increases the collective volume of both the inner volume 311 defined by the housing 301 and the inner volume 333 of the fluid reservoir 330.

[1072] The increase of volume introduces a negative pressure within the inner volume 333 of the fluid reservoir 330 and within the inner volume 311 of the housing 301. Therefore, with the cannula 324 and the second member 360 of the flow control mechanism 340 disposed within the vein of the patient, the negative pressure urges a flow of bodily fluid (e.g., blood) through the lumen 363 and 346 defined by the second member 360 and first

member 341 of the flow control mechanism 340, respectively. As indicated by the arrow GG in FIG. 8, the bodily fluid can flow through the lumen 363 and 346 of the flow control mechanism 340 and enter the collective volume formed and/or defined by the inner volume 311 of the housing 301 and the inner volume 333 of the fluid reservoir 330.

[1073] As shown in FIG. 9, when a predetermined amount of bodily fluid is disposed within the fluid reservoir 330, the flow control mechanism 340 can be moved to its second configuration (e.g., the proximal position relative to the housing 301) to place the transfer device 300 a third configuration. More specifically, the flow control mechanism 340 includes a spring 349 that is in contact with the distal wall 308 of the housing 301 and the distal end portion 343 of the first member 341 included in the flow control mechanism 340. As shown in FIGS. 6-8, the spring 349 is maintained in a compressed configuration while the transfer device 300 is in the first and second configuration. As shown in FIG. 9, when the spring 349 is allowed to expand, the spring 349 exerts a force to move the flow control mechanism 340 in the proximal direction, as indicated by the arrow HH. In some embodiments, the expansion of the spring 349 can be in response to the actuator 380. The actuator 380 can be any suitable mechanism configured to selectively interact with the spring 349 such as, for example, a push button. In other embodiments, the actuator 380 can be a slider, a pull-tab, a lever, a toggle, an electronic switch, or the like.

[1074] The proximal motion of the flow control mechanism 340 can be such that both the first member 341 and the second member 360 of the flow control mechanism 340 are disposed within the collective volume defined by the fluid reservoir 330 and the housing 301. Similarly stated, the spring 349 moves the flow control mechanism 340 in the proximal direction a sufficient distance to move the distal end portion 362 of the second member 360 through the port 305, the seal member 316, and the distal wall 308 to be disposed within the housing 301. Furthermore, the seal member 316 can be configured such that as the distal end portion 362 passes beyond the distal wall 308 of the housing 301, the seal member 316 acts to seal the opening 309 through which the second member 360 was disposed. Thus, when the flow control mechanism 340 is completely disposed within the collective volume defined by the housing 301 and the fluid reservoir 330 (e.g., the combination of the inner volume 311 and the inner volume 333, respectively), the seal member 316 seals the distal end portion 303 of the housing 301 and the fluid reservoir 330 is substantially fluidically isolated from the cannula assembly 320.

[1075] With the fluid reservoir 330 fluidically isolated from the cannula assembly 320, the transfer device 300 can be placed in a fourth configuration, as shown in FIG. 10. More specifically, the housing 301 and the fluid reservoir 330 can be collectively moved in the proximal direction such that the port 305 is physically decoupled from the lock mechanism 321 of the cannula assembly 320, as indicated by the arrow II. In this manner, the fluid reservoir 330 can contain and fluidically isolate a portion of the bodily fluid (e.g., blood) that includes, for example, dermally residing microbes dislodged during the venipuncture event (e.g., the insertion of the distal end portion 362 of the second member 360 of the flow control mechanism 340). Furthermore, with the port 305 decoupled from the lock mechanism 321 of the cannula assembly 320, the cannula assembly 320 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 10) that can deliver a flow of a parenteral fluid that is substantially free from the dermally residing microbes.

[1076] While the fluid reservoir 330 is shown in FIGS. 4-10 as being disposed about a portion of the housing 301, in some embodiments, a transfer device can include a fluid reservoir the is substantially enclosed within a housing. For example, FIGS. 11-15 illustrate a transfer device 400 according to an embodiment. The transfer device 400 includes a housing 401, a cannula assembly 420, a fluid reservoir 430, a flow control mechanism 440, and an actuator 480. As shown in FIGS. 11 and 12, the overall size and shape of the transfer device 400 can be substantially similar to the overall size and shape of the transfer device 300 described above in reference to FIG. 4. In addition, the cannula assembly 420, the flow control mechanism 440, and the actuator 480 can be substantially similar in form and function to the cannula assembly 320, the flow control mechanism 340, and the actuator 380 included in the transfer device 300, described above in reference to FIGS. 4-10. Therefore, the cannula assembly 420, the flow control mechanism 440, and the actuator 480 are not described in further detail herein.

[1077] The housing 401 of the transfer device 400 includes a proximal end portion 402 and a distal end portion 403 and defines an inner volume 411 therebetween. More specifically, the housing 401 is substantially closed at the proximal end portion 402 such that at the proximal end, the inner volume 411 is fluidically isolated from a volume outside the housing 401. The distal end portion 403 of the housing 401 is coupled to a port 405. The port 405 is substantially similar to the port 305 described above, and can be coupled to the distal end portion 403 of the housing 401 such that a seal member 416 is disposed between

the port 405 and a distal wall 408 of the housing 401. In this manner, the seal member 416 can form a substantially fluid tight seal between the distal wall 408 and the port 405 (described in detail with reference the port 305 shown in FIGS. 6 and 7). Furthermore, the port 405 can be configured to removably couple the housing 401 to the cannula assembly 420. For example, the port 405 can be, at least temporarily, physically and fluidically coupled to a lock mechanism 421 included in the cannula assembly 420. In this manner, the housing 401 and the cannula assembly 420 can be selectively placed in fluid communication.

[1078] The fluid reservoir 430 included in the transfer device 400 is movably disposed within the inner volume 411 defined housing 401. More specifically, the fluid reservoir 430 is configured to move within the housing 401 between a first configuration (FIG. 13) and a second configuration (FIG. 14). The fluid reservoir 430 defines an inner volume 433 between a proximal end portion 431 and a distal end portion 432. The inner volume 433 is configured to selectively receive at least a portion of the flow control mechanism 440. Furthermore, the flow control mechanism 440 can moved between a first position and a second position to move the fluid reservoir 430 between the first configuration and the second configuration, as described in further detail herein.

[1079] As shown in FIG. 13, the flow control mechanism 440 is in the first position when disposed in a distal position relative to the housing 401. While in the first position, a first member 441 of the flow control mechanism 440 is completely contained within the inner volume 433 and a second member 460 is configured to extend from the first member 441 through the distal end portion 432 of the fluid reservoir 430. The second member 460 of the flow control mechanism 460 further extends through the housing 401 and the port 405 to be at least partially disposed within the cannula assembly 420 (as described above in detail with reference to the second member 360 shown in FIGS. 6 and 7). In this manner, a distal end portion 462 of the second member 460 can extend beyond a cannula 424 of the cannula assembly 420 to facilitate the insertion of the cannula 424 into a portion of a patient. Moreover, with the distal end portion 462 of the second member 460 disposed within the portion of the patient, a lumen 463 defined by the second member 460 and a lumen 446 defined by the first member 441 can place the fluid reservoir 430 in fluid communication with the portion of the patient.

[1080] In use, the transfer device 400 can be moved from the first configuration (FIG. 13) to the second configuration (FIG. 14) to facilitate the flow of a bodily fluid (e.g., blood) into

the fluid reservoir 430. More specifically, the flow control mechanism 440 includes a mechanical actuator 449 (e.g., a spring) that is in contact with the distal wall 408 of the housing 401 and the first member 441 of the flow control mechanism 440. As shown in FIG. 13, the mechanical actuator 449 is maintained in a compressed configuration while the transfer device 400 is in the first configuration. Similarly stated, the flow control mechanism 440 is in the first position relative to the housing 401 when the mechanical actuator 449 is in the compressed configuration. As shown in FIG. 14, when the mechanical actuator 449 is allowed to expand, the mechanical actuator 449 exerts a force to move the flow control mechanism 440 in the proximal direction, as indicated by the arrow JJ. In some embodiments, the expansion of the mechanical actuator 449 can be in response to an actuation of the actuator 480.

[1081] The proximal motion of the flow control mechanism 440 moves within the inner volume 433 to place the first member 441 in contact with the proximal end portion 441 of the fluid reservoir 430. In this manner, the flow control mechanism 440 urges the proximal end portion 431 of the fluid reservoir 430 to move in the direction of the arrow JJ (e.g., the proximal direction). Moreover, the distal end portion 432 of the fluid reservoir 430 can be coupled to the distal wall 408 of the housing 401 such that as the proximal end portion 431 moves in the proximal direction, the fluid reservoir 430 expands. Similarly stated, the fluid reservoir 430 can form a bellows in which the proximal motion of the flow control mechanism 440 moves the fluid reservoir 430 from a compressed configuration (e.g., the first configuration) to an expanded configuration (e.g., the second configuration).

[1082] The movement of the proximal end portion 431 relative to the distal end portion 432 increases the inner volume 433 defined by the fluid reservoir 430 and introduces a negative pressure within the inner volume 433. Moreover, with the lumen 446 of the first member 441 and the lumen 463 of the second member 460 in fluid communication with the fluid reservoir 430, at least a portion of the negative pressure is transferred through the flow control mechanism 440. Therefore, while the flow control mechanism 440 is being moved to the second position (FIG. 14), the negative pressure urges a flow of bodily fluid (e.g., blood) through the lumen 463 and 446 defined by the second member 460 and first member 441 of the flow control mechanism 440, respectively. Expanding further, as shown in FIG. 14, the proximal motion of the flow control mechanism 440 is such that the second member 460 is retracted to a proximal position relative to the distal wall 408 of the housing 401. Prior to

being disposed in the proximal position relative to the distal wall 408, however, the lumen 463 is maintained in fluid communication with the portion of the patient via the cannula 424. In this manner, the flow control mechanism 440 transfers the bodily fluid to the fluid reservoir 430 while being moved in the proximal direction and prior to being disposed in the second position. Thus, when the second member 460 is retracted to the proximal position relative to the distal wall 408, the flow control mechanism 440 has transferred a predetermined amount of bodily fluid to the fluid reservoir 430 and the seal member 416 can act to fluidically isolate the fluid reservoir 430. Similarly stated, the flow control mechanism 440 is configured to transfer the predetermined amount of bodily fluid to the fluid reservoir 430 concurrently with the proximal motion of both the flow control mechanism 440 and the fluid reservoir 430.

[1083] With the fluid reservoir 430 fluidically isolated from the cannula assembly 420, the transfer device 400 can be placed in a third configuration, as shown in FIG. 15. More specifically, the housing 401 and the fluid reservoir 430 can be collectively moved in the proximal direction to physically decouple the port 405 from the lock mechanism 421 of the cannula assembly 420, as indicated by the arrow KK. In some embodiments, the actuator 480 can facilitate the decoupling of the port 405 from the lock mechanism 421. In other embodiments, a second actuator (not shown) can be engaged to decouple the port 405 from the lock mechanism 421. In other embodiments, an actuator need not be engaged to decouple the port 405 from the lock mechanism 421.

[1084] With the port 405 decoupled from the lock mechanism 421, the fluid reservoir 430 can contain and fluidically isolate a portion of the bodily fluid (e.g., blood) that includes, for example, dermally residing microbes dislodged during the venipuncture event (e.g., the insertion of the distal end portion 462 of the second member 460 of the flow control mechanism 440). Furthermore, with the port 405 decoupled from the lock mechanism 421, the cannula assembly 420 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 15) that can deliver a flow of a parenteral fluid that is substantially free from the dermally residing microbes, as described above.

[1085] While the fluid reservoir 430 is shown in FIGS. 11-15 as being disposed within the inner volume 411 of the housing 401, in some embodiments, a fluid reservoir can be physically and fluidically coupled to a portion of the transfer device. For example, FIGS. 16-23 illustrate a transfer device 500 according to an embodiment. The transfer device 500

includes a housing 501, a cannula assembly 520, a flow control mechanism 540, and an actuator mechanism 580. As shown in FIGS. 16 and 17, the overall size and shape of the transfer device 500 can be substantially similar to the overall size and shape of the transfer device 300 described above in reference to FIG. 4. In other embodiments, the overall size and shape of the transfer device 500 can be square, rectangular, polygonal, and/or any other non-cylindrical shape. In addition, the cannula assembly 520 can be substantially similar in form and function to the cannula assembly 320 included in the transfer device 300, described above in reference to FIGS. 4-10. Therefore, the cannula assembly 520 is not described in further detail herein.

[1086] As shown in FIG. 18, the housing 501 of the transfer device 500 includes a proximal end portion 502 and a distal end portion 503 and defines an inner volume 511 therebetween. The housing 501 is substantially closed at the proximal end portion 502 such that at the proximal end, the inner volume 511 is fluidically isolated from a volume outside the housing 501. The distal end portion 503 of the housing 501 includes a distal wall 508 that defines an opening 509 configured to receive, at least temporarily, a portion of the flow control mechanism 540, as described in further detail herein. The housing 501 further defines an actuator chamber 510 configured to receive at least a portion of the actuator mechanism 580. As shown in FIG. 18, the walls of the housing 501 can be arranged such that the actuator chamber 510 is a bore with a centerline that is substantially perpendicular to a centerline defined by the inner volume 511.

[1087] Referring back to FIG. 17, the actuator mechanism 580 includes a first actuator member 581 and a second actuator member 585. As described in further detail herein, the actuator mechanism 580 can be moved between a first configuration (see e.g., FIG. 16) and a second configuration (see e.g., FIG. 21). The first actuator member 581 can be rotatably coupled to the walls of the housing 501 defining the actuator chamber 510. Similarly stated, the first actuator member 581 is configured to be disposed substantially outside the housing 501 and can be rotatably coupled to the walls of the housing 501 that define the actuator chamber 510. The first actuator member 581 includes an engagement portion 582 and a port 583 configured to be physically and fluidically coupled to a fluid reservoir, as described in further detail herein.

[1088] As shown in FIG. 19, the second actuator member 585 can be substantially cylindrical and is configured to be disposed within the actuator chamber 510 defined by the

housing 501. The second actuator member 585 defines a lumen 587 and a flow control channel 588. The lumen 587 is configured to be in fluid communication with the port 583 of the first actuator member 581. In this manner, the lumen 587 and the port 583 can receive a flow of a bodily fluid when the actuator mechanism 580 is in the first configuration, as described in further detail herein. The flow control channel 588 is configured to receive at least a portion of the flow control mechanism 540 when the actuator mechanism 580 is placed in the second configuration, as described in further detail herein.

[1089] The flow control mechanism 540 included in the transfer device 500 is at least partially disposed within the inner volume 511 of the housing 501 and is configured to be moved between a first position and a second position. Expanding further, the flow control mechanism 540 is in the first position when disposed in a distal position relative to the housing 501 (see e.g., FIG. 20) and is in the second position when disposed in a proximal position relative to the housing 501 (see e.g., FIG. 22). As shown in FIGS. 17 and 20, the flow control mechanism 540 includes a first member 541 and a second member 560. The first member 541 includes a proximal end portion 542 and a distal end portion 543 and defines a lumen 546 therethrough. The first member 541 can be any suitable shape, size, or configuration. For example, as shown in FIG. 17, the first member 541 can be substantially cylindrical with the proximal end portion 542 having a first diameter that substantially corresponds to the diameter of the flow control channel 588 defined by the second actuator member 585. As shown in FIG. 20, the first member 541 can be configured such that when the flow control mechanism 540 is in the first position, the lumen 546 defined by the first member 541 is in fluid communication with the lumen 587 defined by the second actuator member 585, as described in further detail herein.

[1090] The distal end portion 543 of the first member 541 can have a second diameter, smaller than the first diameter, substantially corresponding to an inner diameter of a lock mechanism 521 included in the cannula assembly 520. For example, in some embodiments, the distal end portion 543 can extend through the opening 509 defined by the distal wall 508 of the housing 501 to be disposed within the lock mechanism 521. In some embodiments, the distal end portion 543 can form a friction fit with an inner surface of the lock mechanism 521 to removably couple the flow control mechanism 540 to the cannula assembly 520. Furthermore, with the proximal end portion 542 of the first member 541 disposed in a proximal position relative to the distal wall 508 and with the diameter of the proximal end

portion 542 substantially larger than the diameter of the opening 509, the flow control mechanism 540 operatively couples the housing 501 to the cannula assembly 520.

[1091] The second member 560 of the flow control mechanism 540 includes a proximal end portion 561 and a distal end portion 562 and defines a lumen 563 therethrough. As shown in FIG. 20, at least a portion of the second member 560 is movably disposed within a cannula 524 of the cannula assembly 520. As described above with respect to the flow control mechanism 340, the proximal end portion 561 of the second member 560 is configured to extend through the lock mechanism 521 to be coupled to the first member 541. Expanding further, the proximal end portion 561 of the second member 560 is disposed within the lumen 546 defined by the first member 541. The distal end portion 562 of the second member 560 is configured to extend beyond a distal end of the cannula 524 included in the cannula assembly 520, when the flow control mechanism 540 is in the first configuration. In this manner, the second member 560 can facilitate the insertion of the transfer device 500 into a portion of a patient (e.g., the distal end can include a sharp point) and can further facilitate a transfer of a bodily fluid from the patient to a fluid reservoir (e.g., via the lumen 563).

[1092] For example, as shown in FIG. 20, the transfer device 500 can be in a first configuration when the flow control mechanism 540 is in the first position and the actuator mechanism 580 is in its first configuration. In this manner, the second member 560 of the flow control mechanism 540 and the cannula 524 of the cannula assembly 520 can be inserted into a portion of the patient, such as a vein, to place the transfer device 500 in fluid communication with the portion of the patient. Furthermore, a fluid reservoir (not shown in FIGS. 16-23) can be physically and fluidically coupled to the port 583 of the second actuator member 581. The arrangement of the flow control mechanism 540 and the actuator mechanism 580 is such that when the fluid reservoir is physically and fluidically coupled to the port 583, the fluid reservoir is in fluid communication with the lumen 587 defined by the second actuator member 585 and the two lumen 546 and 563 defined by the first member 541 and the second member 560 of the flow control mechanism 540, respectively. In some embodiments, the fluid reservoir can be, for example, a Vacutainer®. In such embodiments, the fluid reservoir can define a negative pressure such that when fluidically coupled to the port 583, the fluid reservoir introduces a suction force within the portion of the patient (e.g., via the lumen 587, 546, and 563). In this manner, a portion of the suction force can urge a

flow of bodily fluid through the lumen 563, 546, and 587 and into the fluid reservoir, as indicated by the arrow LL in FIG. 20. Moreover, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the flow control mechanism 540 and the cannula 524) become entrained therein and are transferred to the fluid reservoir.

[1093] With a predetermined amount of bodily fluid transferred to the fluid reservoir, the fluid reservoir can be decoupled from the port 583 (e.g., physically and fluidically or only fluidically). In this manner, a user can engage the first actuator member 581 to move the actuator mechanism 580 to its second configuration and thereby place the transfer device in a second configuration. For example, as indicated by the arrow MM in FIG. 21, the user (e.g., a physician, a nurse, a phlebotomist, etc.) can rotate the first actuator member 581 in a clockwise direction relative to the housing 501.

[1094] The actuator mechanism 580 is such that the rotation of the first actuator member 581 urges the second actuator member 585 to also rotate relative to the housing 501. In this manner, a centerline defined by the flow control channel 587 is rotated from a first configuration in which the centerline is substantially perpendicular to the centerline defined by the inner volume 511 to a second configuration in which the centerline is substantially parallel to the centerline of the inner volume 511. Similarly stated, the second actuator member 585 is rotated such that the centerline defined by the flow control channel 587 is aligned with the centerline defined by the inner volume 511.

[1095] As shown in FIG. 22, the rotation of the actuator mechanism 580 toward the second configuration can facilitate the movement of the flow control mechanism 540 from the first position toward the second position. More specifically, the flow control mechanism 540 includes a spring 549 that is disposed about the distal end portion 543 of the first member 541 and is in contact with the distal wall 508 of the housing 501 and a surface of the first member 541. The spring 549 is maintained in a compressed configuration while the transfer device 500 is in the first configuration. For example, as shown in FIG. 20, a proximal surface of the first member 541 of the flow control mechanism 540 can be in contact with a surface of the second actuator mechanism 585 such that the second actuator mechanism 585 prevents proximal movement of the flow control mechanism 540. When the actuator mechanism 580 is moved to the second configuration and the flow control channel 587 is aligned with the inner volume 511 (as described above), however, the proximal surface of the first member

541 is no longer in contact with the surface of the second actuator member 585 and the spring 549 is allowed to expand.

[1096] The expansion of the spring 549 exerts a force on the first member 541 of the flow control mechanism 540 to move the flow control mechanism 540 in the proximal direction, as indicated by the arrow NN in FIG. 22. In this manner, the flow control mechanism 540 can pass through the flow control channel 587 defined by the second actuator member 585 to be disposed in the second position (e.g., the distal position). The proximal motion of the flow control mechanism 540 is such that both the first member 541 and the second member 560 of the flow control mechanism 540 are disposed within the inner volume 511 defined by the housing 501. Similarly stated, the spring 549 moves the flow control mechanism 540 in the proximal direction a sufficient distance to move the distal end portion 562 of the second member 560 through the opening 509 defined by the distal wall 508 to be disposed within the housing 501.

[1097] As shown in FIG. 23, with the flow control mechanism 540 disposed within the housing 501, the distal end portion 543 of the first member 541 is no longer disposed within the lock mechanism 521 of the cannula assembly 520. In this manner, the housing 501 is physically and fluidically decoupled from the cannula assembly 520 and can be moved away from the cannula assembly 520, as indicated by the arrow OO in FIG. 23. Furthermore, with the housing 501 decoupled from the lock mechanism 521, the cannula assembly 520 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 23) that can deliver a flow of a parenteral fluid to the portion of the patient that is substantially free from the dermally residing microbes.

[1098] While the transfer devices described above are configured to include a cannula assembly that is physically and fluidically decoupled from a portion of the transfer device to receive a parenteral fluid, in some embodiments, a transfer device can include a cannula assembly configured to remain physically coupled to a portion of the transfer device. For example, FIGS. 24-30 illustrate a transfer device 600 according to an embodiment. The transfer device 600 includes a housing 601, a cannula assembly 620, a fluid reservoir 630, and a flow control mechanism 640. In use, the transfer device 600 can be moved between a first, a second, and a third configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes.

[1099] As shown in FIGS. 24 and 25, the housing 601 includes a proximal end portion 602 and a distal end portion 603 and defines an inner volume 611 therebetween. The proximal end portion 602 is substantially open such that the inner volume 611 can selectively receive the fluid reservoir 630 and at least a portion of the flow control mechanism 640. In addition, the proximal end portion 602 includes a protrusion 604 configured to engage a portion of the flow control mechanism 640, as described in further detail herein.

[1100] The distal end portion 603 of the housing 601 includes a distal port 605 and a reservoir seat 618. The reservoir seat 618 is configured to engage, at least temporarily, a portion of the fluid reservoir 630, as described in further detail herein. The distal port 605 is configured to be physically and fluidically coupled to a lock mechanism 621 included in the cannula assembly 620. For example, in some embodiments, the lock mechanism 621 can be a Luer-Lok® configured to receive the port 605. In other embodiments, the port 605 and the lock mechanism 621 can be coupled in any suitable manner such as, for example, a threaded coupling, a friction fit, or the like. In still other embodiments, the port 605 and the lock mechanism 621 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 620 to the housing 601. With the lock mechanism 621 coupled to the port 605, the inner volume 611 of the housing 601 is in fluid communication with a cannula 624 included in the cannula assembly 620, as further described herein.

[1101] As described above, the fluid reservoir 630 is disposed within the inner volume 611 of the housing 601. More particularly, the fluid reservoir 630 is movably disposed within the inner volume 611 between a first position in which the fluid reservoir 630 is in a distal position relative to the housing 601 (see e.g., FIG. 28) and a second position in which the fluid reservoir 630 is in a proximal position relative to the housing 601 (see e.g., FIG. 30). As shown in FIG. 26, the fluid reservoir 630 includes a proximal end portion 631 and a distal end portion 632 and defines an inner volume 633 therebetween. The proximal end portion 631 includes a flange 634 and a protrusion 635 and defines a set of openings 636. Furthermore, the proximal end portion 631 of the fluid reservoir 630 is substantially open to receive a portion of the flow control mechanism 640. In this manner, the proximal end portion 631 is configured to engage, interact, or otherwise correspond with a portion of the flow control mechanism 640, as further described herein.

[1102] The distal end portion 632 of the fluid reservoir 630 includes a valve seat 637. The valve seat 637 includes a port 638 and receives a valve 639 (see e.g., FIG. 28-30). The

valve seat 637 is selectively disposed about the reservoir seat 618 of the housing 601, as described in further detail herein. The valve 639 can be any suitable valve such as, for example, a check valve or the like. In this manner, the distal end portion 632 can be selectively placed in fluid communication with the inner volume 611 when the fluid reservoir 630 is disposed within the housing 601, as described in further detail herein.

[1103] As described above, the flow control mechanism 640 can be at least partially disposed within the housing 601. More particularly and as shown in FIG. 27, the flow control mechanism 640 includes an engagement portion 645 configured to be disposed outside the housing 601 and a plunger portion 650 configured to be at least partially disposed within the inner volume 611 defined by the housing 601. As described in further detail herein, the engagement portion 645 can be engaged by a user to move the flow control mechanism 640 between a first configuration and a second configuration.

[1104] The plunger portion 650 of the flow control mechanism 640 is configured to extend in a distal direction from a surface of the engagement portion 645. The plunger 650 includes a first surface 652, a second surface 655, a protrusion 653, a first seal member 658, and a second seal member 659. As shown in FIG. 27, the plunger portion 650 is substantially cylindrical and defines a channel 651 that receives, for example, a cannula 664 that defines a lumen 646. More particularly, the cannula 664 is configured to be disposed within an opening 654 defined by the first surface 652 to place the lumen 646 in fluid communication with an inner volume 656 defined between the first surface 652 and the second surface 655. The plunger 650 is further configured to define a set of openings 657 that can selectively place the inner volume 656 in fluid communication with a portion of the housing 601, as described in further detail herein.

[1105] In use, the transfer device 600 can be moved between a first configuration (FIG. 28), a second configuration (FIG. 29), and a third configuration (FIG. 30). Referring to FIG. 28, while in the first configuration, the cannula 624 of the cannula assembly 620 can be inserted into a portion of a patient to place the cannula 624 in fluid communication with, for example, a vein. In some embodiments, the cannula 624 can include a sharp point at a distal end such that the cannula 624 can pierce the portion of the patient. In other embodiments, the cannula assembly 620 can include a trocar (not shown) to facilitate the insertion of the cannula 624. As described above, the cannula assembly 620 is physically and fluidically coupled to the port 605 of the housing 601 such that when the cannula 624 is placed in fluid

communication with the vein of the patient, the port 605 is concurrently placed in fluid communication with the vein. With the port 605 in fluid communication with the portion of the patient (e.g., the vein), a user (e.g., a physician, nurse, technician, or the like) can engage the engagement portion 645 of the flow control mechanism 640 to place the transfer device 600 in the second configuration.

[1106] As shown in FIG. 29, the transfer device 600 is placed in the second configuration when the plunger portion 650 of the flow control mechanism 640 is moved within the fluid reservoir 630 from a first position (e.g., a distal position) to a proximal position (e.g., a proximal position), as indicated by the arrow PP. More specifically, the transfer device 600 includes a spring 649 configured to engage the protrusion 604 of the housing 601 and the flange 634 of the fluid reservoir 630 to maintain the fluid reservoir 630 in the first position while the flow control mechanism 640 is moved to its second position. Similarly, stated the flow control mechanism 640 is moved in a proximal direction relative to the fluid reservoir 630.

[1107] In addition, the first seal member 658 can engage an inner surface of the fluid reservoir 630 such that the proximal movement of the flow control mechanism 640 produces a negative pressure within a portion of the inner volume 633 of the fluid reservoir 630 (e.g., the portion of the inner volume 633 that is disposed distally relative to the first seal member 658). In this manner, the negative pressure introduces a suction force that can be operable placing the valve 639 in an open configuration. Thus, with the cannula 624 and the port 605 in fluid communication with the portion of the patient (e.g., the vein), a flow of bodily fluid (e.g., blood) can pass through the valve 639 and enter the inner volume 633 of the fluid reservoir 630, as indicated by the arrow QQ.

[1108] As shown in FIG. 29, the proximal movement of the flow control mechanism 640 relative to the fluid reservoir 630 is configured to stop when the flow control mechanism 640 is in the second position (e.g., the proximal position). More specifically, the protrusion 635 of the fluid reservoir 630 can engage the protrusion 653 of the plunger portion 650 to limit the proximal movement of the flow control mechanism 640 relative to the fluid reservoir 630. Furthermore, when the flow control mechanism 640 is in the second position relative to the fluid reservoir 630, the openings 657 of the plunger portion 650 are in fluid communication with the openings 636 defined by the fluid reservoir 630. Thus, the inner volume 656 defined by the plunger portion 650 of the flow control mechanism 640 is placed in fluid

communication with the inner volume 611 of the housing 601, as described in further detail herein.

[1109] With the transfer device 600 in the second configuration, a flow of a predetermined amount of bodily fluid can be transferred to the inner volume 633 of the fluid reservoir 630 that can include, for example, dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 624 into the vein and/or otherwise accessing the vasculature of the patient). In addition, when the predetermined amount of bodily fluid is transferred to the inner volume 633 of the fluid reservoir 630, the valve 639 can be placed in a closed configuration. For example, in some embodiments, the transfer of the predetermined amount of bodily fluid can be such that the negative pressure within the inner volume 633 is brought into equilibrium with the pressure of the vein, thus allowing the valve 639 to move to the closed configuration. In other embodiments, the valve 639 can be manually actuated by user interference (e.g., engagement of an actuator, a switch, a button, a toggle, or the like). In this manner, the bodily fluid disposed in the inner volume 633 between the first seal member 658 and the distal end portion 632 of the fluid reservoir 630 can be fluidically isolated from a volume outside the inner volume 633. Expanding further, the first seal member 658 prevents a flow of the bodily fluid in the proximal direction and the valve 639, being in the closed configuration, prevents a flow of the bodily fluid in the distal direction. Thus, the predetermined amount of bodily fluid is fluidically isolated from a volume outside the inner volume 633 of the fluid reservoir 630 defined between the first seal member 658 and the distal end portion 632.

[1110] As indicated by the arrow RR in FIG. 30, the user can continue to move the flow control mechanism 640 in the proximal direction to place the transfer device 600 in the third configuration. More specifically, with the protrusion 653 of the flow control mechanism 640 in contact with the protrusion 635 of the fluid reservoir 630, the proximal movement of the flow control mechanism 640 is such that the flow control mechanism 640 and the fluid reservoir 630 move, concurrently, in the proximal direction relative to the housing 601. Furthermore, the proximal movement is such that the valve seat 637 is moved in the proximal direction relative to the reservoir seat 618. Similarly stated, the proximal movement of the fluid reservoir 630 is such that the valve seat 637 is no longer disposed about the reservoir seat 618 of the housing 601. In this manner, the port 605 is placed in fluid communication with the inner volume 611 of the housing 601.

[1111] With the transfer device 600 in the third configuration, an external fluid source (not shown in FIG. 30) can be placed in fluid communication with a portion of the transfer device 600 to transfer a flow of parenteral fluid to the portion of the patient. For example, in some embodiments, the transfer device 600 can include a proximal lock mechanism 613 that can physically and fluidically couple the transfer device 600 to the external fluid source. The proximal lock mechanism 613 can be any of those described herein. In this manner, the external fluid source can deliver a flow of parenteral fluid to the lumen 646, as indicated by the arrow SS. Moreover, with the lumen 646 in fluid communication with the inner volume 656 defined between the first surface 652 and the second surface 655, the flow of the parenteral fluid can pass through the openings 657 defined by the plunger portion 650 of the flow control mechanism 640. In addition, the first seal member 658 and the second seal member 659 can act to define a fluid flow path that directs the flow of the parenteral fluid to the openings 636 defined by the fluid reservoir 630. In this manner, the flow of parenteral fluid can pass through the openings 636 of the fluid reservoir 630 to enter the inner volume 611 defined by the housing 601. Similarly stated, upon exiting the openings 636, the parenteral fluid can flow within the inner volume 611 defined by the housing 601 and outside of the fluid reservoir 630, as indicated by the arrows SS. Expanding further, the parenteral fluid can flow within the housing 601 in the distal direction and enter the port 605 to transfer the flow parenteral fluid to the cannula assembly 620. Therefore, the external fluid source can deliver a flow of parenteral fluid to the patient that is fluidically isolated from the predetermined amount of bodily fluid disposed in the fluid reservoir 630 and is thus, substantially free from dermally residing microbes and/or other undesirable external contaminants.

[1112] In some embodiments, user intervention maintains the transfer device 600 in the third configuration. Expanding further and as described above, the proximal movement of the fluid reservoir 630 is such that a portion of the force applied by the user (e.g., the physician, nurse, technician, or the like) to move the flow control mechanism 640 and fluid reservoir 630 is used to move the spring 649 to a compressed configuration. In such embodiments, the removal of the portion of the force would allow the spring 649 to expand and thereby move the fluid reservoir 630 in the distal direction. In other embodiments, a transfer device can include a catch, protrusion, latch or the like configured to maintain the spring in the compressed configuration.

[1113] While the transfer device 600 is shown in FIGS. 24-30 as including a fluid reservoir 630, in other embodiments, a transfer device can include a flow control mechanism with an integrated fluid reservoir. For example, FIGS. 31-34 illustrate a transfer device 700 according to an embodiment. The transfer device 700 includes a housing 701, a cannula assembly 720, and a flow control mechanism 740. In use, the transfer device 700 can be moved between a first configuration and a second configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes and/or other undesirable external contaminants.

[1114] As shown in FIGS. 31 and 32, the housing 701 includes a proximal end portion 702 having a proximal port 706 and a distal end portion 703 having a distal port 705. The proximal port 706 is configured to be physically and fluidically coupled to an external fluid source, as described in further detail herein. The distal port 705 is configured to be physically and fluidically coupled to a lock mechanism 721 included in the cannula assembly 720. For example, in some embodiments, the lock mechanism 721 can be a Luer-Lok® configured to receive the distal port 705. In other embodiments, the distal port 705 and the lock mechanism 721 can be coupled in any suitable manner such as, for example, a threaded coupling, a friction fit, or the like. In still other embodiments, the distal port 705 and the lock mechanism 721 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 720 to the housing 701. With the lock mechanism 721 coupled to the distal port 705, the distal port 705 is placed in fluid communication with a cannula 724 included in the cannula assembly 720, as further described herein.

[1115] The housing 701 defines an inner volume 711 and a set of recess 710. The inner volume 711 is configured to receive at least a portion of the flow control mechanism 740. As shown in FIG. 31, the set of recesses 710 are defined by the housing 701 in a perpendicular orientation relative to the proximal port 706 and distal port 705. Similarly stated, the recesses 710 are perpendicular to a centerline defined by the proximal port 706 and the distal port 705. In this manner, a portion of the flow control mechanism 740 can extend through the recesses 710 when the flow control mechanism 740 is disposed within the inner volume 711 of the housing 701, as described in further detail herein.

[1116] The flow control mechanism 740 defines a first lumen 746, a second lumen 747, and a fluid reservoir 730. The first lumen 746 extends though a portion of the flow control

mechanism 740 and is in fluid communication with the fluid reservoir 730. Similarly stated, the first lumen 746 extends through a portion of the flow control mechanism 740 to selectively place the fluid reservoir 730 in fluid communication with a volume substantially outside of the flow control mechanism 740, as described in further detail herein. As shown in FIG. 33, the second lumen 747 extends through the flow control mechanism 740 and is fluidically isolated from the fluid reservoir 730. In this manner, the second lumen 747 can be selectively placed in fluid communication with the proximal port 706 and the distal port 705 of the housing 701 to deliver a flow of parenteral fluid, as described in further detail herein.

[1117] The flow control mechanism 740 has a circular cross-sectional shape such that when the flow control mechanism 740 is disposed within the inner volume 711, a portion of the flow control mechanism 740 forms a friction fit with the walls of the housing 701 defining the inner volume 711. For example, in some embodiments, the flow control mechanism 740 is formed from silicone and has a diameter larger than the diameter of the inner volume 711. In this manner, the diameter of the flow control mechanism 740 is reduced when the flow control mechanism 740 is disposed within the inner volume 711. Thus, the outer surface of the flow control mechanism 740 forms a friction fit with the inner surface of the walls defining the inner volume 711. In other embodiments, the flow control mechanism 740 can be any suitable elastomer configured to deform when disposed within the inner volume 711 of the housing 701.

[1118] In use, while in the first configuration, the cannula 724 of the cannula assembly 720 can be inserted into a portion of a patient to place the cannula 724 in fluid communication with, for example, a vein. In some embodiments, the cannula 724 can include a sharp point at a distal end such that the cannula 724 can pierce the portion of the patient. In other embodiments, the cannula assembly 720 can include a trocar (not shown) to facilitate the insertion of the cannula 724. As described above, the cannula assembly 720 is physically and fluidically coupled to the distal port 705 of the housing 701 such that when the cannula 724 is placed in fluid communication with the vein of the patient, the distal port 705 is placed in fluid communication with the vein.

[1119] As shown in FIG. 33, when the transfer device 700 is in the first configuration, the first lumen 746 of the flow control mechanism 740 is in fluid communication with the distal port 705 of the housing 701. In this manner, the fluid reservoir 730 defined by the flow control mechanism 740 is placed in fluid communication with the vein of the patient and can

rcccivc a flow of a bodily fluid (c.g., blood). Morcovcr, with thc flow control mcchanism 740 forming a friction fit with the inner surface of the housing 701 (as described above), the flow control mechanism 740 and the housing 701 can form a substantially fluid tight seal about an inlet of the first lumen 746. In this manner, the cannula assembly 720, the distal port 705, and the first lumen 746 collectively define a flow path configured to deliver a flow of bodily fluid from the portion of the patient to the fluid reservoir 730, as indicated by the arrow TT. In addition, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 724) are entrained in the flow of bodily fluid and are transferred to the fluid reservoir 740.

[1120] With a desired amount of bodily fluid transferred to the fluid reservoir 730, a user can engage the transfer device 700 to move the transfer device 700 from the first configuration to the second configuration. In some embodiments, the desired amount of bodily fluid transferred to the fluid reservoir 730 is a predetermined amount of fluid. For example, in some embodiments, the transfer device 700 can be configured to transfer bodily fluid until the pressure within the fluid reservoir 730 is equilibrium with the pressure of the portion of the body in which the cannula 724 is disposed (e.g., the vein). In some cmbodimcnts, at lcast a portion of thc flow control mcchanism 740 can bc transparcnt to allow visualization of the bodily fluid flowing into the fluid reservoir 730. The flow control mechanism 740 can include indicators (e.g., 0.1 mL, 0.5 mL, 1 mL, 1.5 mL, 2 mL, 3 mL, 4 mL, 5 mL, etc. graduation marks) to the user can visualize the volume of bodily fluid that has been received in the fluid reservoir 730.

[1121] As shown in FIG. 34, the transfer device 700 can be moved from the first configuration to the second configuration by moving the flow control mechanism 740 in the direction of the arrow UU. In this manner, the first lumen 746 is fluidically isolated from the distal port 705. While not shown in FIGS. 31-34, the first lumen 746 can include a valve or seal configured to fluidically isolate the bodily fluid disposed within the fluid reservoir 730 from a volume outside the flow control mechanism 740. In some embodiments, the valve can be, for example, a one-way check valve. Thus, the fluid reservoir 730 can receive the flow of fluid from a volume outside the fluid reservoir 730 but prevent a flow of fluid from the fluid reservoir 730.

[1122] When moved to the second configuration, the second lumen 747 defined by the flow control mechanism 740 is placed in fluid communication with the distal port 705 and the

proximal port 706 of the housing 701. As described above, the proximal port 706 can be physically and fluidically coupled to an external fluid source (not shown in FIGS. 31-34) such that when the transfer device 700 is in the second configuration, the proximal port 706, the second lumen 747, the distal port 705, and the cannula assembly 720 collectively define a fluid flow path. In this manner, the transfer device 700 can facilitate the delivery of a flow of parenteral fluid from the external fluid source to the portion of the patient (e.g., the vein), as indicated by the arrow VV in FIG. 34. Expanding further, with the predetermined amount of bodily fluid fluidically isolated within the fluid reservoir 730, the transfer device 700 can facilitate the delivery of the flow of parenteral fluid to the patient that is substantially free from, for example, the dermally residing microbes dislodged during the venipuncture event.

[1123] While the flow control mechanism 740 is shown in FIGS. 31-34 as including the integrated fluid reservoir 730, in other embodiments, a transfer device can be configured to be physically and fluidically coupled to an external fluid reservoir. For example, FIGS. 35-39 illustrate a transfer device 800 according to an embodiment. As shown in FIGS. 35 and 36, the transfer device 800 includes a housing 801, a cannula assembly 820, and a flow control mechanism 880. In use, the transfer device 800 can be moved between a first configuration and a second configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes.

[1124] The housing 801 includes a proximal end portion 802, a distal end portion 803, and defines an inner volume 811. The inner volume 811 can receive at least a portion of the flow control mechanism 880 and the actuator 880, as further described herein. As shown in FIG. 37, the distal end portion 803 of the housing 801 defines a distal port 805 and the proximal end portion 802 of the housing 801 defines a first proximal port 806, and a second proximal port 807. The distal port 805, the first proximal port 806, and the second proximal port 807 are configured to be in fluid communication with the inner volume 811 defined by the housing 801.

[1125] The distal port 805 is configured to receive a distal cannula 817. The distal cannula 817 (e.g., a lumen defining cannula) is configured to be physically and fluidically coupled to a port 822 included in the cannula assembly 820. The port 822 can be any suitable port. For example, in some embodiments, the distal cannula 817 and the port 822 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 820 to the housing

801. With the port 822 of the cannula assembly 820 coupled to the distal cannula 817 and with the distal cannula 817 coupled to the distal port 805, the distal port 805 is in fluid communication with a cannula 824 included in the cannula assembly 820, as further described herein.

[1126] The first proximal port 806 and the second proximal port 807 are configured to receive a first proximal cannula 812 and a second proximal cannula 814, respectively (e.g., lumen defining cannulas). Furthermore, the first proximal cannula 812 is physically and fluidically coupled to a first lock mechanism 813 that can further be physically and fluidically coupled to an external fluid reservoir (not shown in FIGS. 35-39). Similarly, the second proximal cannula 814 is physically and fluidically coupled to a second lock mechanism 815 that can further be physically and fluidically coupled to an external fluid source (not shown in FIGS. 35-39). In this manner, the cannula assembly 820, the external fluid reservoir (not shown), and the external fluid source (not shown) can be selectively placed in fluid communication with the inner volume 811 defined by the housing 801, as described in further detail herein.

[1127] Referring back to FIG. 36, the actuator mechanism 880 includes an engagement portion 882 and an activation surface 884. The activation surface 844 is configured to contact, mate, or otherwise engage the flow control mechanism 840. The engagement portion 882 can be engaged by a user to rotate the actuator mechanism 880 relative to the housing 801 to move the transfer device 800 between a first configuration and a second configuration, as described in further detail herein.

[1128] The flow control mechanism 840 defines a first lumen 846 and a second lumen 847 and is disposed within the inner volume 821 defined by the housing 801. The flow control mechanism 840 defines a circular cross-sectional shape such that when the flow control mechanism 840 is disposed within the inner volume 821, a portion of the flow control mechanism 840 forms a friction fit with the walls of the housing 801 defining the inner volume 821, as described in detail above. The flow control mechanism 840 is operably coupled to and/or otherwise engages the actuator 880. For example, in some embodiments, the actuator mechanism 880 can be coupled to the flow control mechanism 840 via a mechanical fastener and/or adhesive. In other embodiments, the actuator mechanism 880 and the flow control mechanism 840 can be coupled in any suitable manner. Therefore, the flow control mechanism 840 is configured to move concurrently with the actuator mechanism 880

when the actuator mechanism 880 is rotated relative to the housing 801. In this manner, the flow control mechanism 840 can be moved to place the first lumen 846 or the second lumen 847 in fluid communication with the distal port 805, the first proximal port 806, and/or the second proximal port 807, as described in further detail herein.

[1129] In use, while in the first configuration, the cannula 824 of the cannula assembly 820 can be inserted into a portion of a patient to place the cannula 824 in fluid communication with, for example, a vein. In some embodiments, the cannula 824 can include a sharp point at a distal end such that the cannula 824 can pierce the portion of the patient. In other embodiments, the cannula assembly 820 can include a trocar (not shown) to facilitate the insertion of the cannula 824. As described above, the cannula assembly 820 is physically and fluidically coupled to the distal port 805 of the housing 801 such that when the cannula 824 is placed in fluid communication with the vein of the patient, the distal port 805 is placed in fluid communication with the vein.

[1130] Furthermore, a user (e.g., a physician, a nurse, a technician, or the like) can engage the transfer device 800 to physically and fluidically couple the first lock mechanism 813 to an external fluid reservoir (not shown). The external fluid reservoir can be any suitable reservoir. For example, in some embodiments, the external fluid reservoir can be a BacT/ALERT® SN or a BacT/ALERT® FA, manufactured by BIOMERIEUX, INC. In this manner, the external fluid reservoir can define a negative pressure within an inner volume of the reservoir. Therefore, when the flow control mechanism 840 is in the first configuration, a negative pressure differential introduces a suction force within the first proximal cannula 812, the first lumen 846 defined by the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820. In this manner, the first proximal cannula 812, the first lumen 846 defined by the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820 collectively define a fluid flow path configured to transfer a flow of a bodily fluid to the external fluid reservoir, as indicated by the arrow WW in FIG. 37. In addition, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 824) are entrained in the flow of bodily fluid and are transferred to the external fluid reservoir.

[1131] As shown in FIG. 38, in some embodiments, the magnitude of the suction force can be modulated by moving the actuator mechanism 880 in the direction of the arrow XX. For example, in some instances, it can be desirable to limit the amount of suction force

introduced to a vein. In such instances, the user can move the actuator mechanism 880 and the flow control mechanism 840 to reduce the size of the fluid pathway (e.g., an inner diameter) between the distal port 805 of the housing 801 and the first lumen 846 of the flow control mechanism 840, thereby reducing the suction force introduced into the vein of the patient.

[1132] With the desired amount of bodily fluid transferred to the external fluid reservoir, a user can engage the actuator mechanism 880 to move the transfer device 800 from the first configuration to the second configuration. In some embodiments, the desired amount of bodily fluid transferred to the external fluid reservoir is a predetermined amount of fluid. For example, in some embodiments, the transfer device 800 can be configured to transfer bodily fluid until the pressure within the external fluid reservoir is equilibrium with the pressure of the portion of the body in which the lumen-defining device is disposed (e.g., the vein), as described above. In some embodiments, at least a portion of the external fluid reservoir can be transparent to allow visualization of the bodily fluid flowing into the fluid reservoir. The external fluid reservoir can include indicators (e.g., 0.1 mL, 0.5 mL, 1 mL, 1.5 mL, 2 mL, 3 mL, 4 mL, 5mL, etc. graduation marks to accommodate identification of diversion volumes ranging from just a few drops or centiliters of blood to a larger volumes) so the user can visualize the volume of bodily fluid that has been received in the external fluid reservoir.

[1133] The transfer device 800 can be moved from the first configuration to the second configuration by further moving the actuator mechanism 880 in the direction of the arrow XX in FIG. 38. As the actuator mechanism 880 is moved from the first configuration toward the second configuration, the actuator mechanism 880 rotates the flow control mechanism 840 toward its second configuration. In this manner, the first lumen 846 is fluidically isolated from the distal port 805 and the first proximal port 806 and the external fluid reservoir can be physically and fluidically decoupled from the transfer device 800. In addition, the second lumen 847 defined by the flow control mechanism 840 is placed in fluid communication with the distal port 805 and the second proximal port 807, as shown in FIG. 39.

[1134] With the transfer device in the second configuration, the second proximal lock mechanism 815 can be physically and fluidically coupled to the external fluid source (not shown in FIGS. 35-39). In this manner, the second proximal cannula 814, the second lumen 847 of the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820 collectively define a fluid flow path. Thus, the transfer device 800 can facilitate the delivery

of a flow of parenteral fluid from the external fluid source to the portion of the patient (e.g., the vein), as indicated by the arrow YY in FIG. 39. Expanding further, with the predetermined amount of bodily fluid transfer to the external fluid reservoir and with the external fluid reservoir decoupled from the transfer device 800, the transfer device 800 can facilitate the delivery of the flow of parenteral fluid to the patient that is substantially free from, for example, the dermally residing microbes dislodged during the venipuncture event or otherwise introduced to the fluid flow path to the patient.

[1135] FIG. 40 is a flowchart illustrating a method 990 of delivering a fluid to a patient using a fluid transfer device, according to an embodiment. The method 990 includes establishing fluid communication between the patient and the fluid transfer device, at 991. The fluid transfer device can be any of those described herein. As such, the fluid transfer device can include a cannula assembly or the like that can be inserted percutaneously to place the fluid transfer device in fluid communication with the patient (e.g., inserted into a vein of the patient). More specifically, in some embodiments, the cannula assembly of the fluid transfer device can include a sharpened distal end configured to pierce the skin of the patient. In other embodiments, the transfer device can include a flow control mechanism that can include a sharpened distal end portion that is configured to extend beyond a distal end portion of the cannula assembly to pierce the skin of the patient. For example, in some embodiments, the fluid transfer device can include a flow control mechanism that is substantially similar to the flow control mechanism 340 of the transfer device 300 described above with reference to FIGS. 4-10.

[1136] With the cannula assembly in fluid communication with the patient, a predetermined volume of a bodily fluid is withdrawn from the patient, at 991. For example, in some embodiments, the fluid transfer device can include a flow control mechanism, such as those described above, that can be moved between a first configuration and a second configuration. In some embodiments, flow control mechanism can be configured to define a fluid flow path between, for example, the cannula assembly and a fluid reservoir included in and/or fluidically coupled to the fluid transfer device. In other embodiments, any portion of fluid transfer device can define at least a portion of the fluid flow path. For example, the fluid transfer device can include a housing or the like that can define at least a portion of the fluid flow path. Thus, the predetermined volume of the bodily fluid is transferred to the fluid reservoir, at 993. In some embodiments, the predetermined volume of the bodily fluid can

include, for example, dermally residing microbes that were dislodged during, for example, the venipuncture event (e.g., inserting the cannula assembly into the patient).

[1137] Once the predetermined volume of bodily fluid is disposed in the fluid reservoir, the fluid transfer device is fluidically isolated from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir, at 994. For example, in some embodiments, once the predetermined volume of bodily fluid is disposed in the fluid reservoir, the fluid transfer device can be physically and/or fluidically decoupled from the fluid reservoir. In other embodiments, the flow control mechanism (as described above) can be moved from the first configuration to the second configuration to fluidically isolate the fluid reservoir from a volume outside of the fluid reservoir. For example, in some embodiments, the flow control mechanism can define a lumen or the like that can define a fluid flow path between the cannula assembly and the fluid reservoir when in the first configuration. In such embodiments, the flow control mechanism can be transitioned (e.g., moved, rotated, and/or otherwise reconfigured) from the first configuration to the second configuration in which the lumen is removed from fluid communication with the cannula assembly and/or the fluid reservoir, thereby fluidically isolating the fluid reservoir from the cannula assembly. In some embodiments, the flow control mechanism can be configured to transition from the first configuration to the second configuration automatically once the predetermined volume of bodily fluid is disposed in the fluid reservoir.

[1138] With the fluid reservoir fluidically isolated from at least a portion of the fluid transfer device, fluid communication is established between the patient and a fluid source via the fluid transfer device, at 995. For example, in some embodiments, the fluid source can be operably coupled to the fluid transfer device to place the fluid source in fluid communication with at least a portion of the fluid transfer device. In some embodiments, the flow control mechanism (described above) can define a second lumen that can place the fluid source in fluid communication with the cannula assembly when in the second configuration. In other embodiments, with the fluid reservoir decoupled from the fluid transfer device that fluid source can be placed in fluid communication with the cannula assembly via any other portion of the fluid transfer device (e.g., a portion of a housing and/or the like). In this manner, a fluid can flow from the fluid source, through the fluid transfer device and into the patient. Moreover, by fluidically isolating the predetermined volume of bodily fluid the flow of fluid

from the fluid source can be substantially free of contaminants such as, for example, the dermally residing microbes, as described above.

[1139] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Where methods and steps described above indicate certain events occurring in certain order, those of ordinary skill in the art having the benefit of this disclosure would recognize that the ordering of certain steps may be modified and that such modifications are in accordance with the variations of the invention. Additionally, certain of the steps may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above. Additionally, certain steps may be partially completed before proceeding to subsequent steps.

[1140] While various embodiments have been particularly shown and described, various changes in form and details may be made. For example, while the actuator 580 is shown and described with respect to FIG. 21 as being rotated in a single direction, in other embodiments, an actuator can be rotated in a first direction (e.g., in the direction of the arrow MM in FIG. 21) and a second direction, opposite the first. In such embodiments, the rotation in the second direction can be configured to move a transfer device through any number of configurations. In other embodiments, the rotation of the actuator in the second direction can be limited.

[1141] Although various embodiments have been described as having particular features and/or combinations of components, other embodiments are possible having any combination or sub-combination of any features and/or components from any of the embodiments described herein.

[1142] The specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. More specifically, the size and shape of the various components can be specifically selected for a desired rate of bodily fluid flow into a fluid reservoir or for a desired rate of parenteral fluid flow into the patient.

Claims

1. An apparatus, comprising:

a cannula assembly;

a housing including a proximal end portion and a distal end portion and defining an inner volume therebetween, the housing having an inlet port configured to be removably coupled to the cannula assembly;

a fluid reservoir fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from the patient;

a flow control mechanism at least partially disposed in the inner volume of the housing and configured to move relative to the housing between a first configuration and a second configuration, the flow control mechanism defining a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration; and

an actuator operably coupled to the flow control mechanism and configured to move the flow control mechanism from the first configuration in which the inlet port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

2. The apparatus of claim 1, wherein the flow control mechanism includes a fluid communicator configured to be moved from a first position to a second position to place the flow control mechanism in the second configuration.

3. The apparatus of claim 2, wherein the fluid communicator is configured to extend through the inlet port and beyond the distal end portion of the housing in the first position.

4. The apparatus of claim 2, wherein the fluid communicator is retracted into the inner volume of the housing in the second position.

5. The apparatus of claim 1, wherein the flow control mechanism includes a first member movably disposed in the inner volume of the housing, and a second member coupled to the first member and configured to extend through the inlet port and beyond the distal end portion of the housing in the first configuration.

6. The apparatus of claim 5, wherein the first member includes a proximal end portion and a distal end portion, and defines a lumen therethrough.

7. The apparatus of claim 6, wherein the second member includes a proximal end portion and a distal end portion, and defines a lumen therethrough.

8. The apparatus of claim 7, wherein the proximal end portion of the second member is configured to be disposed in the lumen defined by the first member.

9. The apparatus of claim 7, wherein the distal end portion of the second member is configured to extend beyond a distal end of the cannula assembly when the flow control mechanism is in the first configuration.

10. The apparatus of claim 9, wherein the second member is a needle configured to be inserted into the patient

11. The apparatus of claim 1, wherein the cannula assembly is removably coupled to the housing.

12. The apparatus of claim 1, wherein the flow control mechanism includes a spring configured to expand and move the flow control mechanism from the first configuration to the second configuration.

13. The apparatus of claim 12, wherein the actuator is configured to release the spring from a compressed state when actuated by a user.

14. The apparatus of claim 1, wherein the fluid reservoir is movably coupled to the housing and configured to be moved from a first position to a second position, the movement from the first position to the second position configured to create a negative pressure in the fluid reservoir.

15. The apparatus of claim 1, wherein the fluid reservoir is movably disposed within the inner volume of the housing, the fluid reservoir including a proximal end portion and a

distal end portion and defining an inner volume therebetween, the inner volume configured to selectively receive at least a portion of the flow control mechanism.

16. The apparatus of claim 15, wherein the proximal end portion of the fluid reservoir is configured to move relative to the distal end portion of the fluid reservoir to increase the inner volume defined by the fluid reservoir and create a negative pressure within the inner volume.

17. The apparatus of claim 1, wherein the fluid reservoir is movably disposed within the inner volume of the housing and configured to move from a first configuration to a second configuration to create a negative pressure in the fluid reservoir.

18. The apparatus of claim 17, wherein the actuator is configured to move the fluid reservoir from the first configuration to the second configuration when actuated by a user.

19. The apparatus of claim 1, wherein the actuator includes an outlet port configured to be fluidically coupled to the fluid reservoir.

20. The apparatus of claim 19, wherein the actuator defines a lumen configured to allow fluid communication between the fluid flow path and the outlet port when the flow control mechanism is in the first configuration.

21. The apparatus of claim 20, wherein the actuator is configured to rotate from a first position in which bodily fluid can flow from the flow control mechanism, through the outlet port and to the fluid reservoir, to a second position, in which the flow control mechanism is placed in the second configuration and the fluid reservoir is fluidically isolated from the cannula assembly.

22. A device for delivering a fluid to a patient with reduced contamination, the device comprising:

a housing including a proximal end portion and a distal end portion and defining an inner volume therebetween, the housing having a first port configured to be removably coupled to a cannula assembly, and a second port configured to be fluidically coupled to a fluid source;

a fluid reservoir fluidically couplcablc to a cannula assembly and configured to receive and isolate a predetermined volume of bodily fluid withdrawn from the patient; and

a flow control mechanism at least partially disposed in the inner volume of the housing and configured to move relative to the housing between a first configuration in which the first port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through first port and to the fluid reservoir, and a second configuration in which (a) the fluid reservoir is fluidically isolated from the cannula assembly, and (b) fluid can flow from the fluid source, in the second port, through the flow control mechanism, out the first port and to the cannula assembly.

23. The device of claim 22, wherein the fluid reservoir is disposed in the inner volume of the housing and is at least partially defined by the flow control mechanism.

24. The device of claim 23, wherein the fluid reservoir includes an inlet port configured to be fluidically coupled to the first port of the housing.

25. The device of claim 24, further comprising a valve disposed in the inlet port of the fluid reservoir.

26. The device of claim 25, wherein the valve is a check valve.

27. The device of claim 24, wherein the fluid reservoir is configured to move relative to the housing from a first position in which the inlet port is fluidically coupled to the first port of the housing, to a second position in which the inlet port is fluidically isolated from the first port of the housing.

28. The device of claim 22, wherein the flow control mechanism includes a first sealing member and a second sealing member spaced apart from the first sealing member, the first sealing member at least partially defining the fluid reservoir.

29. The device of claim 28, wherein the flow control mechanism is configured to move the first sealing member and the second sealing member from a first position to a second position to place the flow control mechanism in the second configuration.

30. The device of claim 29, wherein the movement of the first sealing member from the first position to the second position is configured to create a negative pressure in the fluid reservoir.

31. The device of claim 22, wherein the fluid reservoir is defined by the flow control mechanism.

32. The device of claim 31, wherein the fluid reservoir includes an inlet port configured to be fluidically coupled to the first port of the housing in the first configuration, and fluidically isolated from the first port of the housing in the second configuration.

33. The device of claim 22, wherein the flow control mechanism defines a lumen, the lumen configured to be fluidically isolated from the first port and the second port of the housing in the first configuration, and in fluid communication with the first port and the second port of the housing in the second configuration such that fluid can flow from the fluid source, in the second port of the housing, through the lumen of the flow control mechanism, and out the first port of the housing.

34. The device of claim 22, wherein the flow control mechanism is configured to rotate from a first position in which the flow control mechanism is in the first configuration, to a second position in which the flow control mechanism is placed in the second configuration.

35. A method of delivering a fluid to a patient using a fluid transfer device, the method comprising:

establishing fluid communication between the patient and the fluid transfer device;

withdrawing a predetermined volume of a bodily fluid from the patient;

transferring the predetermined volume of the bodily fluid to a fluid reservoir;

fluidically isolating the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir; and

establishing fluid communication between the patient and a fluid source with the fluid transfer device.

36. The method of claim 35, whereby sequestering the predetermined volume of the bodily fluid in the fluid reservoir establishes a sterile fluid flow path between the fluid source and the patient.

37. The method of claim 35, wherein the fluid transfer device includes a flow control mechanism, the method further comprising:

disposing the flow control mechanism in a first configuration prior to withdrawing the predetermined volume of bodily fluid from the patient, the first configuration establishing fluid communication between the patient and the fluid reservoir.

38. The method of clam 37, further comprising:

after the predetermined volume of bodily fluid has been transferred the fluid reservoir, moving the flow control mechanism to a second configuration, the second configuration establishing fluid communication between the fluid source and the patient.

39. The method of claim 38, wherein the flow control mechanism is automatically moved from the first configuration to the second configuration after the predetermined volume of bodily fluid has been transferred to the fluid reservoir.

40. The method of claim 35, further comprising:

delivering fluid from the fluid source to the patient.

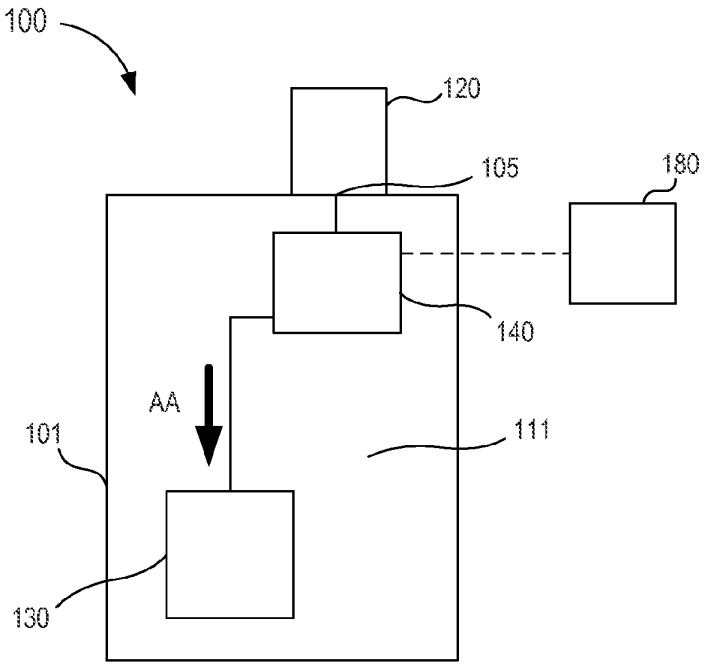

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FIG. 1

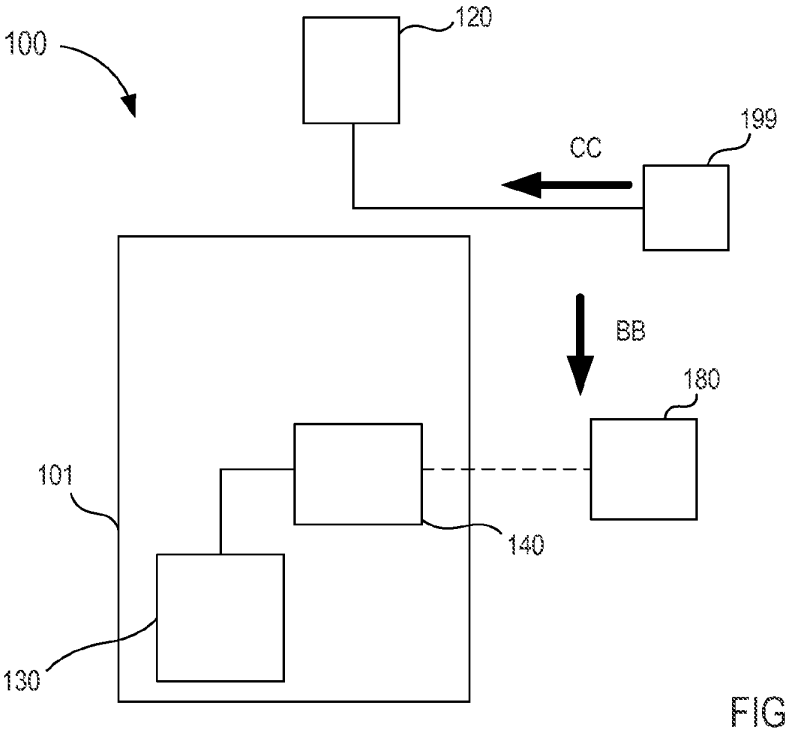

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FIG. 2

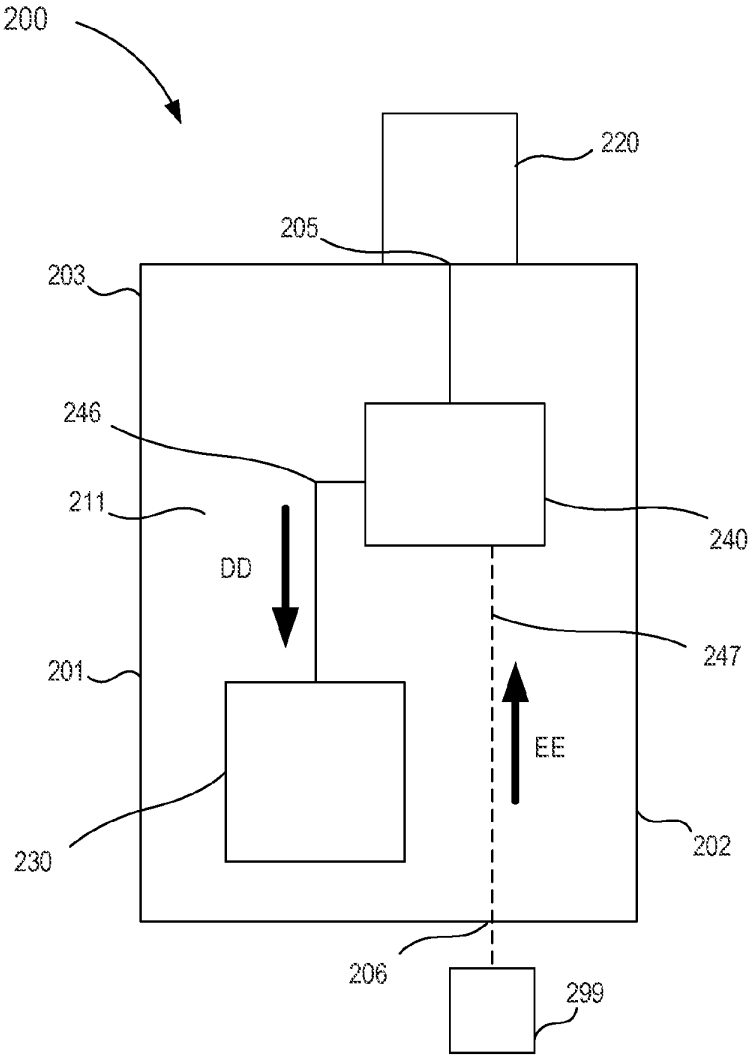


FIG. 3

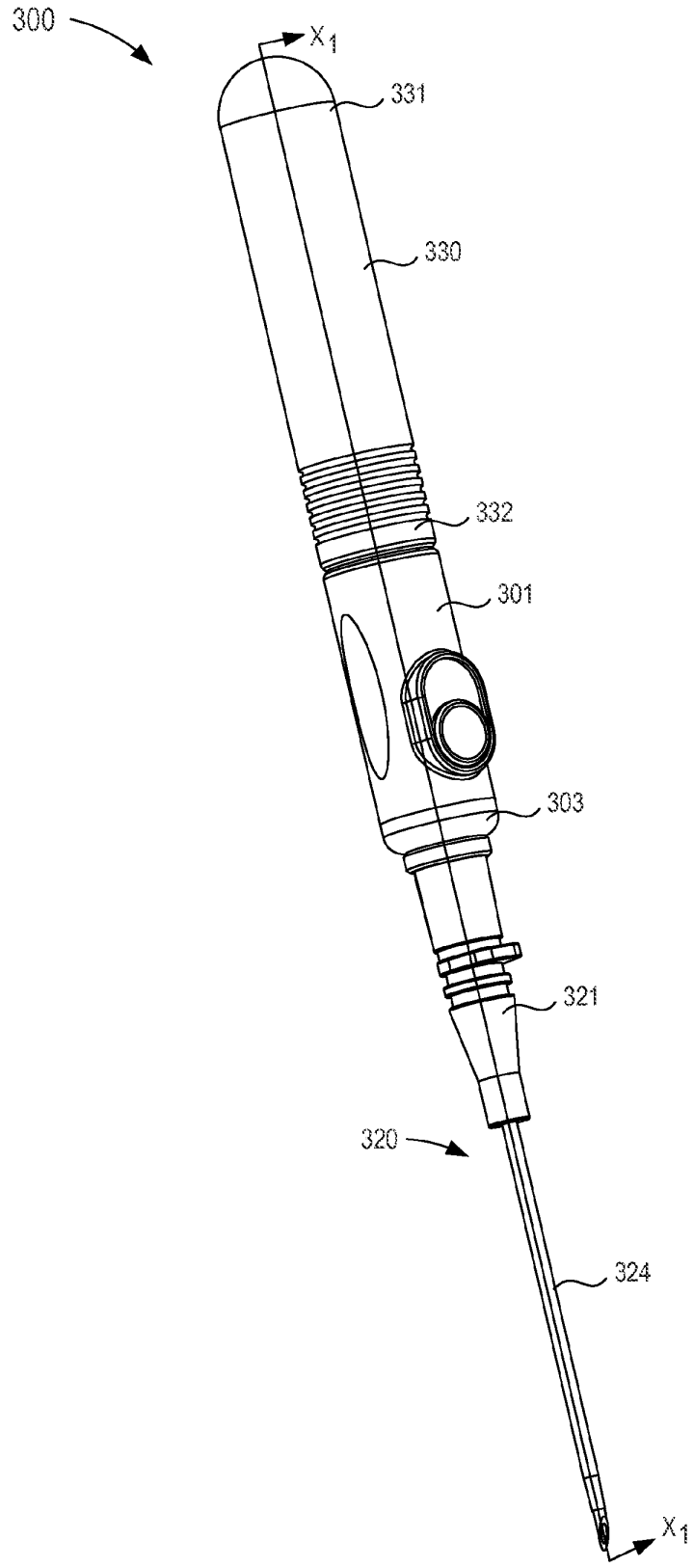


FIG. 4

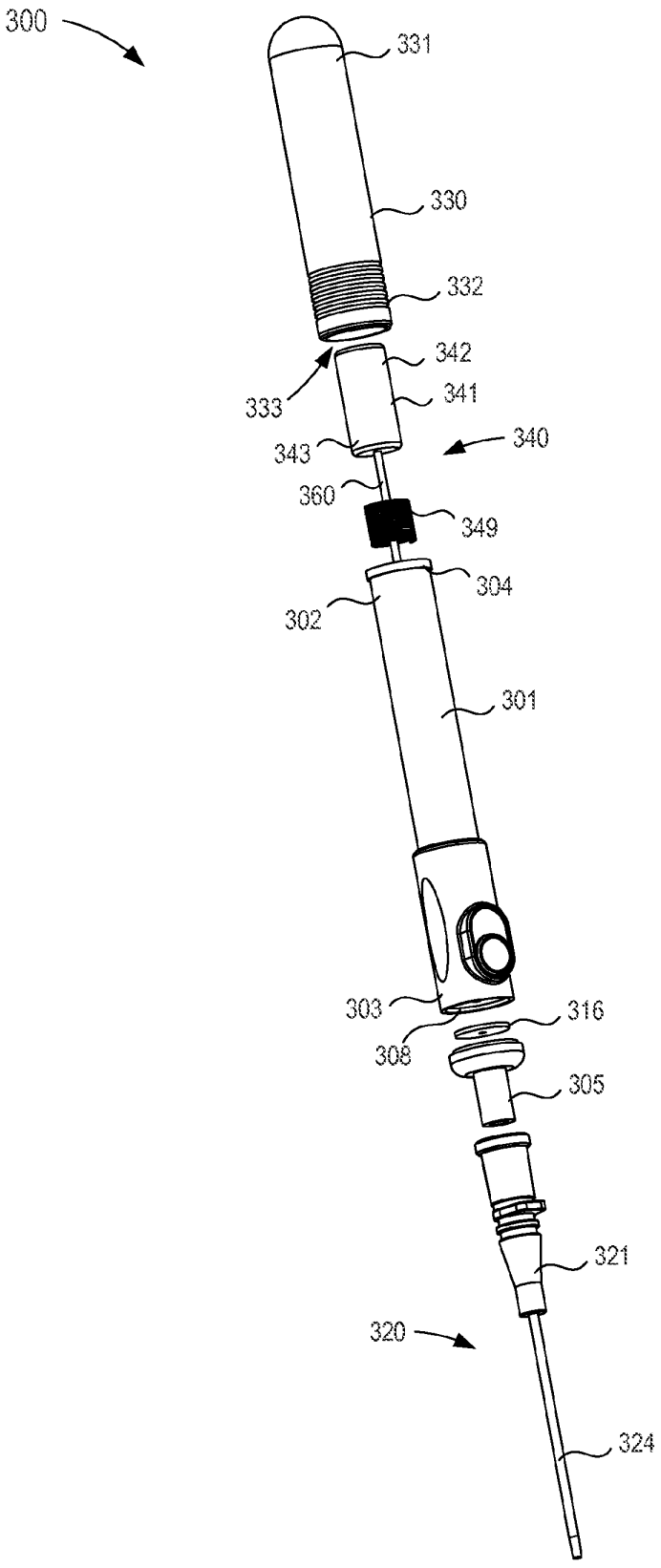

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FIG. 5

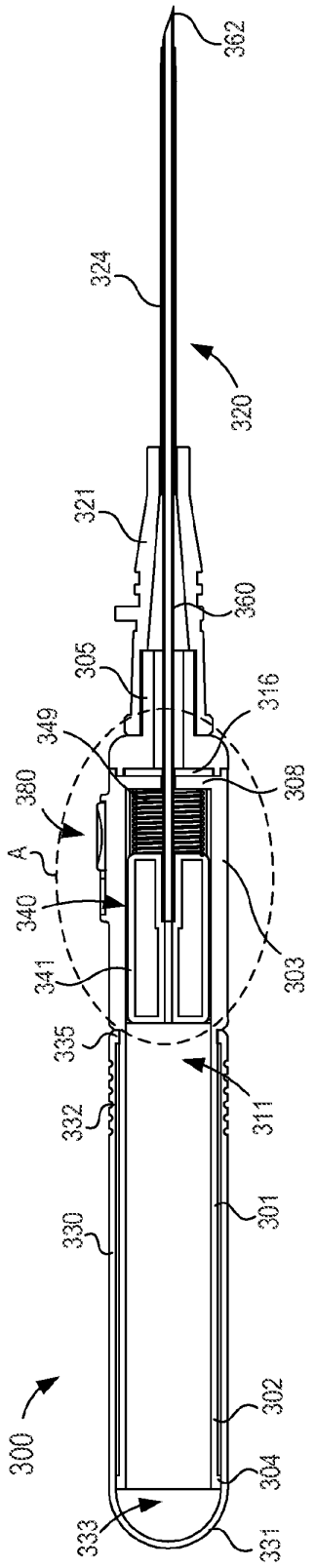

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FIG. 6

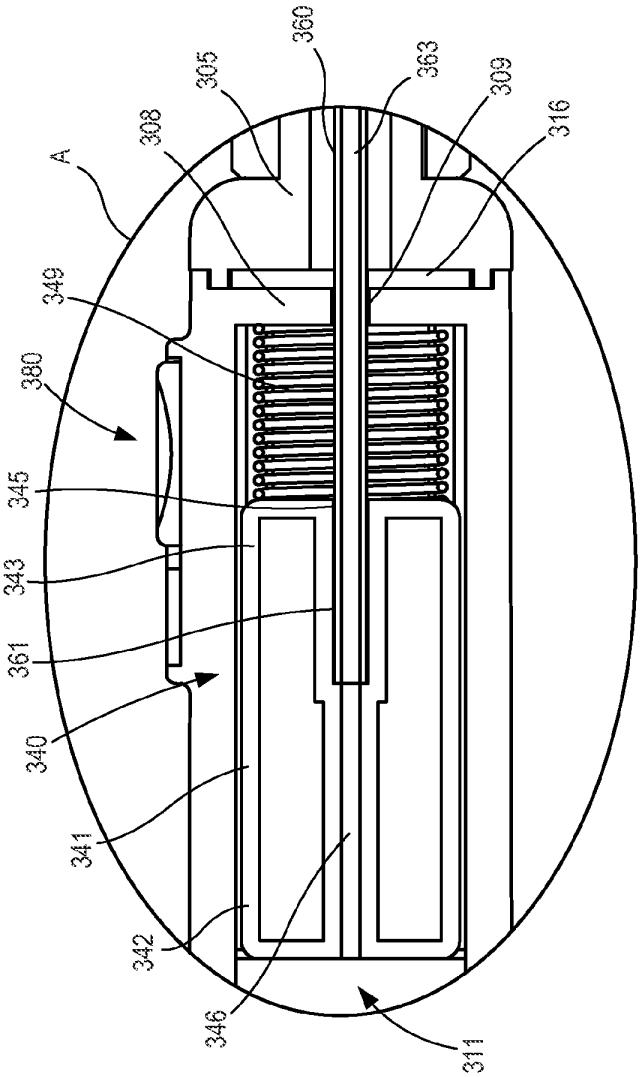

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FIG. 7

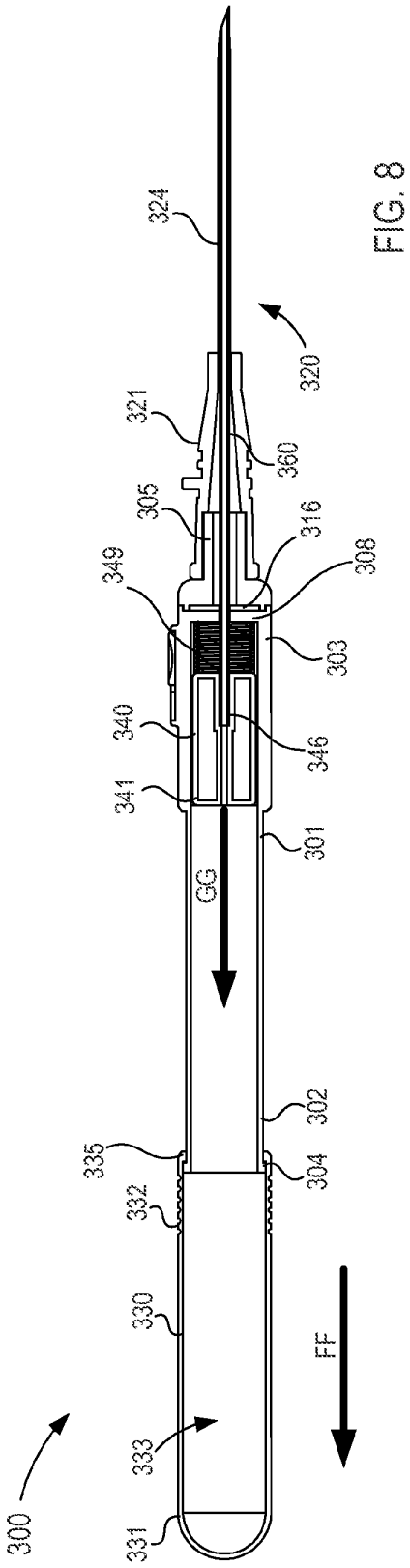

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FIG. 8

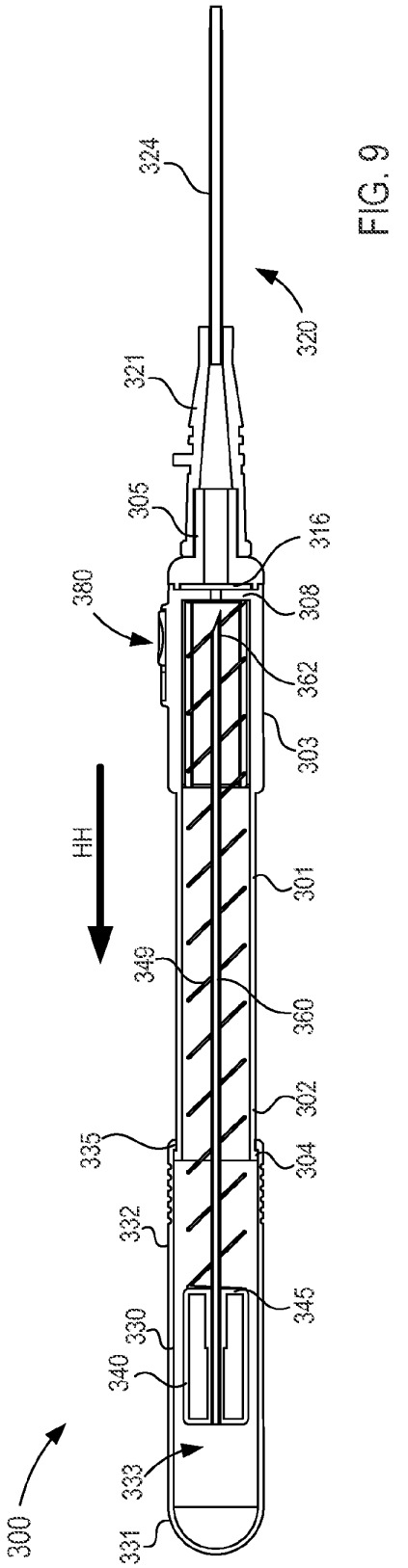

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FIG. 9

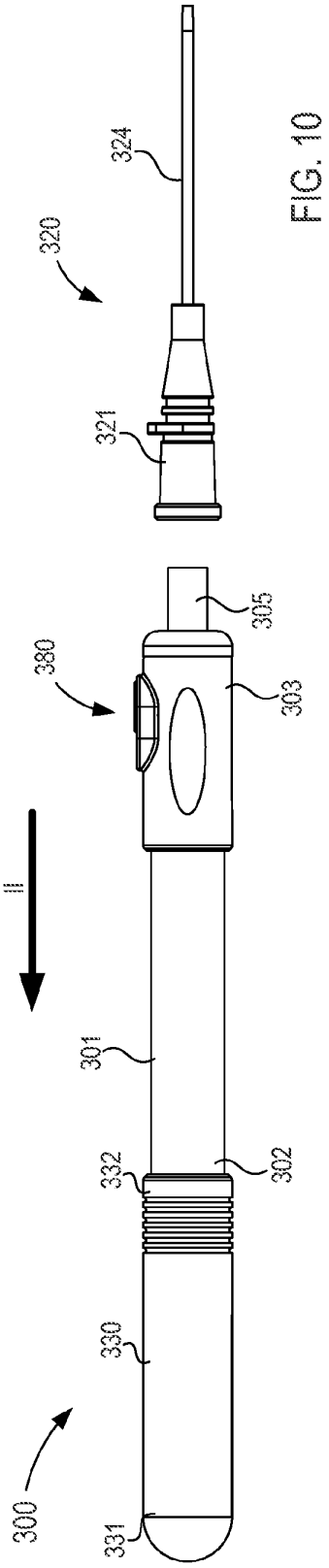


FIG. 10

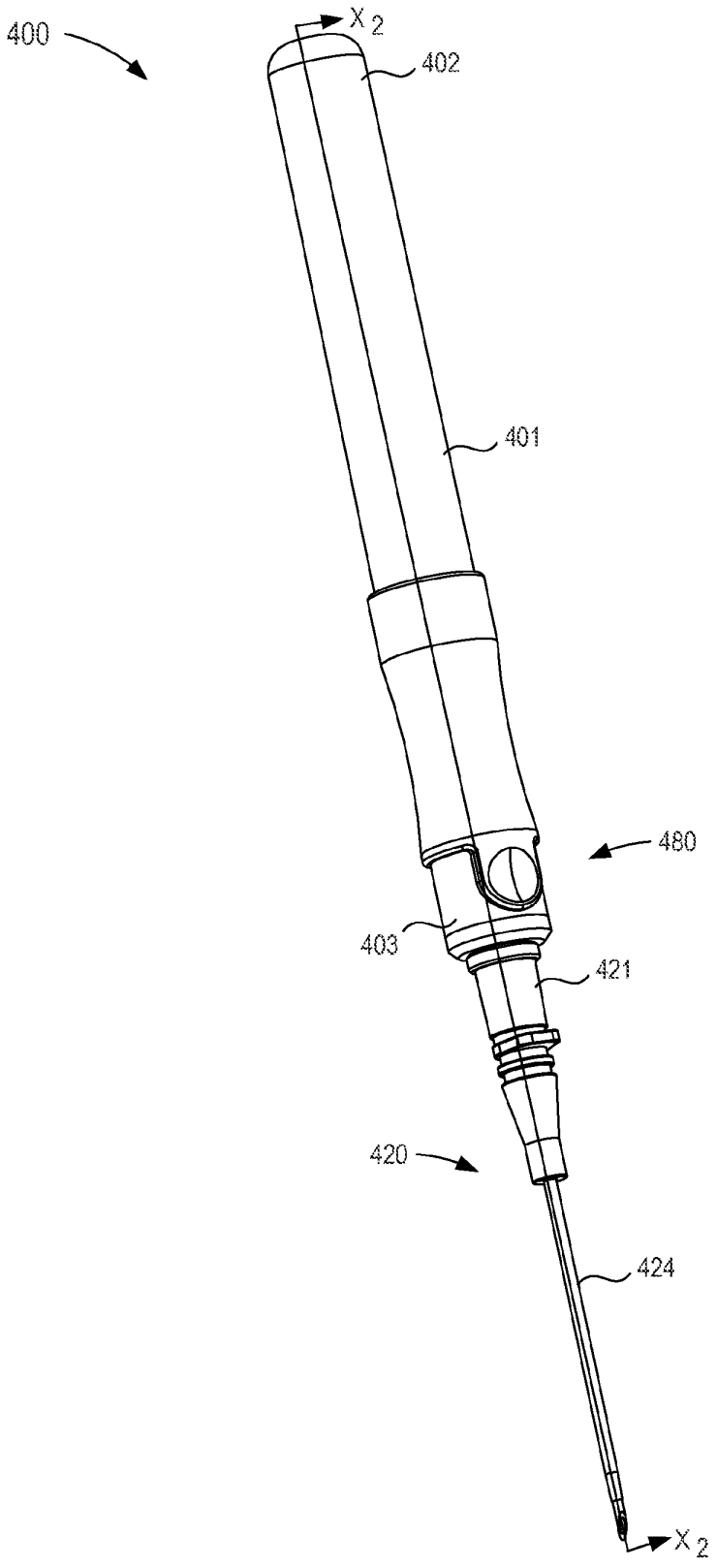


FIG. 11

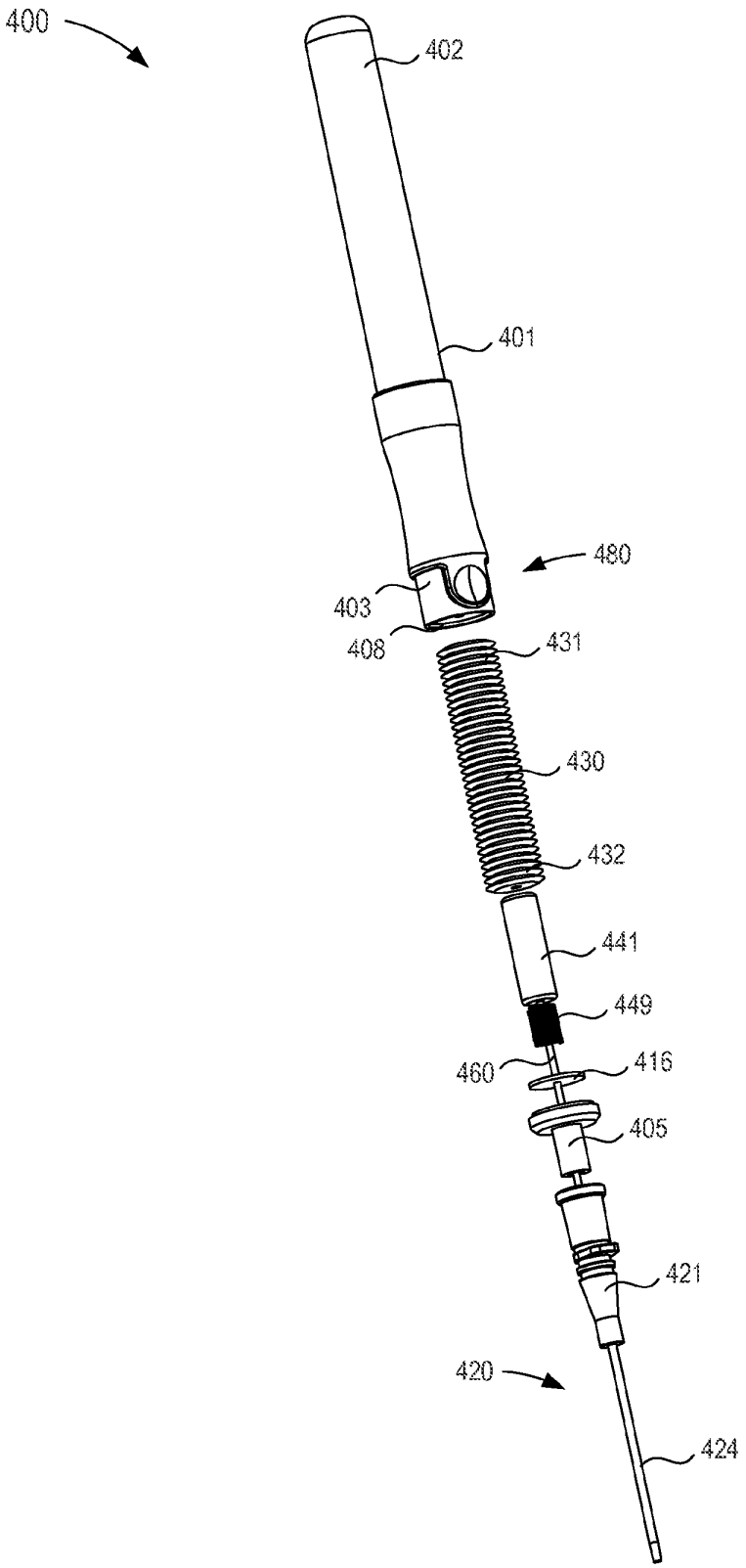

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FIG. 12

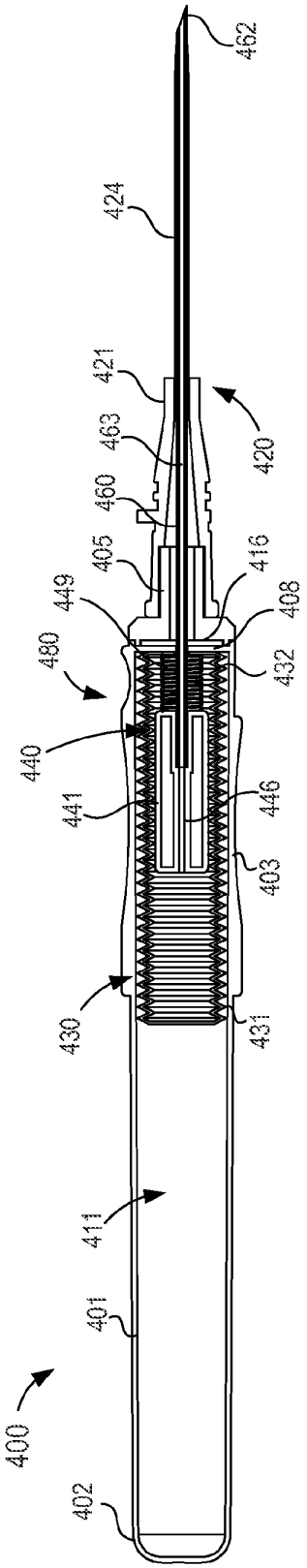

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FIG. 13

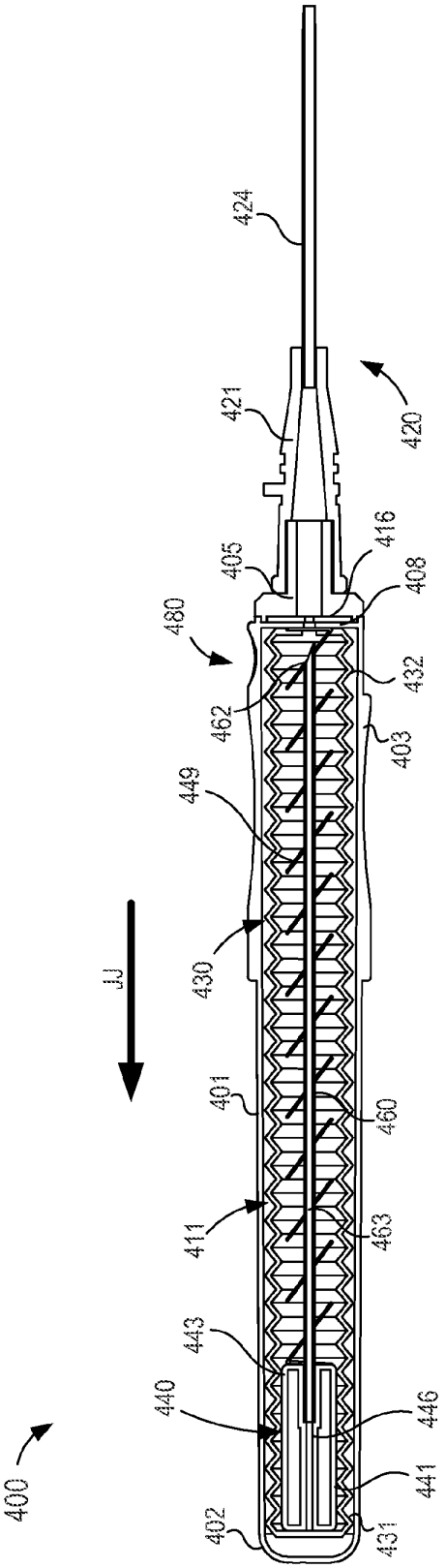

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FIG. 14

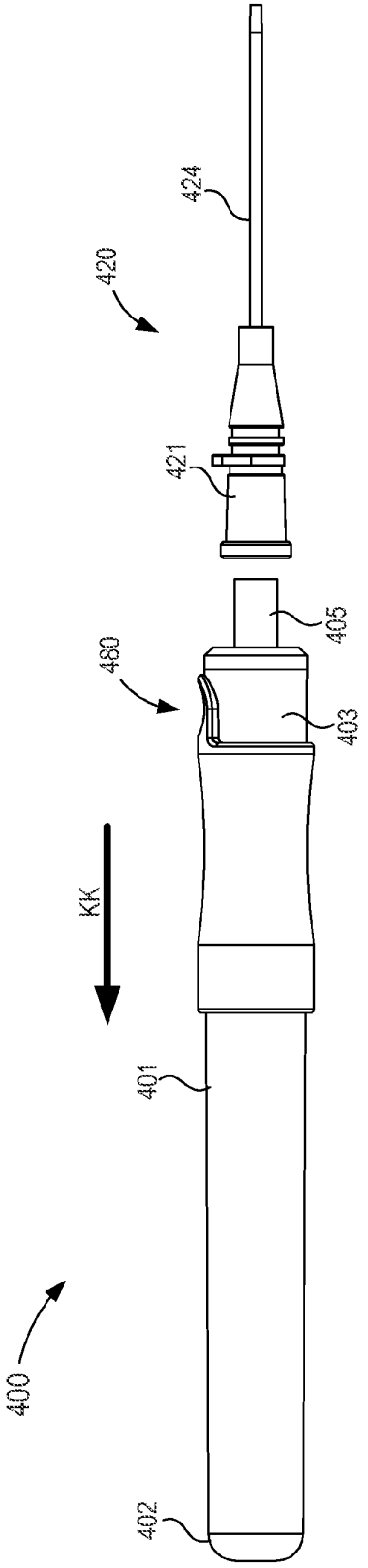


FIG. 15

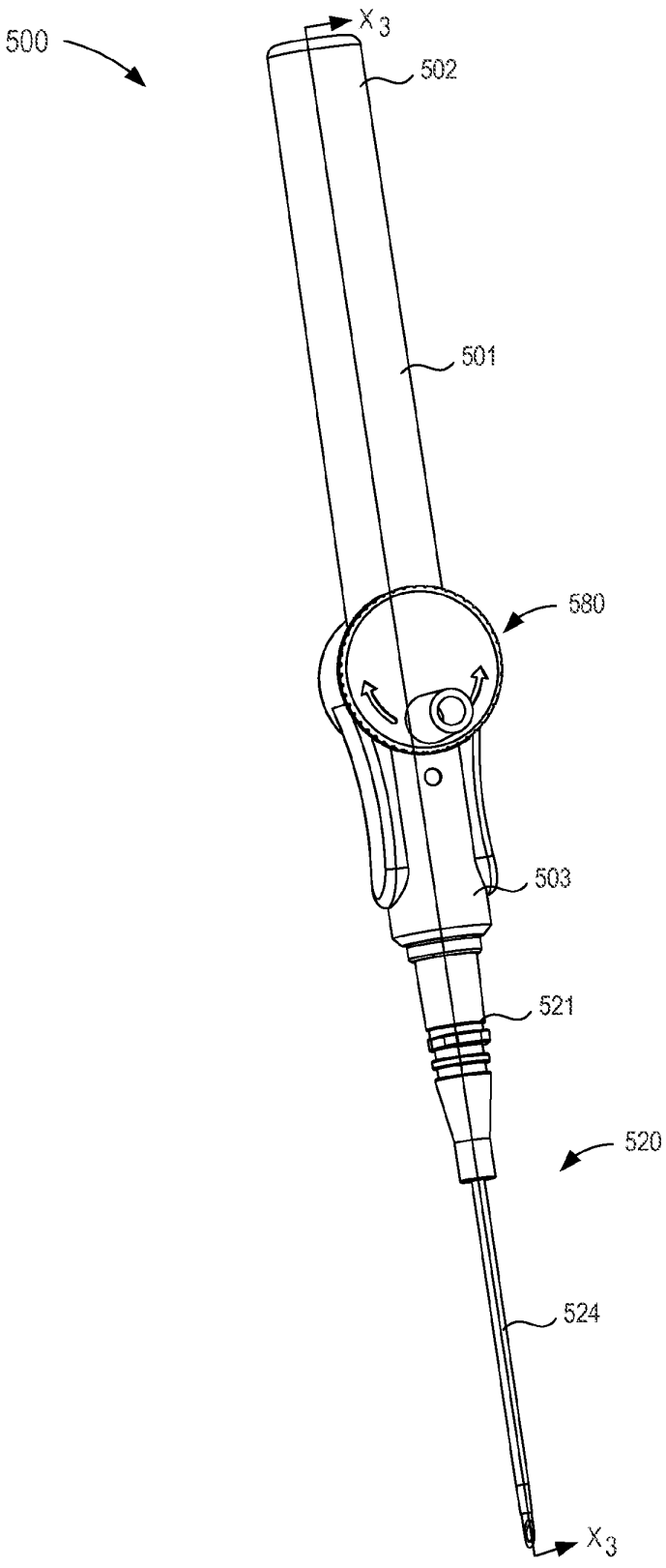


FIG. 16

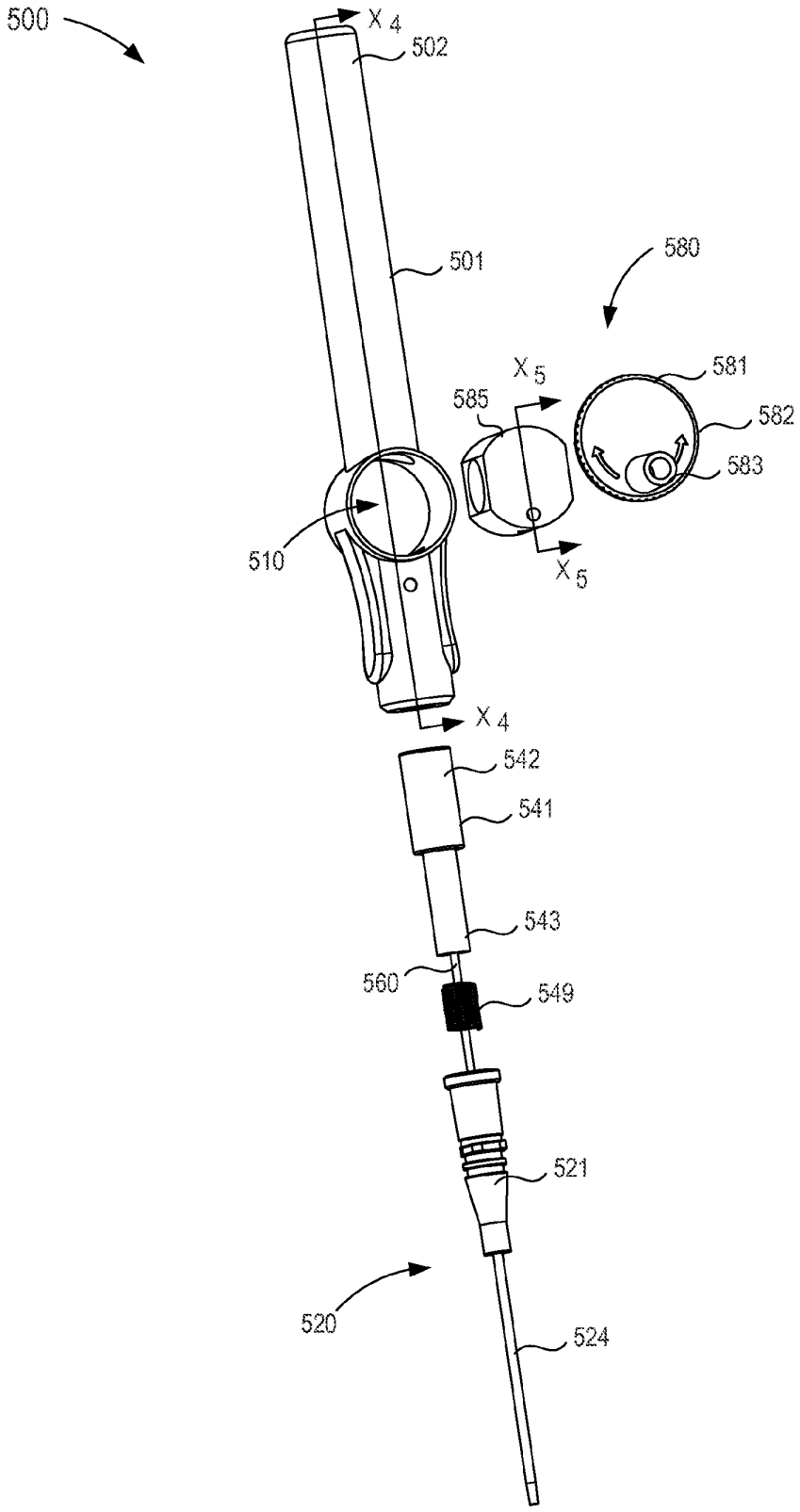

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FIG. 17

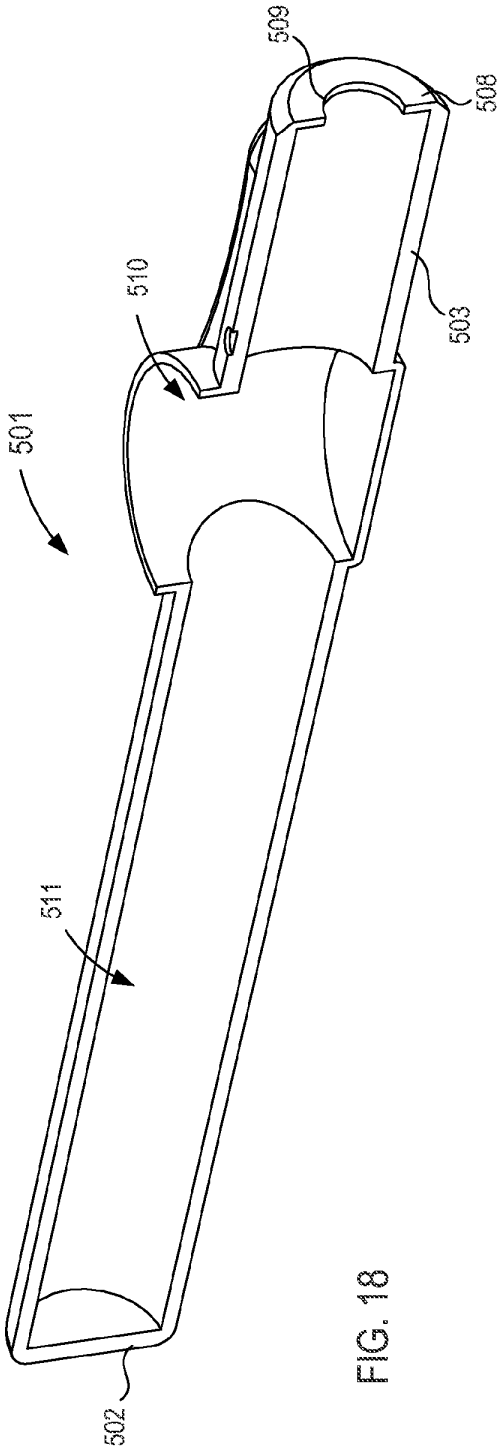


FIG. 18

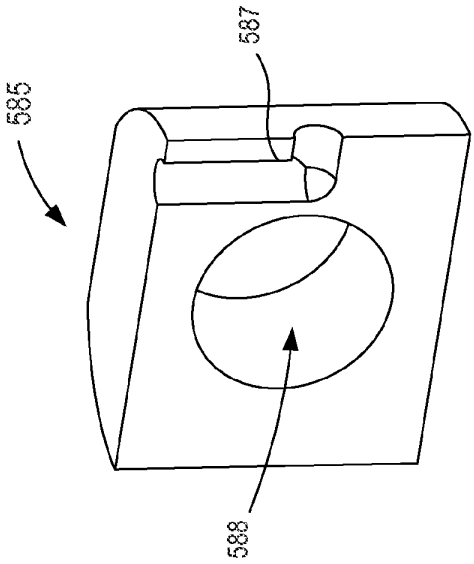


FIG. 19

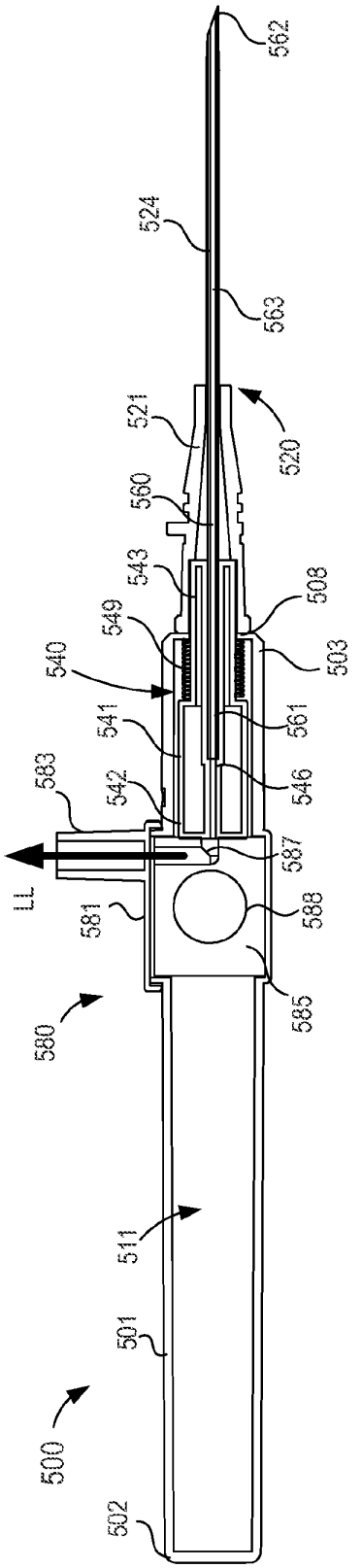

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FIG. 20

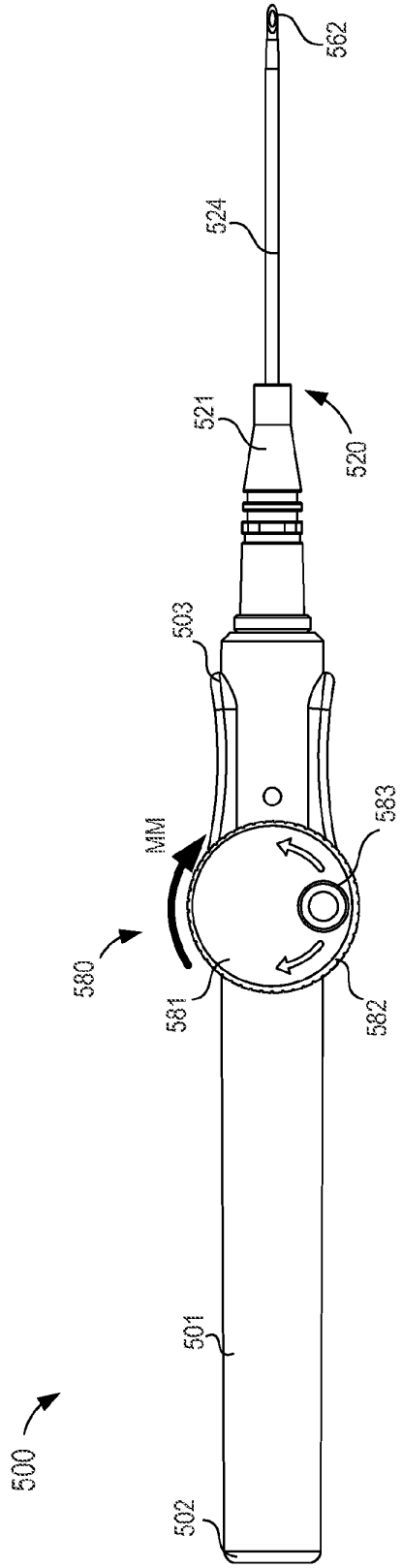

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FIG. 21

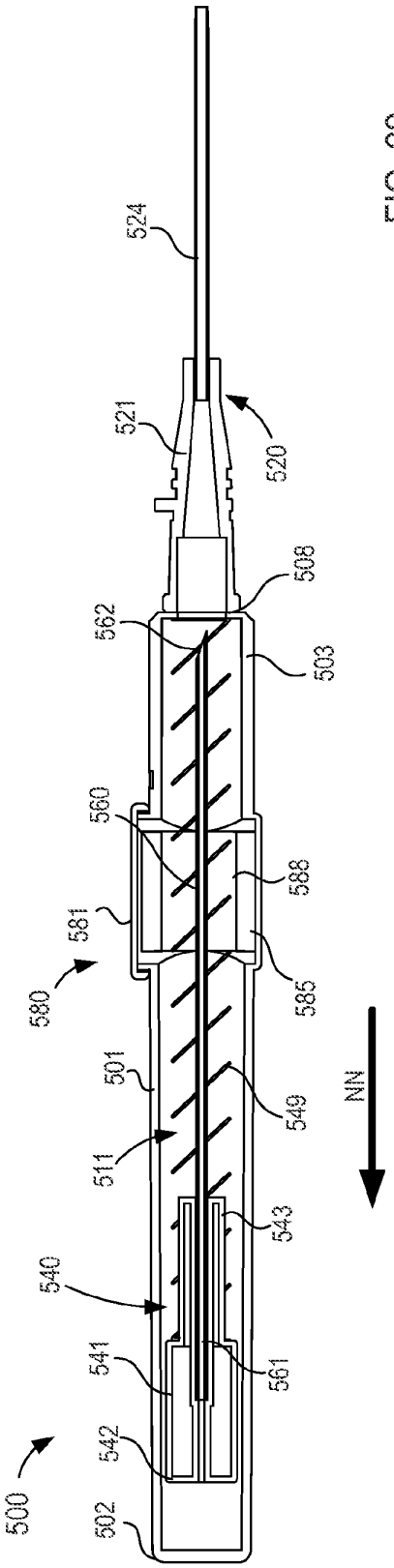

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FIG. 22

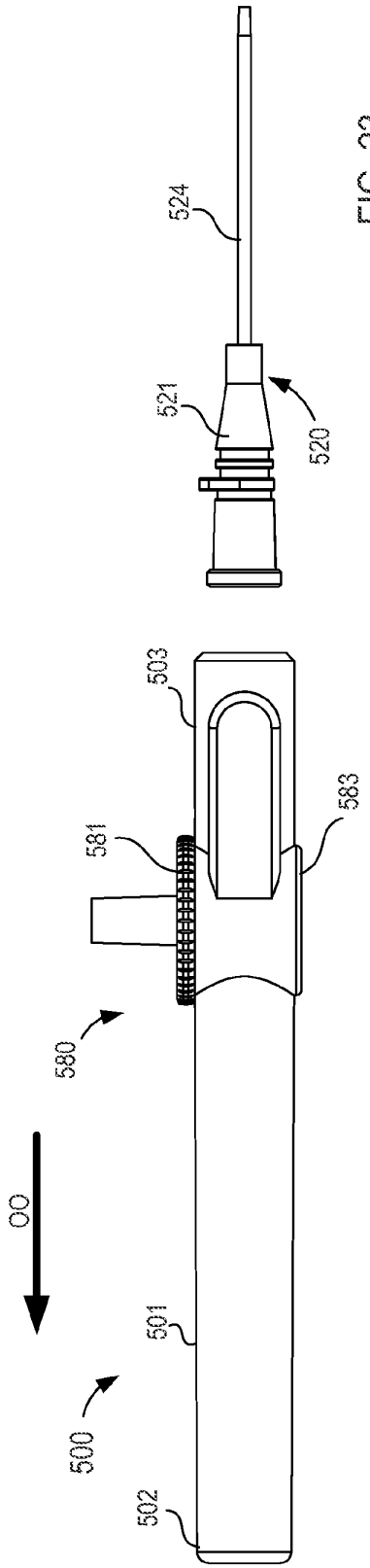

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FIG. 23

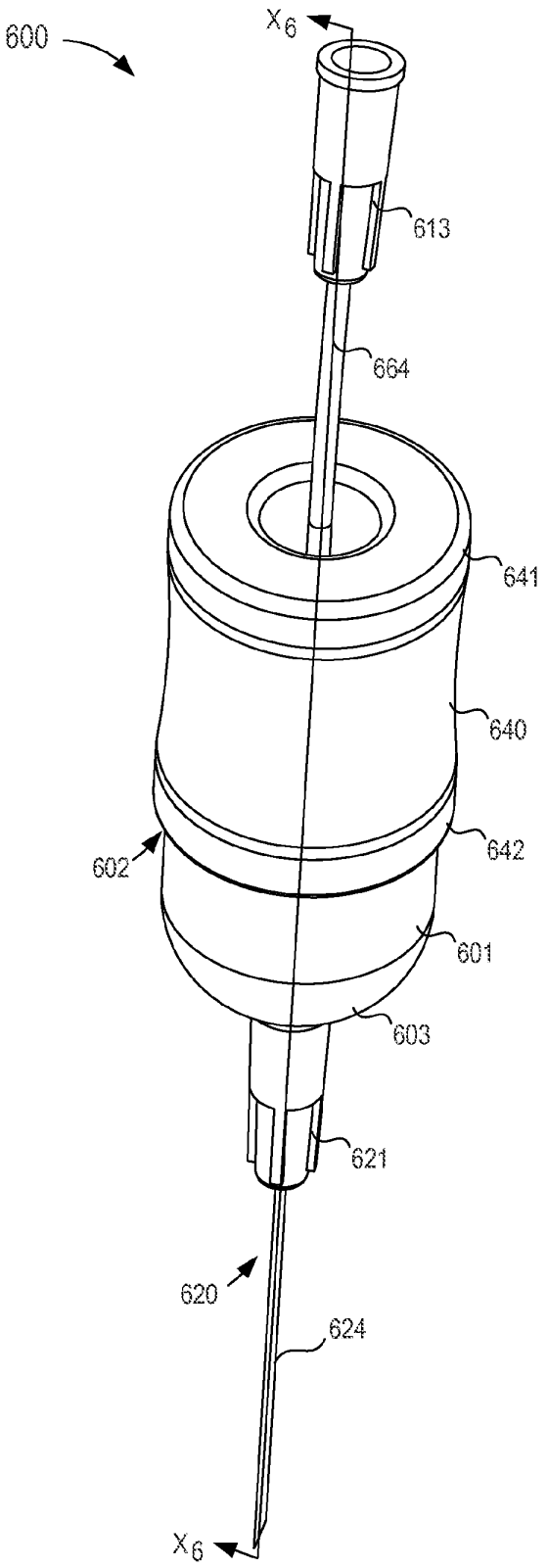


FIG. 24

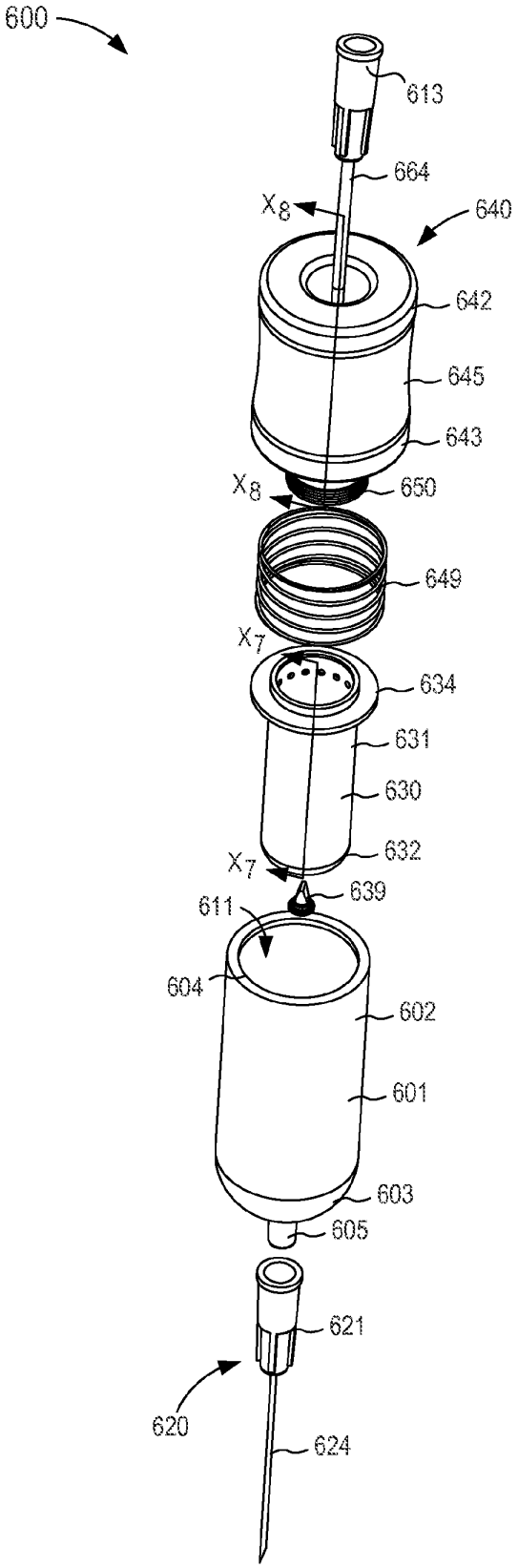

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FIG. 25

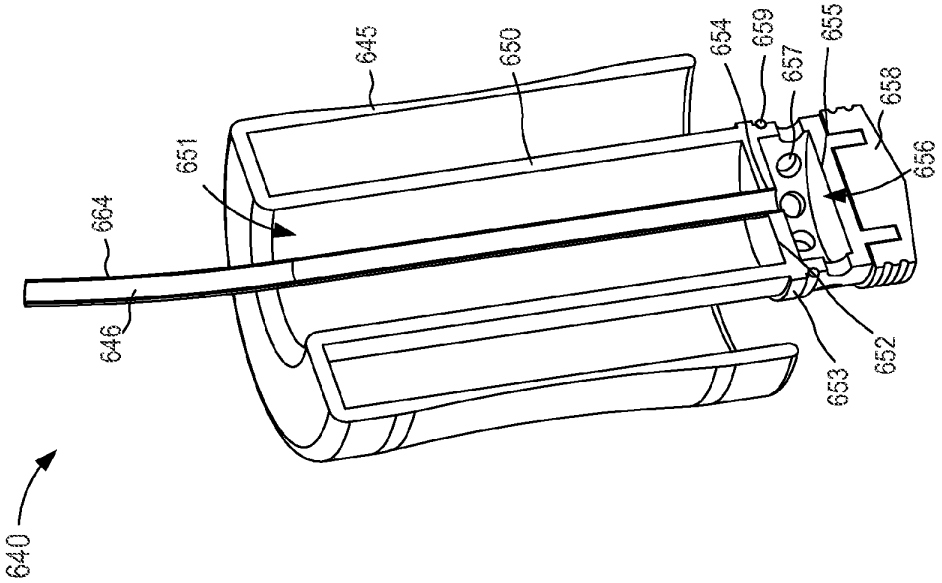

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FIG. 27

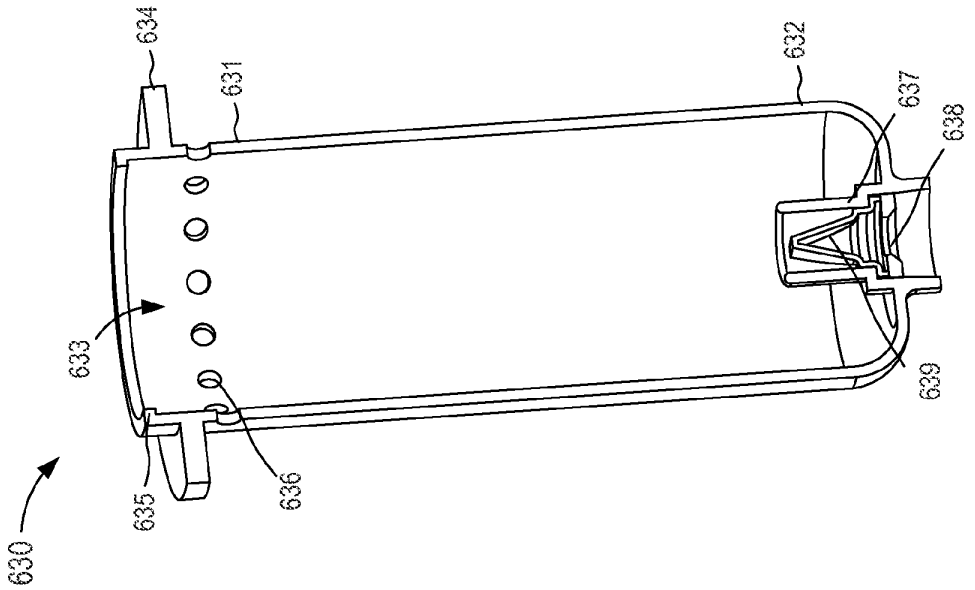

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FIG. 26

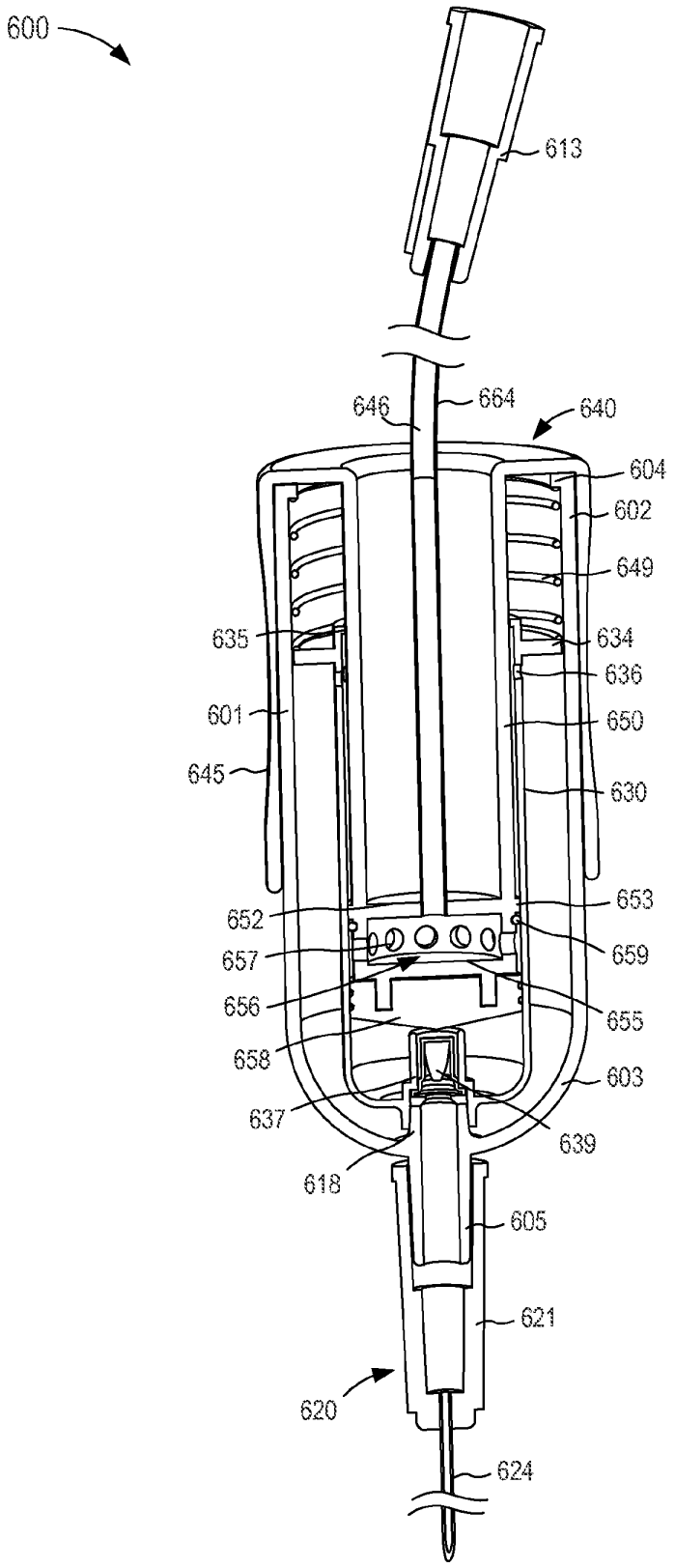

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FIG. 28

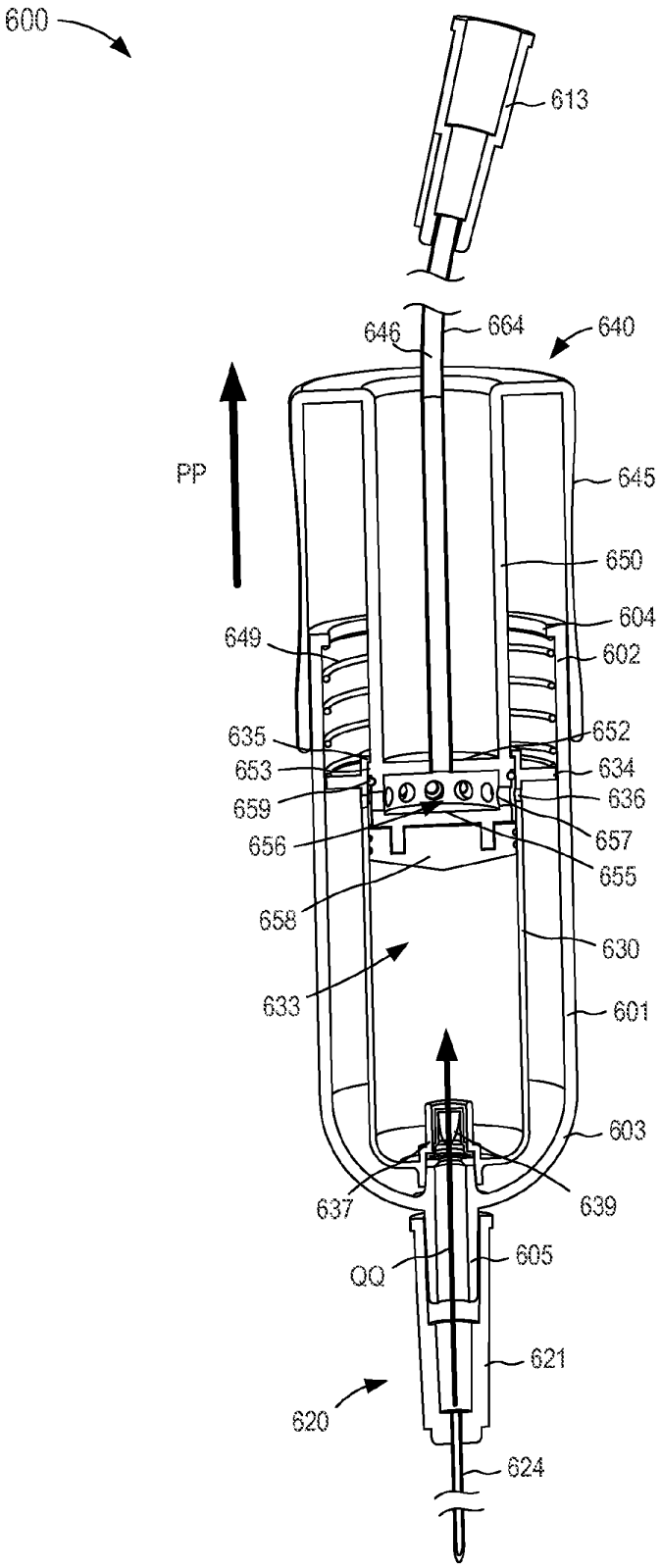

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FIG. 29

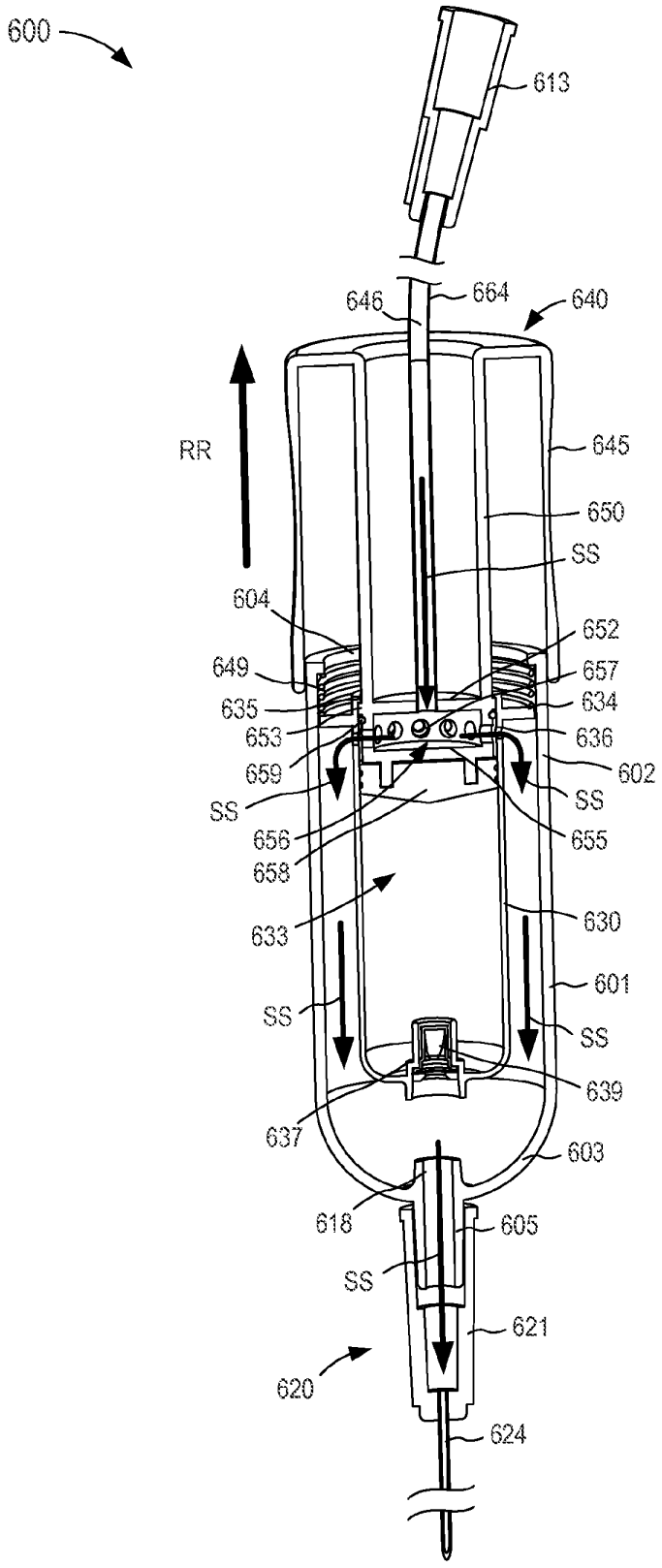

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FIG. 30

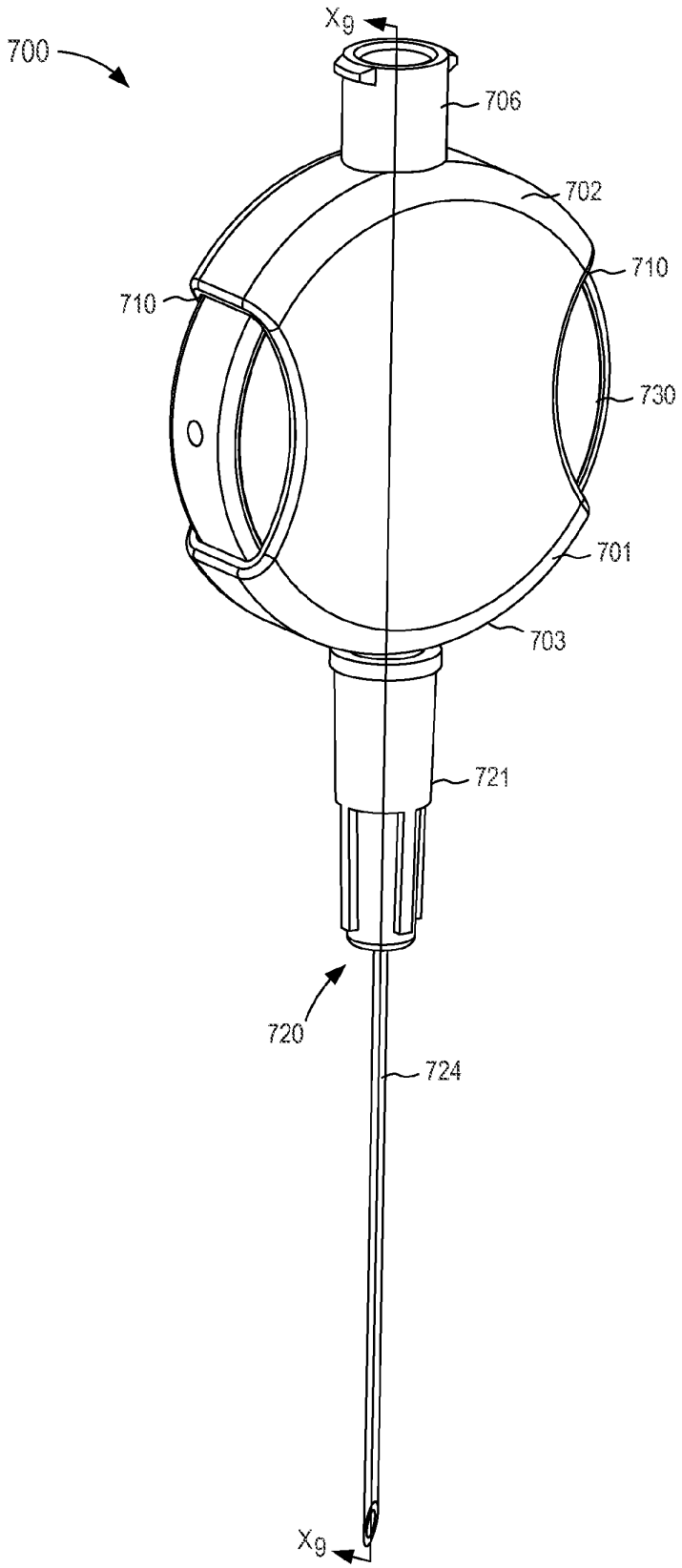


FIG. 31

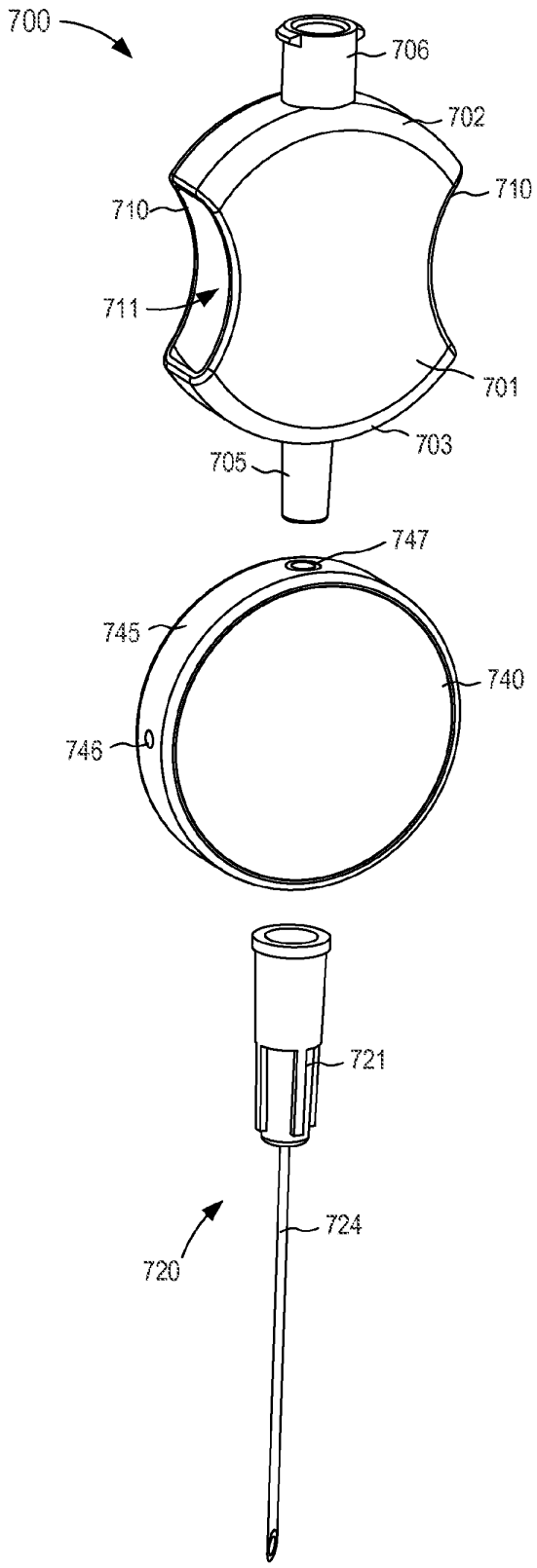


FIG. 32

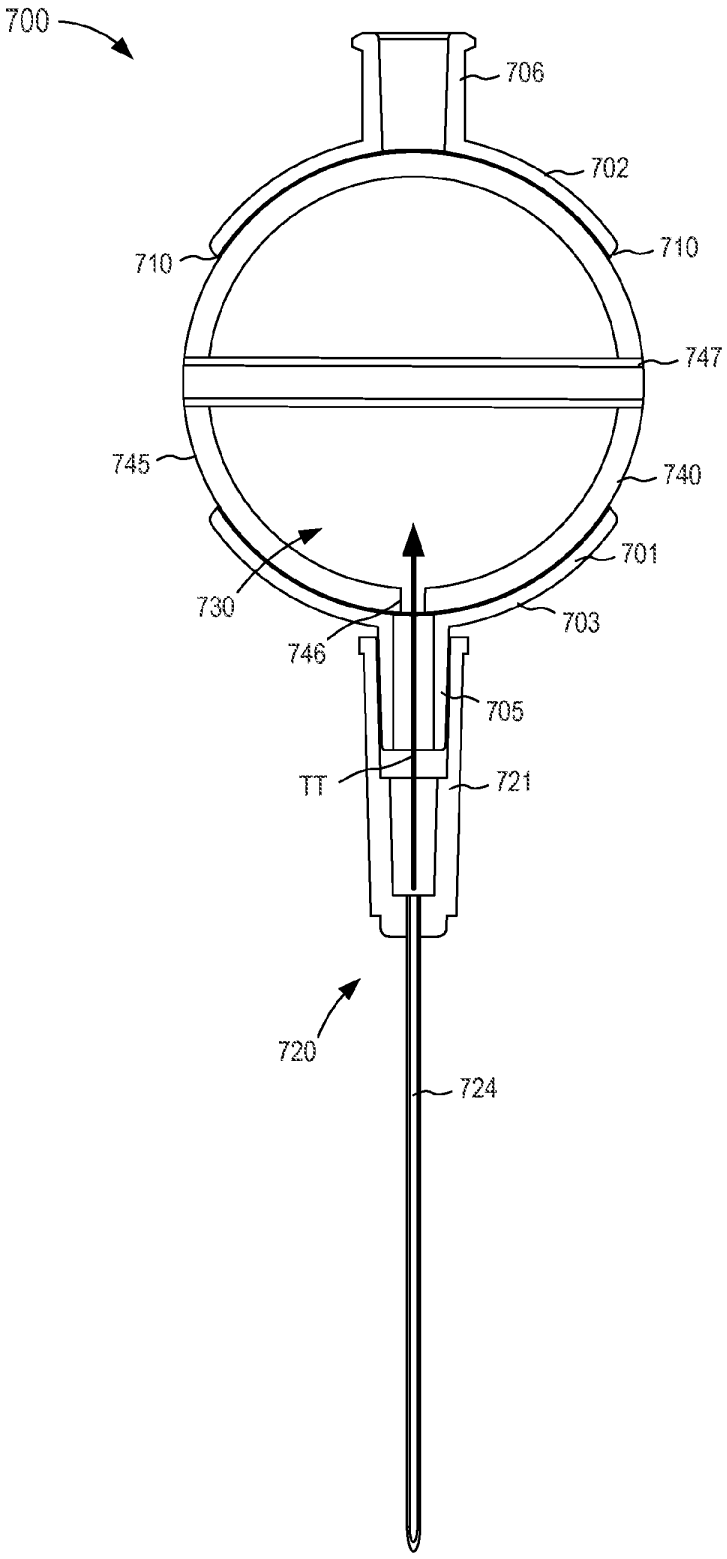

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FIG. 33

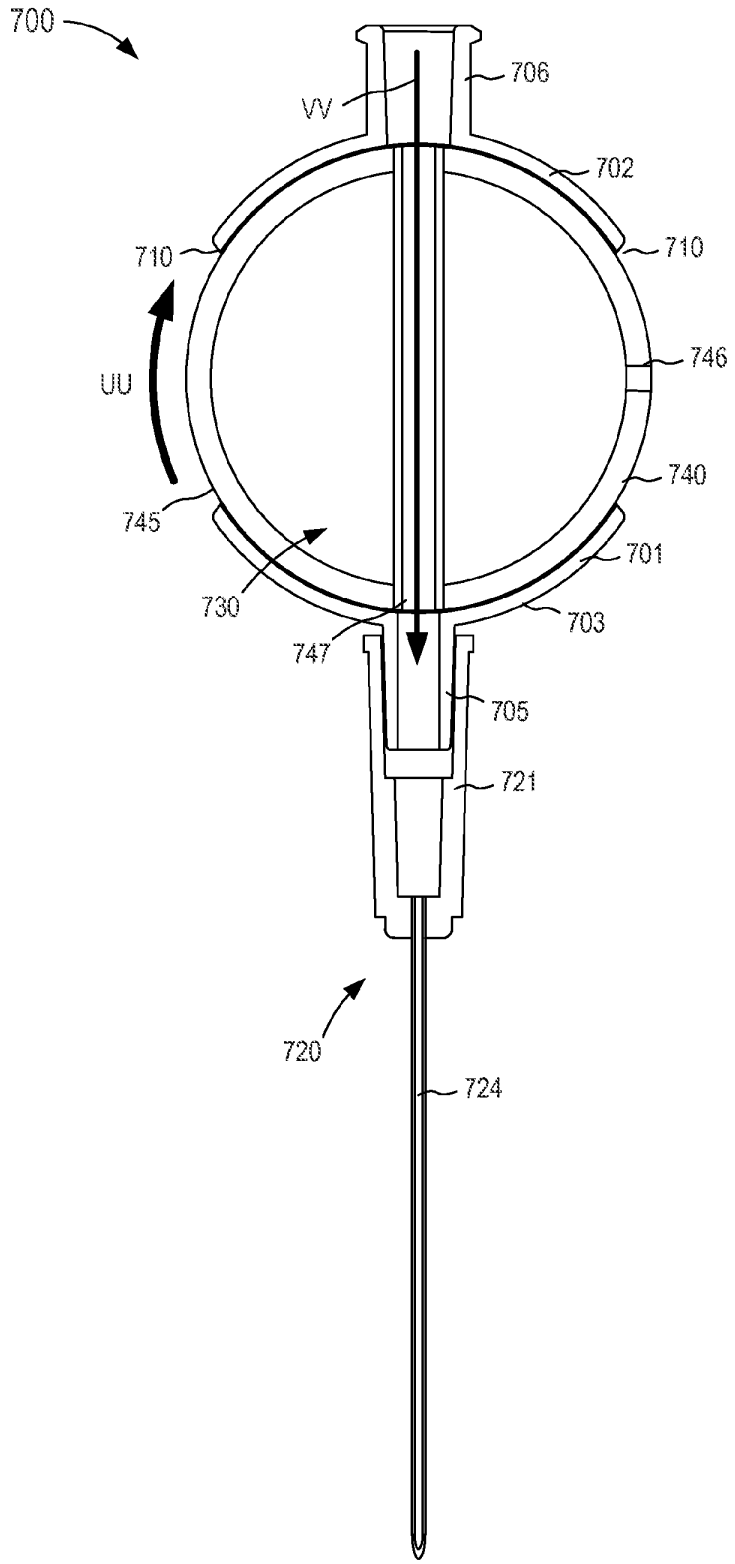

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FIG. 34

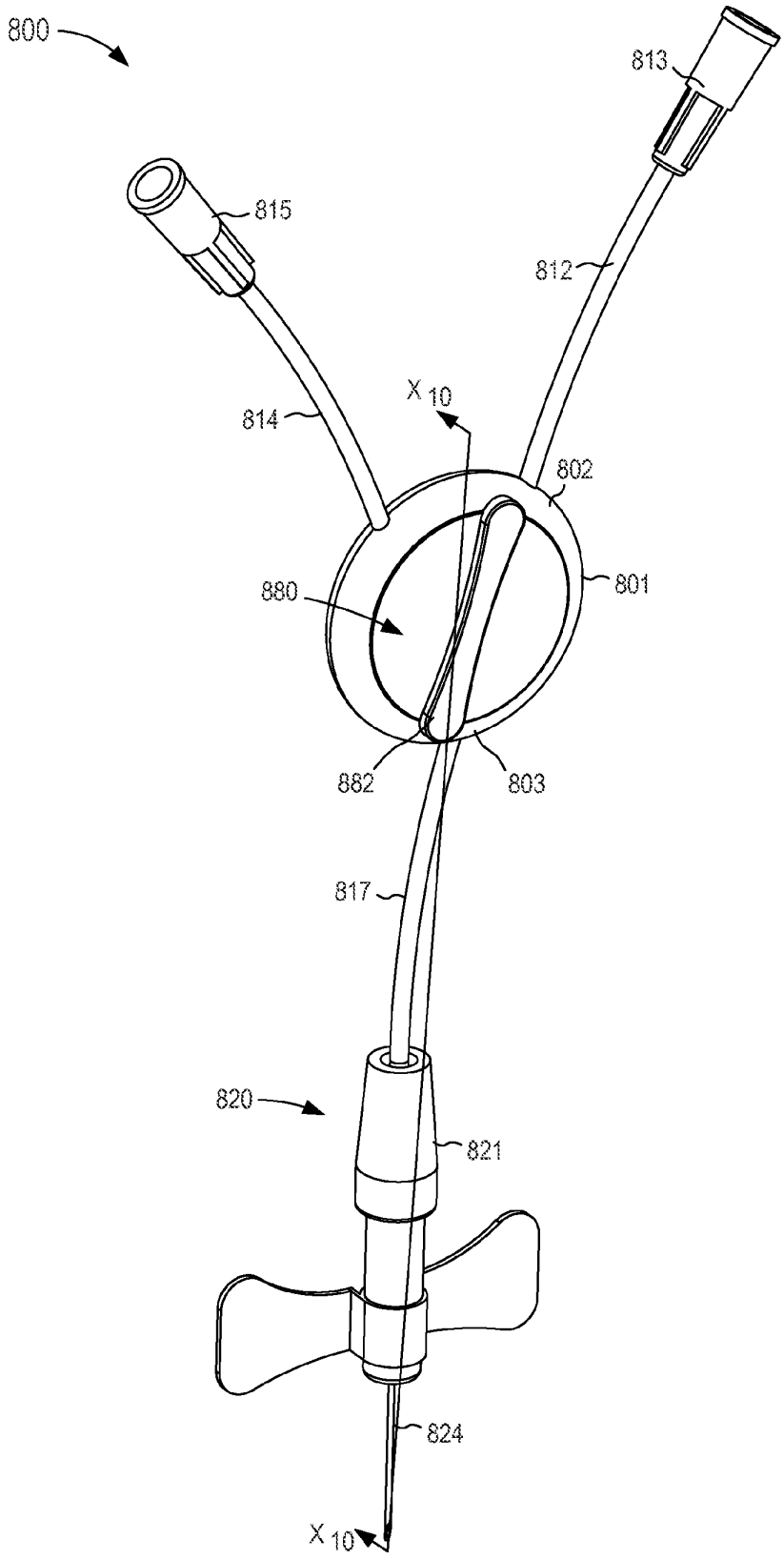


FIG. 35

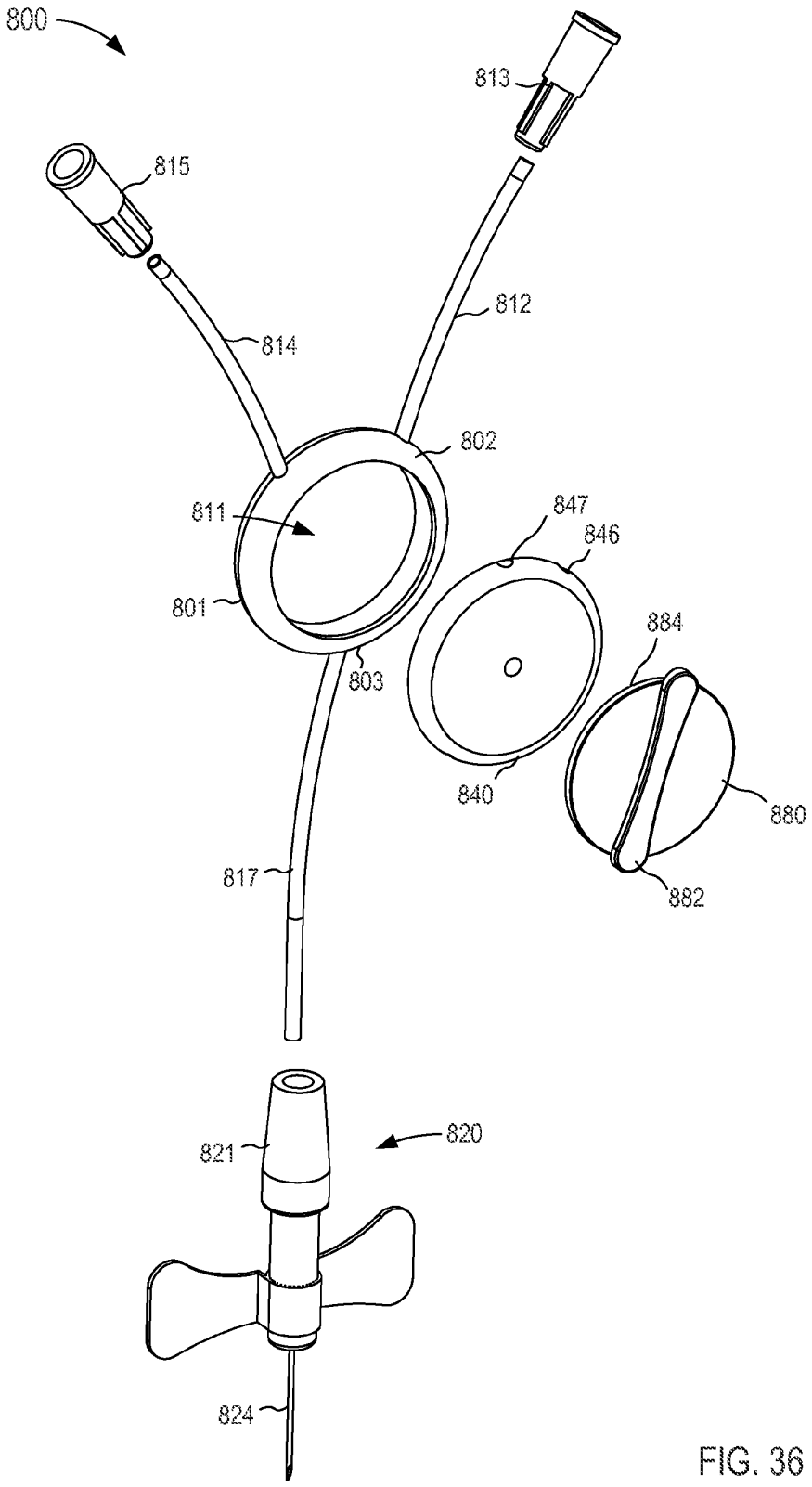

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FIG. 36

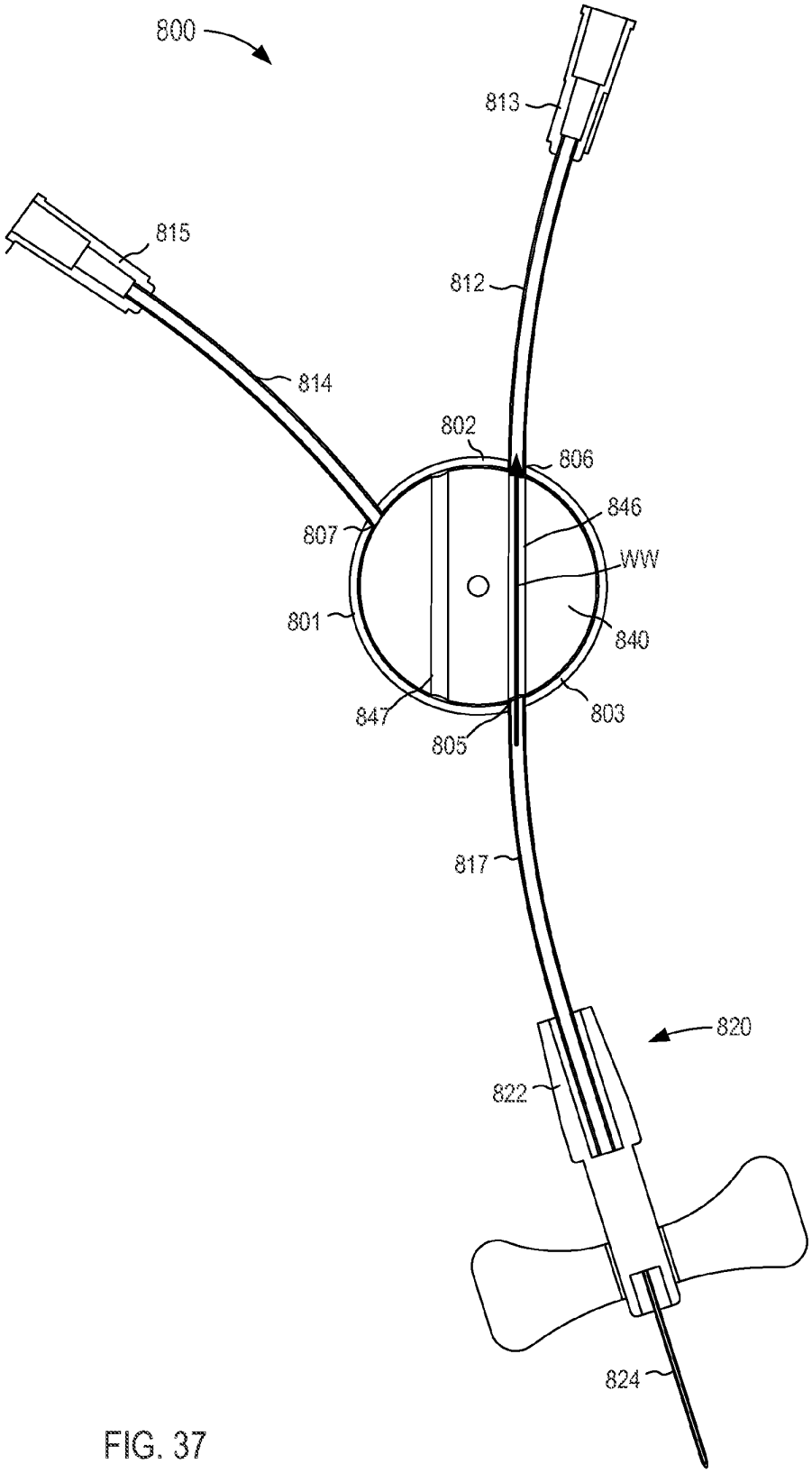

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FIG. 37

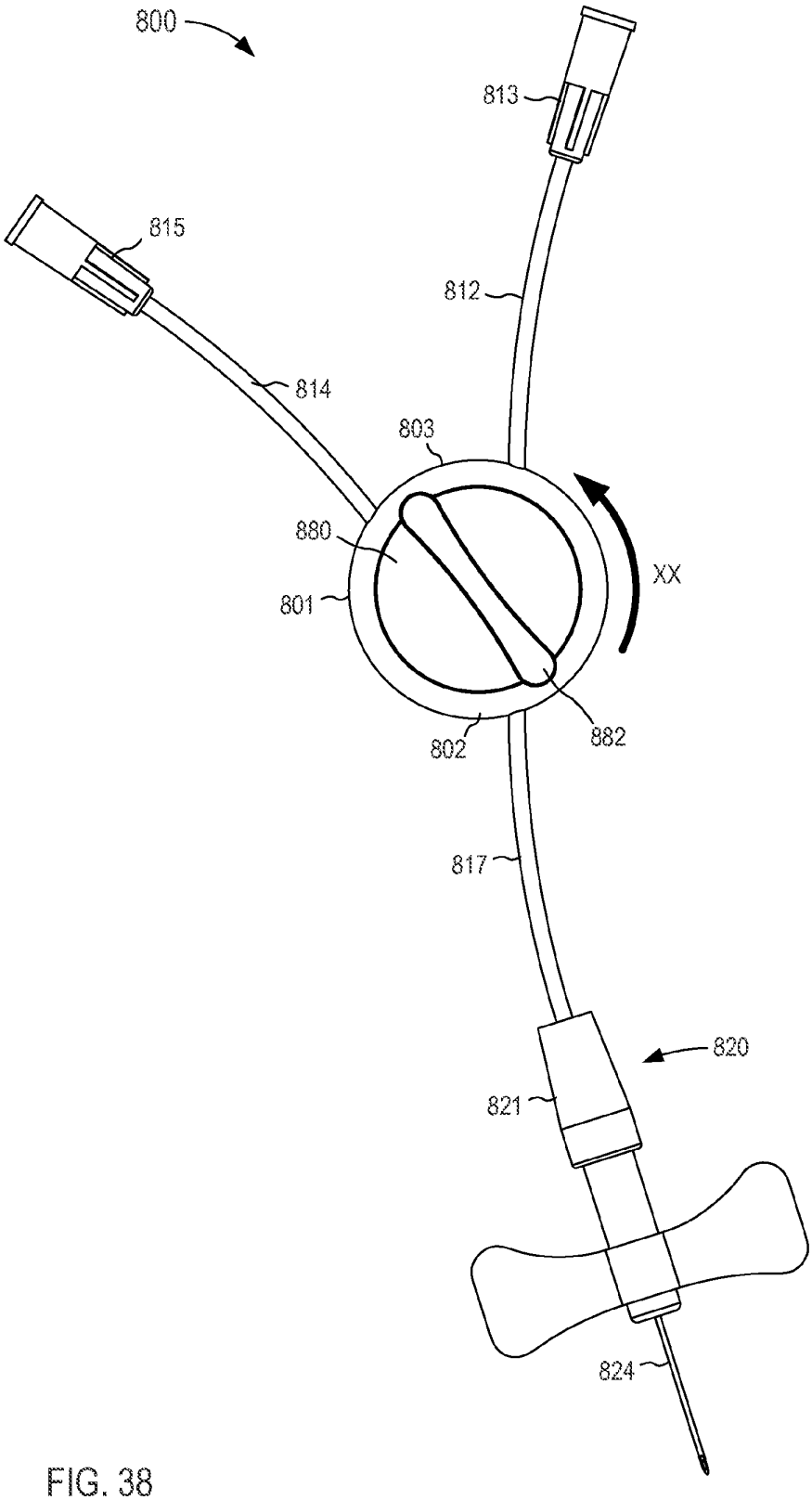


FIG. 38

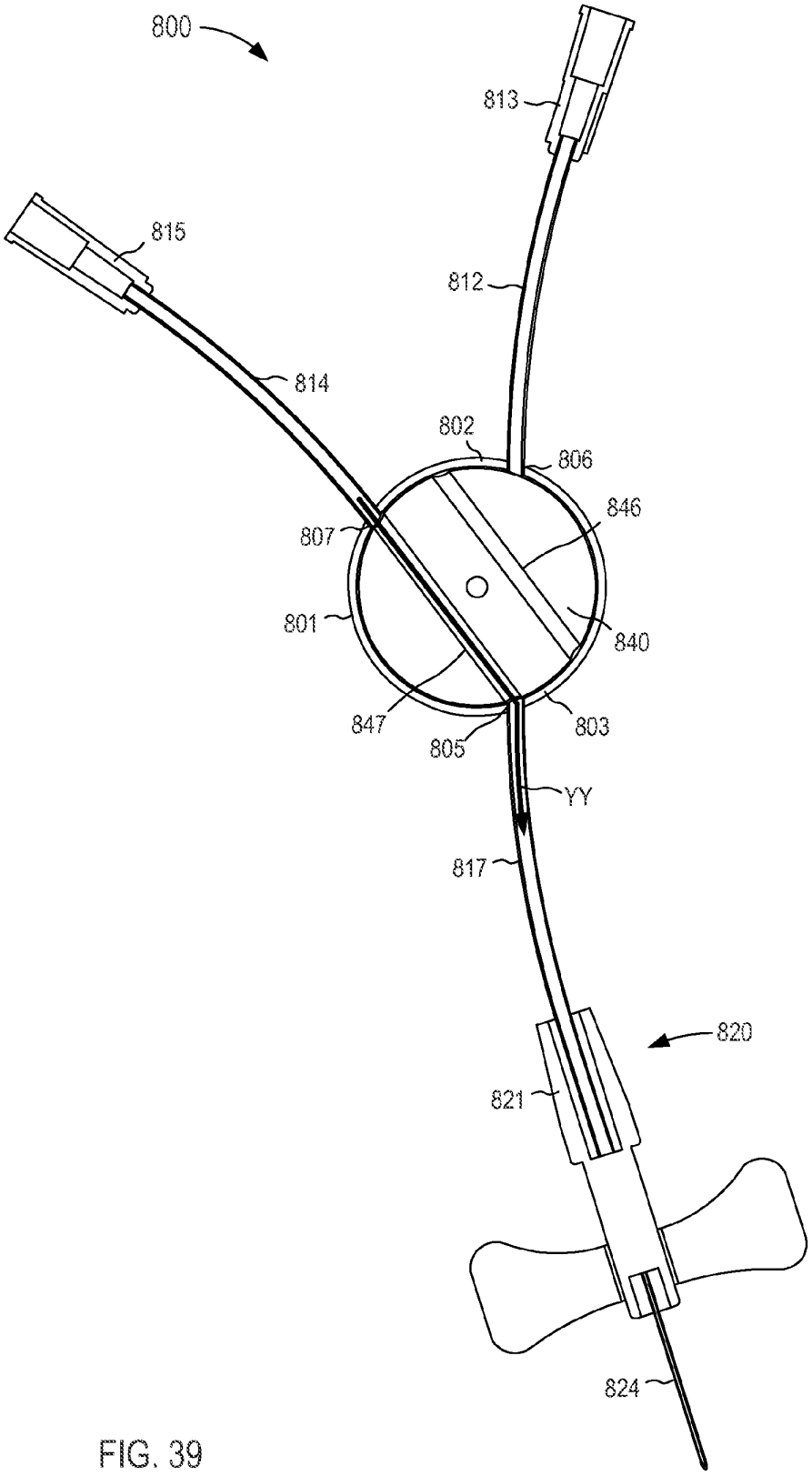

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FIG. 39

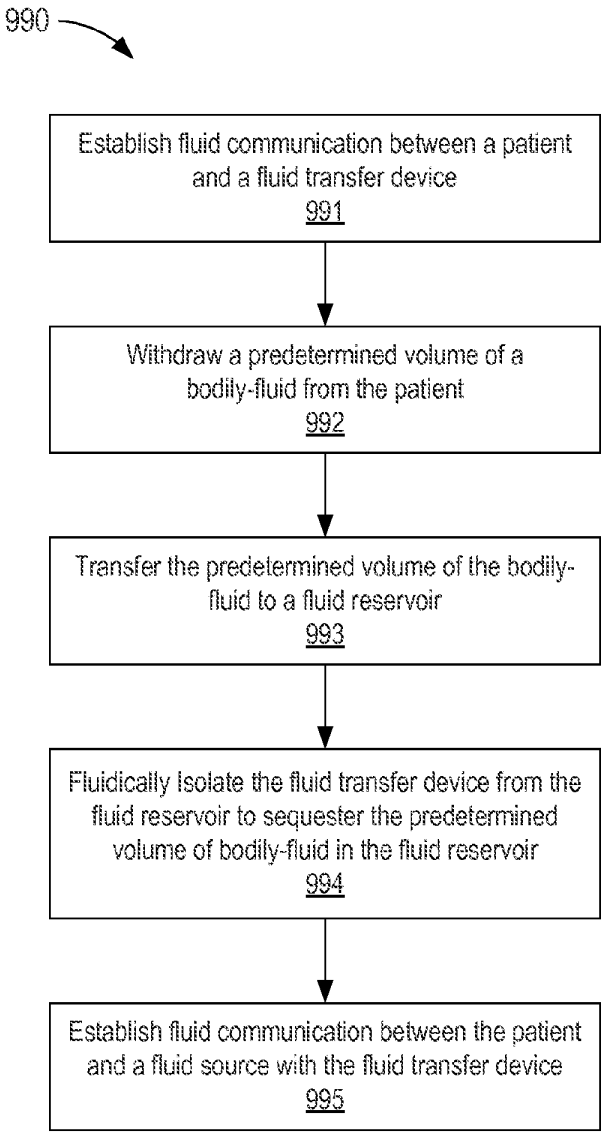

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Establish fluid communication between a patient and a fluid transfer device
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Withdraw a predetermined volume of a bodily-fluid from the patient
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Transfer the predetermined volume of the bodily-fluid to a fluid reservoir
993
Fluidically isolate the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily-fluid in the fluid reservoir
994
Establish fluid communication between the patient and a fluid source with the fluid transfer device
995

FIG. 40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/063975

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/155 (2014.01)
USPC - 600/575
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/15, 5/155; A61M 1/00, 5/00, 5/31, 5/32, 5/178, 5/315, 25/06; B01L 3/14 (2014.01)
USPC - 600/573, 575, 576, 577, 578, 579; 604/110, 164.01, 164.08, 191, 228, 246, 403, 411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61B 5/1405, 5/1427, 5/1428 (2013.01)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0306601 A1 (SHAW et al) 10 December 2009 (10.12.2009) entire document	1-30, 33, 34
Y	US 2012/0215131 A1 (PATTON) 23 August 2012 (23.08.2012) entire document	1-30, 33, 34
Y	US 5,573,510 A (ISAACSON) 12 November 1996 (12.11.1996) entire document	14-18, 23-27
Y	US 4,988,339 A (VADHER) 29 January 1991 (29.01.1991) entire document	14-17, 28-30
Y	US 2002/0193751 A1 (THEEUWES et al) 19 December 2002 (19.12.2002) entire document	22-30, 33, 34
Y	US 6,016,712 A (WARDEN et al) 25 January 2000 (25.01.2000) entire document	26
Y	US 2003/0208151 A1 (KRAUSE et al) 06 November 2003 (06.11.2003) entire document	33

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 March 2014	20 MAR 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/063975

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

SEE CONTINUATION SHEET ATTACHED

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-34

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2013/063975

CONTINUATION OF BOX III

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-34 are drawn to an apparatus.

Group II, claims 35-40 are drawn to a method of delivering a fluid to a patient using a fluid transfer device.

The inventions listed as Groups I - II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I, housing including a proximal end portion and a distal end portion; a fluid reservoir fluidically coupled to the housing; and a flow control mechanism, are not present in Group II; and the special technical features of Group II, establishing fluid communication between the patient and the fluid transfer device; fluidically isolating the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir, are not present in Group I.

Further, Groups I and II share the technical features of a fluid reservoir fluidically coupled and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient.
However, these technical features do not represent a contribution over the prior art. Specifically, US 2011/0306853 A1 to Black et al teaches a body fluid sampling system (10; Abstract; Fig. 2A) comprising a fluid reservoir (18) fluidically coupled to an array of microchannels (16; para. [00060]) and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient (paras. [0061] and [0062]).

Since none of the special technical features of the Groups I - II inventions is found in more than one of the inventions, unity is lacking.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 3 622 890 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
18.03.2020 Bulletin 2020/12

(51) Int Cl.:
A61B 5/15 *(2006.01)* ***A61B 5/153*** *(2006.01)*
A61B 5/154 *(2006.01)*

(21) Application number: **19200766.4**

(22) Date of filing: **22.07.2016**

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **24.07.2015 US 201562196797 P**
07.10.2015 US 201562238636 P
04.04.2016 US 201662318194 P
27.04.2016 US 201615140448
27.04.2016 US 201615140443

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
16747682.9 / 3 324 845

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81541 München (DE)

Remarks:
This application was filed on 01-10-2019 as a divisional application to the application mentioned under INID code 62.

(54) BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE

(57) Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

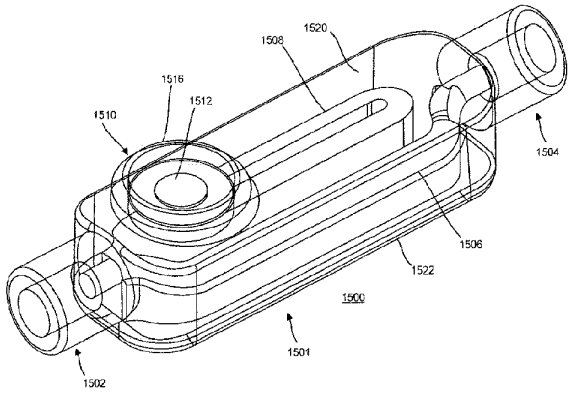


FIG. 15C

EP 3 622 890 A1

Printed by Jouve, 75001 PARIS (FR)

Description

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Non-Provisional Application Serial No. 15/140,443, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD" and U.S. Non-Provisional Application Serial No. 15/140,448, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD", both of which claim priority to U.S. Provisional Application Serial No. 62/196,797, filed on July 24, 2015 and titled "BLOOD CULTURE IMPROVEMENT SYSTEM AND METHOD"; U.S. Provisional Application Serial No. 62/238,636, filed on October 7, 2015 and titled "BLOOD SEQUESTRATION SYSTEM FOR NON-CONTAMINATED BLOOD SAMPLING"; and U.S. Provisional Application Serial No. 62/318,194, filed on April 4, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

[0002] Bacteraemia is the presence of microorganisms in the blood. Sepsis, on the other hand, is bacteraemia in the presence of clinical symptoms and signs such as fever, tachycardia, tachypnea and hypotension. Bacteraemia and sepsis are associated with a high mortality and an increased incidence and duration of hospital stay and associated costs. Many bacteraemias, sepsis, fungaemias and other pathogens actually occur within a hospital or other healthcare settings with catheters and venipunctures being a source of contamination as potential carriers of these pathogens.

[0003] Blood cultures are the standard test used to detect microbial pathogens related to bacteraemia and sepsis in a patient's blood. The term blood culture refers to a single venipuncture, either from a peripheral site or central or arterial line, with the blood inoculated into one or more blood culture bottles or containers. One bottle is considered a blood culture where two or more are considered a set. Multiple sets may be obtained from multiple venipunctures and are associated with different sites on the patient.

[0004] These methods allow for microbial identification and susceptibility testing to be performed, which is a critical component to managing sepsis, however the lack of rapid results and decreased sensitivity for fastidious pathogens has led to the development of improved systems and adjunctive molecular or proteomic testing.

[0005] Collection of blood samples for conducting blood cultures is a critical component of modern patient care and can either positively affect the patient outcome by providing an accurate diagnosis, or can adversely affect the outcome by prolonging unnecessary antimicrobial therapy, the length of hospital stays, and increasing costs.

[0006] One outcome of collection of blood cultures is contamination. Blood culture contamination can lead to a false positive culture result and/or significant increase in healthcare related costs. Sources of blood culture contamination include improper skin antisepsis, improper collection tube disinfection, and contamination of the initial blood draw which may then skew results.

[0007] Blood culture collection kits generally consist of a "butterfly" set, infusion set, or other type of venipuncture device as offered by companies like BD, Smiths, B. Braun and others, and aerobic and anaerobic blood culture bottles. Various different bottles are also available depending on the test requirements. These bottles are specifically designed to optimize recovery of both aerobic and anaerobic organisms. In conventional kits, a bottle used is known generally as a "Vacutainer," which is a blood collection tube formed of a sterile glass or plastic tube with a closure that is evacuated to create a vacuum inside the tube to facilitate the draw of a predetermined volume of liquid such as blood.

[0008] False positive blood cultures are typically a result of poor sampling techniques. They cause the use of antibiotics when not needed, increasing hospital costs and patient anxiety. Blood cultures are drawn from a needlestick into the skin, and then a Vacutainer is attached to capture a sample of blood. Contamination may occur from improper or incomplete disinfection of the skin area in and around the puncture site. It may also occur from the coring of the skin by the needle during insertion, with the cored skin cells and any associated contamination being pulled into the sample.

[0009] Blood flow through a hypodermic needle is laminar, and as such, a velocity gradient can be developed over the flow tube as a pressure drop is applied to the hypodermic needle. Either forceful aspiration of blood, or using a very small hypodermic needle, can cause lysis and a release of potassium from the red blood cells, thereby rendering the blood samples abnormal.

[0010] In other instances, some patients have delicate veins that can collapse under a pressure drop or vacuum, particularly as applied by a syringe's plunger that is drawn too quickly for the patient's condition. Since such condition is impossible to know beforehand, such vein collapses are a risk and very difficult to control.

[0011] Various strategies have been implemented to decrease blood culture contamination rates, e.g. training staff with regard to aseptic collection technique, feedback with regard to contamination rates and implementation of blood culture collection kits. Although skin antisepsis can reduce the burden of contamination, 20% or more of skin organisms are located deep within the dermis and are unaffected by antisepsis. Changing needles before bottle inoculation is not advisable as it increases the risk to acquire needle stick injuries without decreasing con-

tamination rates.

[0012] Some conventional systems and techniques for reducing blood culture contamination include discarding the initial aliquot of blood taken from central venous catheters, venipunctures, and other vascular access systems. However, these systems require the user to mechanically manipulate an intravascular device, or require a complex series of steps that are difficult to ensure being followed.

SUMMARY

[0013] This document presents systems and methods for reducing blood culture contamination, lysing of cells, and vein collapse. In some implementations, a system and method can eliminate user variability in disinfection, and also eliminate the risk of skin cells getting into the blood culture sample. The systems and methods disclosed herein do not require a change in existing clinical processes, other than to potentially indicate when a vacutainer or other blood collection device (i.e., syringe) should be attached for drawing contaminant-free blood samples.

[0014] In some implementations of the systems and methods disclosed herein the withdrawal of blood is accomplished passively by use of the patient's own blood pressure, thereby reducing the risk of vein collapse and eliminating any additional user steps over current practice. The systems and methods can be applied to accommodate short-path direct stick or butterfly venipuncture systems. They can also be used with samples drawn through a catheter.

[0015] In one aspect, a blood sequestration device is presented. The blood sequestration device includes an inlet port and an outlet port. The blood sequestration device further includes a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port.

[0016] In another aspect, a blood sequestration device connected with a blood sampling pathway is described. The blood sampling pathway has a patient needle and a sample collection device. The blood sequestration device includes an inlet port connected with the patient needle, and a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, and an outlet port connected with a distal end of the sampling channel and with the sample collection device.

[0017] In yet another aspect, a blood sequestration device connected with a blood sampling system is described. The blood sampling system includes a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed and adapted for receiving an evacuated blood collection tube. The blood sequestration device includes an inlet port connected with the patient needle to receive the blood sample from the patient. The blood sequestration device further includes a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed by the evacuated blood collection tube. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a subsequent portion of the blood sample once the sample needle is unsealed by the evacuated blood collection tube. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel for conveying the subsequent portion of the blood sample to the sample needle.

[0018] In yet another aspect, a blood sample optimization system is disclosed and described. The blood sample optimization system includes a blood sampling system for accessing and acquiring one or more samples of a patient's blood, and a blood sequestration device for receiving and sequestering a first portion of the one or more samples of the patient's blood which might be contaminated by a venipuncture process and which could result in a false positive identification of a pathogen in the patient's blood.

[0019] The blood sampling system includes a patient needle configured for a venipuncture of a patient to access a sample of blood of a patient, a blood sampling pathway connected with the patient needle for conveying the sample of blood, and a sample needle configured for receiving an evacuated blood collection container to collect and contain a subsequent portion of the sample of blood.

[0020] In yet another aspect, a blood sequestration device is disclosed and described. In some implementations, the blood sequestration device can include an inlet port, an outlet port connected with the inlet port, and a sequestration chamber connected with the inlet port. The sequestration chamber can have a vent comprising an air permeable blood barrier.

[0021] The blood sequestration device is connected along the blood sampling pathway between the patient needle and the sample needle, and includes an inlet port for receiving the sample of blood. The blood sequestration device further includes a sequestration chamber connected with the inlet port for receiving a first amount of the sample of blood, the sequestration chamber having a vent comprising an air permeable blood barrier for sequestering at least a first portion of the first amount of the sample of blood. The blood sequestration device may further include a sampling channel having a proximal end connected with the inlet port, the sampling channel conveying a subsequent amount of the sample of blood to the evacuated blood collection container upon the sequestration chamber sequestering at least the first por-

tion of the first amount of the sample of blood. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel, the outlet port for outputting the subsequent amount of the sample of blood.

[0022] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features and advantages will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other aspects will now be described in detail with reference to the following drawings.

FIG. 1 illustrates a blood sample optimization system.

FIG. 2 illustrates a blood sample optimization system in accordance with an alternative implementation.

FIG. 3 illustrates a blood sample optimization system in accordance with another alternative implementation.

FIG. 4 illustrates a blood sample optimization system in accordance with another alternative implementation.

FIG. 5 illustrates a blood sample optimization system in accordance with another alternative implementation.

FIG. 6 illustrates a blood sample optimization system in accordance with an alternative implementation.

FIG. 7 is a flowchart of a method for optimizing a quality of a blood culture.

FIGS. 8A - 8E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with some implementations.

FIG. 9 illustrates a pathway splitter for use in a blood sequestrations system.

FIGS. 10A - 10D illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with alternative implementations.

FIGS. 11A - 11E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with other alternative implementations.

FIGS. 12A-12D illustrate a blood sample optimization system including a blood sequestration device in accordance with yet other alternative implementations.

FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet another alternative implementations.

FIGS. 14A-14E illustrate yet another implementation of a blood sampling system to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample.

FIGS. 15A-15G illustrate a blood sequestration device and method of using the same, in accordance with yet another implementation.

FIGS. 16A-16D illustrate a blood sequestration device in accordance with yet another implementation.

FIGS. 17A - 17E illustrate a bottom member of a housing for a blood sequestration device.

FIGS. 18A - 18F illustrate a top member of a housing for a blood sequestration device.

FIGS. 19A and 19B illustrate a blood sequestration device having a top member mated with a bottom member.

FIG. 20 shows a blood sample optimization system including a blood sequestration device.

FIG. 21 illustrates a non-vented blood sequestration device using a wicking material chamber.

FIGS. 22A and 22B illustrate a material makeup of a filter for sequestering blood in a sequestration chamber of a blood sequestration device.

FIGS. 23A and 23B illustrate another implementation of a blood sequestration device that uses a vacuum force from a blood collection device.

[0024] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0025] This document describes blood sample optimization systems and methods for reducing or eliminating contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. In some implementations, a blood sample optimization system includes a patient needle for vascular access to a patient's bloodstream, a sample needle for providing a blood sample to a blood collection container, such as an evacuated blood collection container or tube like a Vacutainer™ or

the like, or other sampling device, and a blood sequestration device located between the patient needle and the sample needle. The blood sequestration device includes a sequestration chamber for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

[0026] FIG. 1 illustrates a blood sample optimization system in accordance with some implementations. The system includes a patient needle 1 to puncture the skin of a patient to access the patient's vein and blood therein. The system further includes a sample needle (i.e., a resealably closed needle for use with Vacutainers™ or the like) 5, which may be contained within and initially sealed by a resealable boot 10, a Luer activated valve, or another collection interface or device. The resealable boot 10 can be pushed aside or around the sample needle 5 by application of a Vacutainer™ bottle (not shown) for drawing the patient's blood. The system can further include a low volume chamber 30 that leads to the sample needle 5, but also includes an orifice or one or more channels 45 that lead to a sequestration chamber 55 formed by a housing 50.

[0027] The sequestration chamber 55 is a chamber, channel, pathway, lock, or other structure for receiving and holding a first aliquot of the patient's blood, which may be in a predetermined or measured amount, depending on a volume of the sequestration chamber 55. The first draw of blood typically contains or is more susceptible to containing organisms that cause bacteraemia and sepsis or other pathogens than subsequent blood draws. The sequestration chamber 55 can be a vessel encased in a solid housing, formed in or defined by the housing itself, or can be implemented as tubing or a lumen. The sequestration chamber 55, regardless how formed and implemented, may have a predetermined volume. In some implementations, the predetermined volume may be based on a volume of the patient needle, i.e. ranging from less than the volume of the patient needle to any volume up to or greater than 20 times or more of the volume of the patient needle. The predetermined volume of the sequestration chamber 55 may also be established to economize or minimize an amount of blood to be sequestered and disposed of.

[0028] The sequestration chamber 55 can be formed, contained or housed in a chamber housing 50, and can be made of plastic, rubber, steel, aluminum or other suitable material. For example, the sequestration chamber 55 could be formed of flexible tubing or other elastomeric materials. The sequestration chamber 55 further includes an air permeable blood barrier 20 that allows air to exit the sequestration chamber 55. As used herein the term "air permeable blood barrier" means an air permeable but substantially blood impermeable substance, material, or structure. Examples may include hydrophobic membranes and coatings, a hydrophilic membrane or coating combined with a hydrophobic membrane or coating, mesh, a filter, a mechanical valve, antimicrobial material, or any other means of allowing air to be displaced from the sequestration chamber 55 as it is filled with blood. In various exemplary embodiments, an air permeable blood barrier may be formed by one or more materials that allow air to pass through until contacted by a liquid, such material then becomes completely or partially sealed to prevent or inhibit the passage of air and/or liquid. In other words, prior to contact with liquid, the material forms a barrier that is air permeable. After contact with a liquid, the material substantially or completely prevents the further passage of air and/or liquid.

[0029] The orifice or channel 45 can be any desired length, cross-sectional shape or size, and/or can be formed to depart from the low volume chamber 30 at any desired angle or orientation. The orifice or channel 45 may also include a one-way flap or valve 60 that maintains an initial aliquot of blood sample within the sequestration chamber 55. In some specific implementations, the orifice or channel 45 can include a "duck bill" or flapper valve 60, or the like, for one-way flow of blood from low volume chamber 30 to the sequestration chamber 55. The air permeable blood barrier 20 can also be constructed of a material that allows air to exit but then seals upon contact with blood, thereby not allowing external air to enter sequestration chamber 55. This sealing would eliminate the need for a valve.

[0030] Valve 60 can be any type of valve or closing mechanism. Chamber 30 is designed to hold virtually no residual blood, and can be designed to be adapted to hold or allow pass-through of a particular volume or rate of blood into sequestration chamber 55. Likewise, sequestration chamber 55 may also include any type of coating, such as an anti-microbial coating, or a coating that aids identification and/or diagnosis of components of the first, sequestered blood draw.

[0031] Housing 50 and 40 can be formed of any suitable material, including plastic, such as acrylonitrile butadiene styrene (ABS) or other thermoplastic or polymeric material, rubber, steel, or aluminum. The air permeable blood barrier 20 can include a color-providing substance, or other signaling mechanism, that is activated upon contact with blood from the initial blood draw, or when air displacement is stopped, or any combination of events with blood in the sequestration chamber 55. The air permeable barrier may also include an outer layer such as a hydrophobic membrane or cover that inhibits or prevents the inadvertent or premature sealing of the filter by an external fluid source, splash etc. Sequestration chamber 55 can also be translucent or clear to enable a user to visually confirm the chamber is filled.

[0032] FIG. 2 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown in FIG. 2, a sequestration chamber 55, or waste chamber, surrounds the patient needle 1, with an open-ended cuff or housing con-

nected with the waste chamber and encircling the sample needle housing base and housing. The patient needle 1 and sample needle 5 are connected together by a boot 56, which forms a continuous blood draw channel therethrough. The boot 56 includes a single orifice or channel leading from the blood draw channel into sequestration chamber 55. The device can include more than one single orifice or channel, in other implementations. Each orifice or channel can include a one-way valve, and can be sized and adapted for predetermined amount of blood flow.

[0033] The sequestration chamber 55 includes an air permeable blood barrier. The filter can further include a sensor or indicator to sense and/or indicate, respectively, when a predetermined volume of blood has been collected in the sequestration chamber 55. That indication will alert a user to attach an evacuated blood collection tube or bottle, such as a Vacutainer™ to the sample needle 5. The housing for the sequestration chamber 55 can be any size or shape, and can include any type of material to define an interior space or volume therein. The interior space is initially filled only with air, but can also be coated with an agent or substance, such as a decontaminate, solidifying agent, or the like. Once evacuated blood collection tube is attached to the sample needle 5, blood will flow automatically into the patient needle 1, through the blood draw channel and sample needle 5, and into the bottle. The sample needle 5 is covered by a resealable boot, coating or membrane that seals the sample needle when a blood collection bottle is not attached thereon or thereto.

[0034] FIG. 3 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is surrounded by a resealable boot or membrane, and is further connected with a patient needle 1. A blood flow channel is formed through the sample needle and the patient needle. The connection between the sample needle and patient needle includes a "T" or "Y" connector 102, which includes a channel, port or aperture leading out from the main blood flow channel to a sequestration chamber 104.

[0035] The T or Y connector 102 may include a flap or one-way valve, and have an opening that is sized and adapted for a predetermined rate of flow of blood. The sequestration chamber 104 can be formed from tubing, or be formed by a solid housing, and is initially filled with air. The sequestration chamber 104 will receive blood that flows out of a patient automatically, i.e. under pressure from the patient's own blood pressure. The sequestration chamber 104 includes an air permeable blood barrier 106, preferably at the distal end of tubing that forms the sequestration chamber 104, and which is connected at the proximal end to the T or Y connector 102. The T or Y connector 102 can branch off at any desired angle for most efficient blood flow, and can be formed so as to minimize an interface between the aperture and channel and the main blood flow channel, so as to minimize or eliminate mixing of the initial aliquot of blood with main blood draw samples.

[0036] In some alternative implementations, the sample needle may be affixed to a tubing of any length, as shown in FIG. 4, connecting at its opposite end to the T or Y connector 102. The sequestration chamber 104 can be any shape or volume so long as it will contain a predetermined amount of blood sample in the initial aliquot. The T or Y connector 102 may also include an opening or channel that is parallel to the main blood flow channel. The air permeable blood barrier may further include an indicator 107 or other mechanism to indicate when a predetermined amount of blood has been collected in the sequestration chamber, or when air being expelled reaches a certain threshold, i.e. to zero. The tubing can also include a clip 109 that can be used to pinch off and prevent fluid flow therethrough.

[0037] Once the air permeable blood barrier and primary chamber are sealed the initial aliquot of blood is trapped in the sequestration chamber 104, an evacuated blood collection tube, such as a Vacutainer™ bottle may be attached to the sample needle 5 to obtain the sample. The blood collection tube can be removed, and the sample needle 5 will be resealed. Any number of follow-on blood collection tubes can then be attached for further blood draws or samples. Upon completion of all blood draws, the system can be discarded, with the initial aliquot of blood remaining trapped in the sequestration chamber 104.

[0038] FIG. 5 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is connected with a patient needle by tubing. A "T" or "Y" connector 120 is added along the tubing at any desired location, and includes an aperture, port or channel leading to a sequestration chamber 204, substantially as described above.

[0039] FIG. 6 illustrates a blood sample optimization system in accordance with some alternative implementations, in which a sequestration chamber 304, formed as a primary collection channel, receives an initial aliquot of blood, and is provided adjacent to the blood sampling channel. The sequestration chamber 304 can encircle the blood sampling channel, the patient needle 1, and/or the sample needle 5. The primary collection channel can include a T or Y connector 120, or other type of aperture or channel. The sequestration chamber 304 includes an air permeable blood barrier, which can also include an indicator of being contacted by a fluid such as blood, as described above.

[0040] In some implementations, either the patient needle 1 or the sample needle 5, or both, can be replaced by a Luer lock male or female connector. However, in various implementations, the connector at a sample needle end of the blood sample optimization system is initially sealed to permit the diversion of the initial aliquot of blood to the sequestration chamber, which is pressured at ambient air pressure and includes the air outlet of the air permeable blood barrier. In this way, the system passive-

ly and automatically uses a patient's own blood pressure to overcome the ambient air pressure of the sequestration chamber to push out air through the air permeable blood barrier and displace air in the sequestration chamber with blood.

[0041] FIG. 7 is a flowchart of an exemplary method for optimizing the quality of a blood culture. At 702, a clinician places a needle into a patient's vein. At 704, blood then flows into a sequestration chamber, pushing the air in the sequestration chamber out of the sequestration chamber through an air permeable blood barrier. In some implementations, the volume of the sequestration chamber is less than 0.1 to more than 5 cubic centimeters (cc's), or more. The sequestration chamber is sized and adapted to collect a first portion of a blood sample, which is more prone to contamination than secondary and other subsequent portion of the blood sample or subsequent draws. Since the sequestration chamber has an air-permeable blood barrier through which air can be displaced by blood pushed from the patient's vein, such blood will naturally and automatically flow into the sequestration chamber before it is drawn into or otherwise enters into a Vacutainer or other bottle for receiving and storing a blood sample.

[0042] When the sequestration chamber fills, the blood will gather at or otherwise make contact with the air permeable blood barrier, which will inhibit or prevent blood from passing therethrough. At 706, when the blood comes into contact with the entire internal surface area of the air permeable blood barrier, the air permeable blood barrier is then closed and air no longer flows out or in. At 708, the clinician may be provided an indictor or can see the full chamber, to indicate the evacuated blood collection tube, such as a Vacutainer™ can be attached. The indicator can include visibility into the primary chamber to see whether it is full, the blood barrier changing color, for example, or other indicator. The fill time of the sequestration chamber may be substantially instantaneous, so such indicator, if present, may be only that the sequestration chamber is filled.

[0043] Prior to an evacuated blood collection tube being attached, communication between the needle, sampling channel, and the sequestration chamber is restricted by the sealing of the sequestration chamber blood barrier thereby not permitting air to reenter the system through the sequestration. Sealing the communication path could also be accomplished with a mechanical twist or other movement, a small orifice or tortuous pathway, eliminating the need for a separate valve or mechanical movement or operation by the clinician. At 710, once the evacuated blood collection tube is removed, the self-sealing membrane closes the sample needle, and at 712, additional subsequent evacuated blood collection tubes may be attached. Once samples have been taken, at 714 the device is removed from the patient and discarded.

[0044] FIGS. 8A - 8E illustrate an exemplary blood sample optimization system 800 for non-contaminated blood sampling, in accordance with some implementations. The blood sample optimization system 800 includes an inlet port 802 that can be connected to tubing, a patient needle (or both), or other vascular or venous access device, and a pathway splitter 804 having a first outlet to a sequestration chamber tubing 806 and a second outlet to sample collection tubing 808. One or both of the sequestration chamber tubing 806 and the sample collection tubing 808 can be formed of tubing. In some implementations, the sequestration chamber tubing 806 is sized so as to contain a particular volume of initial blood sample. The sample collection tubing 808 will receive a blood sample once the sequestration chamber tubing 806 is filled. The sample collection tubing 808 can be connected to a Vacutainer™ base or housing 810, or other blood sample collection device.

[0045] The blood sequestration system 800 further includes a blood sequestration device 812 which, as shown in more detail in FIGS. 8B - 8D, includes a housing 818 that includes a sampling channel 820 defining a pathway for the non-contaminated sample collection tubing 808 or connected at either end to the non-contaminated sample collection tubing 808. The sampling channel 820 can be curved through the housing 818 so as to better affix and stabilize the housing 818 at a location along the non-contaminated sample collection tubing 808.

[0046] The blood sequestration device 812 further includes a sequestration chamber 822 connected with the sequestration chamber tubing 806 or other chamber. The sequestration chamber 822 terminates at an air permeable blood barrier 824. The air permeable blood barrier 824 can also include a coloring agent that turns a different color upon full contact with blood, as an indicator that the regular collection of blood samples (i.e. the non-contaminated blood samples) can be initiated. Other indicators may be used, such as a small light, a sound generation mechanism, or the like. In some implementations, the air permeable blood barrier is positioned at a right angle from the direction of sequestration chamber 822, but can be positioned at any distance or orientation in order to conserve space and materials used for the housing 818. The housing 818 and its contents can be formed of any rigid or semi-rigid material or set of materials.

[0047] FIG. 9 illustrates a pathway splitter 900 for use in a blood sequestrations system, such as those shown in FIGS. 8A - 8E, for example. The pathway splitter 900 includes an inlet port 902, a main line outlet port 904, and a sequestration channel outlet port 906. The inlet port 902 can be connected to main tubing that is in turn connected to a patient needle system, or directly to a patient needle. The main line outlet port 904 can be connected to main line tubing to a blood sampling system, such as a vacutainer base or housing, or directly to such blood sampling system. The sequestration channel outlet port 906 can be connected to sequestration tubing for receiving and sequestering a first sample of blood, up to a measured amount or predetermined threshold. Alternatively, the sequestration channel outlet port 906 can be connected to a sequestration chamber. The sequestra-

tion channel outlet port 906 is preferably 20-70 degrees angled from the main line outlet port 904, which in turn is preferably in-line with the inlet port 902. Once the predetermined amount of initial blood sample is sequestered in the sequestration tubing or chamber, in accordance with mechanisms and techniques described herein, follow-on blood samples will flow into the inlet port 902 and directly out the main line outlet port 904, without impedance.

[0048] FIGS. 10A - 10D illustrate a blood sequestration device 1000 in accordance with alternative implementations. The blood sequestration device 1000 includes an inlet port 1002, a main outlet port 1004, and a sequestration channel port 1006. The inlet port 1002 can be connected to a patient needle or related tubing. The main outlet port 1004 can be connected to a blood sample collection device such as a Vacutainer, associated tubing, or a Luer activated valve, or the like. The sequestration channel port 1006 splits off from the main outlet port 1004 to a sequestration chamber 1008. In some implementations, the sequestration chamber 1008 is formed as a helical channel within a housing or other container 1001.

[0049] The sequestration chamber 1008 is connected at the distal end to an air permeable blood barrier 1010, substantially as described above. Air in the sequestration chamber 1008 is displaced through the air permeable blood barrier 1010 by an initial aliquot of blood that is guided into the sequestration channel port 1006. Once the sequestration chamber 1008 is filled, further blood draws through the main outlet port 1004 can be accomplished, where these samples will be non-contaminated.

[0050] FIGS. 11A - 11E illustrate a blood sequestration device 1100 in accordance with other alternative implementations. The blood sequestration device 1100 includes an inlet port 1102, similar to the inlet ports described above, a main outlet port 1104, and a sequestration channel port 1106 that splits off from the main outlet port 1104 and inlet port 1102. The sequestration channel port is connected to a sequestration chamber 1108. In the implementation shown in FIGS. 11A - 11E, the blood sequestration device includes a base member 1101 having a channel therein, which functions as the sequestration chamber 1108. The channel can be formed as a tortuous path through the base member 1101, which is in turn shaped and formed to rest on a limb of a patient.

[0051] A portion of the sequestration chamber 1108 can protrude from the base member or near a top surface of the base member, just before exiting to an air permeable blood barrier 1110, to serve as a blood sequestration indicator 1109. The indicator 1109 can be formed of a clear material, or a material that changes color when in contact with blood.

[0052] In some implementations, the blood sequestration device 1100 can include a blood sampling device 1120 such as a normally closed needle, Vacutainer™ shield or other collection device. The blood sampling device 1120 can be manufactured and sold with the blood sequestration device 1100 for efficiency and convenience, so that a first aliquot of blood that may be contaminated by a patient needle insertion process can be sequestered. Thereafter, the blood sampling device 1120 can draw non-contaminated blood samples to reduce the risk of false positive testing and ensure a non-contaminated sample.

[0053] FIGS. 12A-12D illustrate a blood sample optimization system 1200 in accordance with yet other alternative implementations. The system 1200 includes a blood sequestration device 1202 for attaching to a blood sampling device 1204, such as a Vacutainer™ or other collection and sampling device. The blood sequestration device 1202 is configured and arranged to receive, prior to a Vacutainer™ container or vial being attached to a collection needle of the blood sampling device 1204, a first aliquot or amount of blood, and sequester that first aliquot or amount in a sequestration channel of the blood sequestration device 1202.

[0054] In some implementations, the blood sequestration device 1202 can include an inlet port 1212, a main outlet port, and a sequestration channel port. The inlet port 1212 can be connected to a patient needle or related tubing. The main outlet port 1214 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port splits off from the main outlet port to a sequestration chamber 1218.

[0055] In some implementations, the sequestration chamber 1218 is formed as a channel within the body of a sequestration device 1202. The sequestration chamber 1218 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel. The sequestration device 1202 can include a housing or other containing body, and one or more channels formed therein. As shown in FIGS. 12A and 12B, the sequestration device 1202 includes a main body 1206 and a cap 1208. The main body 1206 is formed with one or more cavities or channels, which are further formed with one or more arms 1210 that extend from the cap 1208, and which abut the cavities or channels in the main body 1206 to form the primary collection port and main outlet port.

[0056] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet other alternative implementations. The system 1300 includes a blood sequestration device 1302 for attaching to a blood sampling device 1304, such as a Vacutainer or other bodily fluid collection and sampling device. The blood sequestration device 1302 is configured and arranged to receive, prior to a Vacutainer container or vial being attached to a collection needle of the blood sampling device 1304, a first aliquot or amount of blood, and to sequester that first aliquot or amount of blood or other bodily fluid in a sequestration channel of the blood sequestration device 1302.

[0057] The blood sequestration device 1302 includes a housing 1301 having an inlet port 1314, a main outlet port 1312, and a sequestration channel port 1316. The inlet port 1314 can be connected to a patient needle or associated tubing. The main outlet port 1312 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port 1316 splits off from the main inlet port 1314 to a sequestration chamber 1318.

[0058] In the implementation shown in FIGS. 13A-D, the sequestration chamber 1318 is formed as a cavity or chamber within housing 1301 or formed by walls that define housing 1301. The sequestration chamber 1318 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel, that is defined by the cooperation and connection of housing 1301 with cap 1307 which cap 1307 can include a protrusion 1305 that provides one or more walls or directors for the winding channel in the sequestration chamber 1318. The protrusion 1305 from the cap 1307 can be straight or curved, and may have various channels, apertures or grooves embedded therein, and can extend from the cap 1307 any angle or orientation. When the cap 1307 is connected with the housing 1301 to complete the formation of the sequestration chamber 1318, the protrusion 1305 forms at least part of the winding channel to sequester a first aliquot or amount of blood or other bodily fluid in a sequestration channel formed in the sequestration chamber 1318 and by the winding channel.

[0059] The sequestration chamber 1318 includes an air permeable blood barrier 1310, substantially as described above. Air in the sequestration chamber 1318 is displaced through the air permeable blood barrier 1310 by an initial aliquot of blood that is provided into the sequestration chamber 1318 by the blood pressure of the patient. Once the sequestration chamber 1318 is filled and the air in the sequestration chamber 1318 displaced, the blood pressure of the patient will be insufficient to drive or provide further blood into the blood sequestration device 1302, and in particular the outlet port 1312, until a force such as a vacuum or other pressure, such as provided by the blood sample collection device like Vacutainer is provided to draw out a next aliquot or amount of blood or bodily fluid. Further blood draws through the main outlet port 1312 can be accomplished, where these samples will be non-contaminated since any contaminants would be sequestered in the sequestration chamber 1318 with the first aliquot of blood.

[0060] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system 1400 to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample. The blood sampling system 1400 includes a blood sequestration device 1401 that can be connected between a blood sample collection device 1403 and a patient needle (not shown). The blood sample collection device 1403 can be a Vacutainer or the like. The blood sequestration device 1401 includes an inlet port 1402 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1402 may also be connected with tubing or other conduit that is in turn connected with the patient needle.

[0061] The inlet port 1402 defines an opening into the blood sequestration device 1401, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more. The blood sequestration device 1401 further includes an outlet port 1404, which defines an opening out of the blood sequestration device 1401 and to the blood sample collection device 1403. The outlet port 1404 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device 1403. The outlet port 1404 can further include a connector device such as a threaded cap, a Luer connector (male or female), a non threaded interference or glue joint fitting for attachment of various devices including but not limited to tubing, or the like.

[0062] The blood sequestration device 1401 further includes a sampling channel 1406 between the inlet port 1402 and the outlet port 1404, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1406 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1406 has a substantially similar cross sectional area as the opening of the inlet port 1402. In other implementations, the sampling channel 1406 can gradually widen from the inlet port 1402 to the outlet port 1404.

[0063] The blood sequestration device 1401 further includes a sequestration chamber 1408 that is connected to and split off or diverted from the sampling channel 1406 at any point between the inlet port 1402 and the outlet port 1404, but preferably from a proximal end of the sampling channel 1406 near the inlet port 1402. The sequestration chamber 1408 is at first maintained at atmospheric pressure, and includes an air outlet 1412 at or near a distal end of the sequestration chamber 1408 opposite the diversion point from the sampling channel 1406. The air outlet 1412 includes an air permeable blood barrier 1412. As shown in FIG. 14B, the air permeable blood barrier 1412 can be overlaid with a protective cover 1416. The protective cover 1416 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1412 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1412 as the air is displaced from the sequestration chamber 1408 by blood being forced into the sequestration chamber 1408 by a patient's own blood

pressure. In addition the protective cover 1416 can be constructed to inhibit or prevent accidental exposure of the air permeable blood barrier to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0064] As shown in FIGS. 14C and 14D, the sampling channel 1406 can be cylindrical or frusto-conical in shape, going from a smaller diameter to a larger diameter, to minimize a potential to lyse red blood cells. Likewise, the sampling channel 1406 is formed with a minimal amount of or no sharp turns or edges, which can also lyse red blood cells. The sampling channel 1406 splits off to the sequestration chamber 1408 near the inlet port 1402 via a diversion pathway 1409. The diversion pathway 1409 can have any cross-sectional shape or size, but is preferably similar to the cross-sectional shape of at least part of the inlet port 1402.

[0065] In some implementations, the sampling channel 1406 and the sequestration chamber 1408 are formed by grooves, channels, locks or other pathways formed in housing 1414. The housing 1414 can be made of plastic, metal or other rigid or semi-rigid material. The housing 1414 can have a bottom member that sealably mates with a top member. One or both of the bottom member and the top member can include the sampling channel 1406 and the sequestration chamber 1408, as well as the diversion pathway 1409, the inlet port 1402, and the outlet port 1404. In some other implementations, one or more of the diversion pathway 1409, the inlet port 1402, and/or the outlet port 1404 can be at least partially formed by a cap member that is connected to either end of the housing 1414. In some implementations, the top member and the bottom member, as well as the cap member(s), can be coupled together by laser welding, heat sealing, gluing, snapping, screwing, bolting, or the like. In other implementations, some or all of the interior surface of the diversion pathway 1409 and/or sequestration chamber 1408 can be coated or loaded with an agent or substance, such as a decontaminate, solidifying agent, or the like. For instance, a solidifying agent can be provided at the diversion pathway 1409 such that when the sequestration chamber 1408 is filled and the initial aliquot of blood backs up to the diversion pathway 1409, that last amount of sequestered blood could solidify, creating a barrier between the sequestration chamber 1408 and the sampling channel 1406.

[0066] FIGS. 15A-15G illustrate a blood sequestration device 1500. The blood sequestration device 1500 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like.

[0067] The blood sequestration device 1500 includes an inlet port 1502 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1502 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1502 defines an opening into the blood sequestration device 1500, which opening may be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[0068] The inlet port 1502 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1502, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 1500 can be fabricated and sold with the patient needle as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1500 at the time of blood draw or sampling.

[0069] The blood sequestration device 1500 further includes an outlet port 1504, which defines an opening out of the blood sequestration device 1500 and to the blood sample collection device. The outlet port 1504 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1500 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1500 at the time of blood draw or sampling.

[0070] The blood sequestration device 1500 further includes a sampling channel 1506 between the inlet port 1502 and the outlet port 1504, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1506 can be any sized, shaped or configured channel or conduit. In some implementations, the sampling channel 1506 has a substantially similar cross sectional area as the opening of the inlet port 1502. In other implementations, the sampling channel 1506 can gradually widen from the inlet port 1502 to the outlet port 1504.

[0071] The blood sequestration device 1500 further includes a sequestration chamber 1508 that is connected to and split off or diverted from the sampling channel 1506 at any point between the inlet port 1502 and the outlet port 1504, but preferably from a proximal end of the sampling channel 1506 near the inlet port 1502. In some implementations, the diversion includes a Y-shaped junction. The sequestration chamber 1508 is preferably maintained at atmospheric pressure, and includes a vent 1510 at or near a distal end of the sequestration chamber 1508. The vent 1510 includes an air per-

meable blood barrier 1512. FIG. 15C illustrates the blood sequestration device 1500 with the sequestration chamber 1508 filled with a first aliquot or sample of blood from the patient.

[0072] The air permeable blood barrier 1512 can be covered with a protective cover 1516. The protective cover 1516 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1512 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1512 as the air is displaced from the sequestration chamber 1508 by blood being forced into the sequestration chamber 1508 by a patient's own blood pressure. The protective cover 1516 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0073] FIG. 15B is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating an initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before a sample collection device is activated. FIG. 15G is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and bottom side of the housing 1501 of the blood sequestration device 1500, and illustrating the initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before the sample collection device is activated. FIG. 15C is another perspective view of the blood sequestration device 1500 from the inlet port 1502 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating blood now being drawn through sampling channel 1506 while the sequestered blood remains substantially in the sequestration chamber 1508.

[0074] FIG. 15D is a cross section of the blood sequestration device 1500 in accordance with some implementations, showing the housing 1501 that defines the sampling channel 1506 and the sequestration chamber 1508. FIGS. 15E and 15F illustrate various form factors of a housing for a blood sequestration device, in accordance with one or more implementations described herein.

[0075] The sequestration chamber 1508 can have a larger cross-sectional area than the sampling channel 1506, and the cross-sectional area and length can be configured for a predetermined or specific volume of blood to be sequestered or locked. The sampling channel 1506 can be sized to be compatible with tubing for either or both of the patient needle tubing or the blood collection device tubing.

[0076] The housing 1501 can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIG. 15D, the housing 1501 includes a top member 1520 and a bottom member 1522 that are mated together, one or both of which having grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc. The top member 1520 can be connected with the bottom member 1522 by any mating or connection mechanism, such as by laser welding, thermal bonding, ultrasonic welding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like.

[0077] In some implementations, such as shown in FIG. 15D, the top member 1520 can include the grooves, channels, locks, conduits or other pathways, while the bottom member 1522 can include a protrusion 1524 that is sized and adapted to fit into at least one of the grooves, channels, locks or other pathways of the top member 1520. The protrusion 1524 can provide a surface feature, such as a partial groove or channel, for instance, to complete the formation of either the sampling channel 1506 and/or the sequestration chamber 1508. In some implementations, the protrusion 1524 can be formed with one or more angled sides or surfaces for a tighter fit within the corresponding groove, channel, lock or other pathway. In yet other implementations, both the top member 1520 and the bottom member can include grooves, channels, locks or other pathways, as well as one or more protrusions 1524.

[0078] In some implementations, the sampling channel 1506 and the sequestration chamber 1508 are formed by grooves, channels, locks or other pathways formed in housing 1501. The housing 1501 can be made of any suitable material, including rubber, plastic, metal or other material. The housing 1501 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1501 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1506 and/or the sequestration chamber 1508 is clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 1508 is first filled to the extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1506. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1512 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[0079] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will make its way into the input port 1502 blood sequestration device 1500 and flow into the sequestration chamber 1508 by following the path of least resistance, as the patient's own blood pressure overcomes the atmospheric pressure in the sequestration chamber 1508 to displace air therein through

the air permeable blood barrier 1512. The patient's blood pressure will not be sufficient to overcome the air pressure that builds up in the sealed sampling channel 1506. Eventually, the sequestration chamber 1508, which has a predetermined volume, is filled with blood that displaces air through the air permeable blood barrier 1512. Once the blood hits the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1512 material to completely or partially seal the vent 1510. A signal or indication may be provided that the practitioner can now utilize the Vacutainer capsule or other blood sample collection device to acquire a next amount of the patient's blood for sampling. The blood in the sequestration chamber 1508 is now effectively sequestered in the sequestration chamber.

[0080] Upon filling the blood sequestration pathway 1508 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1506, possibly resulting in a small amount of blood moving past the diversion point to the sequestration chamber 1508 and into the sampling channel 1506, queuing up the uncontaminated blood to be drawn through the sampling channel 1506.

[0081] FIGS. 16-19 illustrate yet another implementation of a blood sequestration device. FIGS. 16A-16D illustrate a blood sequestration device 1600 that can be connected between a blood sample collection device, such as an evacuated blood collection container like a Vacutainer™ (not shown), and a patient needle (not shown) and/or associated tubing. FIG. 17 illustrates a bottom member of the blood sequestration device, and FIG. 18 illustrates a top member of the blood sequestration device, which top member and bottom member can be mated together to form an input port, and output port, a sequestration chamber and a sampling channel, as explained more fully below. FIGS. 19A and B show the top member and bottom member mated together. It should be understood that FIGS. 16-19 illustrate one exemplary manner of constructing a blood sequestration device as described herein, and other forms of construction are possible.

[0082] Referring to FIGS. 16A - D, the blood sequestration device 1600 includes an inlet port 1602 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1602 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1602 defines an opening into the blood sequestration device 1600, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[0083] The inlet port 1602 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1602, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1600 at the time of blood draw or sampling.

[0084] The blood sequestration device 1600 further includes an outlet port 1604, which defines an opening out of the blood sequestration device 1600 and to the blood sample collection device. The outlet port 1604 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1600 at the time of blood draw or sampling.

[0085] The blood sequestration device 1600 further includes a sampling channel 1606 between the inlet port 1602 and the outlet port 1604, and a sequestration chamber 1608 that is connected to and split off or diverted from the sampling channel 1606 at any point between the inlet port 1602 and the outlet port 1604. The sampling channel 1606 functions as a blood sampling pathway once a first aliquot of blood has been sequestered in the sequestration chamber 1608. The sampling channel 1606 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1606 has a substantially similar cross sectional area as the opening of the inlet port 1602. In other implementations, the sampling channel 1606 can gradually widen from the inlet port 1602 to the outlet port 1604. The sequestration chamber 1608 may have a larger cross section to form a big reservoir toward the sequestration channel path so that the blood will want to enter the reservoir first versus entering a smaller diameter on the sampling channel 1606, as is shown more fully in FIGS. 17 and 19.

[0086] In some exemplary implementations, the diversion between the sampling channel 1606 and the sequestration chamber 1608 is by diverter junction 1607. Diverter junction 1607 may be a substantially Y-shaped, T-shaped, or U-shaped. In some preferred exemplary implementations, and as shown in FIG. 17A -17B, the diverter junction 1607 is configured such that the flow out of the inlet port 1602 is preferentially directed toward the sequestration chamber 1608. The sequestration chamber 1608 may also include or form a curve or ramp to direct the initial blood flow toward and into the sequestration chamber 1608.

[0087] The sequestration chamber 1608 is preferably maintained at atmospheric pressure, and includes a vent

1610 at or near a distal end of the sequestration chamber 1608. The vent 1610 may include an air permeable blood barrier 1612 as described above.

[0088] The blood sequestration device 1600 can include a housing 1601 that can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIGS. 17A - 17D and FIGS. 18A - 18F, the housing 1601 includes a top member 1620 and a bottom member 1622 that are mated together. The blood sequestration device 1600 can also include a gasket or other sealing member (not shown) so that when the top member 1620 is mechanically attached with the bottom member 1622, the interface between the two is sealed by the gasket or sealing member. The FIGS. 17A - 17D illustrate a bottom member 1622 of a housing for a blood sequestration device 1600. The bottom member 1622 can include grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc., to form the sampling channel 1606, the sequestration chamber 1608, and diverter junction 1607.

[0089] The sequestration chamber 1608 may have a larger cross section than the sampling channel 1606 so that the blood will preferentially move into the sequestration chamber first versus entering a smaller diameter on the sampling channel 1606.

[0090] FIGS. 18A - 18F illustrate the top member 1620, which can be connected with the bottom member 1622 by any mating or connection mechanism, such as by laser welding, thermal bonding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like. The top member 1620 can include some or all of the grooves, channels, locks, conduits or other pathways to form the sampling channel 1606, the sequestration chamber 1608, and the diverter junction 1607. In yet other implementations, both the top member 1620 and the bottom member 1622 can include the grooves, channels, locks or other pathways.

[0091] In some implementations, the sampling channel 1606 and the sequestration chamber 1608 are formed by grooves, channels, locks or other pathways formed in housing 1601. The housing 1601 can be made of rubber, plastic, metal or any other suitable material. The housing 1601 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1601 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1606 and/or the sequestration chamber 1608 may be clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 1608 is first filled to the extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1606. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1612 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[0092] As shown in FIGS. 18A - 18F, the air permeable blood barrier 1612 can be covered with, or surrounded by, a protective member 1616. The protective member 1616 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1612 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1612 as the air is displaced from the sequestration chamber 1608. In some implementations, the protective member 1616 includes a protrusion that extends up from a top surface of the top member 1620 and around the air permeable blood barrier 1612. The protective cover 1616 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0093] In use, the blood sequestration device 1600 includes a sampling channel 1606 and a sequestration chamber 1608. Both pathways are initially air-filled at atmospheric pressure, but the sampling channel 1606 is directed to an output port 1604 that will be initially sealed by a Vacutainer or other such sealed blood sampling device, and the sequestration chamber 1608 terminates at a vent 1610 to atmosphere that includes an air permeable blood barrier 1612.

[0094] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will pass through input port 1602 of blood sequestration device 1600. This initial volume of potentially contaminated blood will preferentially flow into the sequestration chamber 1608 by finding the path of least resistance. The patient's own blood pressure overcomes the atmospheric pressure in the vented sequestration chamber 1608 to displace air therein through the air permeable blood barrier 1612, but is not sufficient to overcome the air pressure that builds up in the sealed sampling channel 1606. In various exemplary embodiments, the sequestration chamber 1608 and sampling channel 1606 can be configured such that the force generated by the patient's blood pressure is sufficient to overcome any effect of gravity, regardless of the blood sequestration device's orientation.

[0095] Eventually, the sequestration chamber 1608 fills with blood that displaces air through the air permeable blood barrier 1612. Once the blood contacts the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1612 material to completely or partially seal the vent 1610. A signal or indication may be provided that the practitioner can now utilize the Vacutainer or other blood sampling device.

[0096] Upon filling the blood sequestration pathway 1608 but prior to use of the Vacutainer or other blood

sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1606, possibly resulting in a small amount of blood moving past the diversion point into the sampling channel 1606, queuing up the uncontaminated blood to be drawn through the sampling channel 1606.

[0097] FIG. 19A is a side view, and FIG. 19B is a cross-sectional view, of the blood sequestration device 1600, illustrating the top member 1620 mated with the bottom member 1622.

[0098] FIG. 20 shows a blood sample optimization system 2000 that includes a patient needle 2002 for vascular access to a patient's bloodstream, a blood sample collection device 2004 to facilitate the collecting of one or more blood samples, and a conduit 2006 providing a fluid connection between the patient needle 2002 and the blood sample collection device 2004. In some implementations, the blood sample collection device 2004 includes a protective shield that includes a sealed collection needle on which a sealed vacuum-loaded container is placed, which, once pierced by the collection needle, draws in a blood sample under vacuum pressure or force through the conduit 2006 from the patient needle 2002.

[0099] The blood sample optimization system 2000 further includes a blood sequestration device 2008, located at any point on the conduit 2006 between the patient needle 2002 and the blood sample collection device 2004 as described herein.

[0100] FIG. 21 illustrates a non-vented blood sequestration device 2100 using a wicking material chamber. The blood sequestration device 2100 includes a housing 2101 that has a sampling channel 2104 that is at least partially surrounded or abutted by a sequestration chamber 2102 that is filled with a wicking material. An initial aliquot of blood is drawn in from the patient needle into the sampling channel 2104 where it is immediately wicked into the wicking material of the sequestration chamber 2102. The wicking material and/or sequestration chamber 2102 is sized and adapted to receive and hold a predetermined amount of blood, such that follow-on or later blood draws pass by the wicking material and flow straight through the sampling channel 2104 to a sampling device such as a Vacutainer. The wicking material can include a substance such as a solidifier, a decontaminate, or other additive.

[0101] As described herein, an air permeable blood barrier may be created using a wide variety of different structures and materials. As shown in FIGS. 22A and B, an air permeable blood barrier 2202 of a blood sequestration device 2200 can include a polymer bead matrix 2204, in which at least some beads are treated to make them hydrophilic. The air permeable blood barrier 2202 further includes a self-sealing material 2206, such as carboxymethyl cellulose (CMC) or cellulose gum, or other sealing material. The air permeable blood barrier 2202 can further include voids 2208 that permit air flow before contact or during partial contact with a fluid such as blood. As shown in FIG. 22B, contact with a fluid causes the self-sealing material 2206 to swell and close off the voids 2208, occluding air flow through the voids 2208 and creating a complete or partial seal.

[0102] FIGS. 23A and B illustrate yet another implementation of a blood sequestration device 2300, having an inlet port 2302 to connect with a patient needle, an outlet port 2304 to connect with a blood sample collection device, a sequestration chamber 2306, and a sampling channel 2308 that bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be sequestered. The sequestration chamber 2306 includes a hydrophobic plug 2312 at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302. A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. A small amount of blood may make its way into the sampling channel 2308, which is initially closed off by valve 2308. Upon release of the valve 2308, and under further force of the vacuum or other force, follow-on amounts of blood will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 toward the outlet port 2304 and to the collection device.

[0103] The sampling channel 2308 can have any suitable geometry and can be formed of plastic tubing or any other suitable material. Valve 2308 can be a clip or other enclosing device to pinch, shunt, bend or otherwise close off the sampling channel before the initial aliquot of blood is sequestered in the sequestration chamber 2306.

[0104] Although a variety of embodiments have been described in detail above, other modifications are possible. Other embodiments may be within the scope of the following claims.

Aspects useful for understanding the invention:

[0105]

1. A blood sequestration device comprising;
an inlet port;
an outlet port;
a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;
a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port; and
a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

2. The blood sequestration device in accordance

with aspect 1, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

3. The blood sequestration device in accordance with aspect 1 or 2, wherein the sequestration chamber includes a sequestration channel defined in the housing.

4. The blood sequestration device in accordance with aspect 3, further comprising a blood sampling pathway connected with the inlet port, and wherein the inlet port defined by the housing has a cross-sectional geometry consistent with the blood sampling pathway.

5. The blood sequestration device in accordance with aspect 3 or 4, wherein the sampling channel defined by the housing has a cross-sectional geometry consistent with the inlet port.

6. The blood sequestration device in accordance with one of the previous aspects, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

7. The blood sequestration device in accordance with one of the previous aspects, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

8. A blood sequestration device connected with a blood sampling pathway having a patient needle and a sample collection device, the blood sequestration device comprising;
an inlet port connected with the patient needle;
a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;
a sampling channel having a proximal end connected with the inlet port; and
an outlet port connected with a distal end of the sampling channel and with the sample collection device; and
a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

9. The blood sequestration device in accordance with aspect 8, wherein the inlet port is connected with the patient needle via a first portion of the blood sampling pathway.

10. The blood sequestration device in accordance with aspect 8 or 9, wherein the outlet port is connected with the sample collection device via a second portion of the blood sampling pathway.

11. The blood sequestration device in accordance with one of aspects 8 to 10, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

12. The blood sequestration device in accordance with one of aspects 8 to 11, wherein the sequestration chamber includes a sequestration channel defined in the housing.

13. The blood sequestration device in accordance with aspect 12, wherein the sequestration channel has a proximal end connected with the inlet port, and a distal end having the vent comprising an air permeable blood barrier.

14. The blood sequestration device in accordance with one of aspects 8 to 13, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

15. The blood sequestration device in accordance with one of aspects 8 to 14, wherein the sampling channel has a substantially uniform cross-sectional geometry that is consistent with the blood sampling pathway.

16. The blood sequestration device in accordance with aspect 15, wherein the sequestration chamber includes a sequestration chamber that has a cross-sectional area that is larger than the cross-sectional geometry of the sampling channel.

17. A blood sequestration device connected with a blood sampling system comprising a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed, the blood sequestration device comprising;
an inlet port connected with the patient needle to receive the blood sample from the patient;
a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed; and
a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a second portion of the blood sample once the sample needle is unsealed;
an outlet port connected with a distal end of the sampling channel for conveying the second portion of

the blood sample to the sample needle; and
a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

18. The blood sequestration device in accordance with aspect 17, wherein the sequestration chamber is at ambient air pressure, and wherein the sequestration chamber receives the first portion of the blood sample by blood pressure of the patient overcoming the ambient air pressure in the sequestration chamber.

19. The blood sequestration device in accordance with aspect 17 or 18, wherein the sampling channel causes the second portion of the blood sample to bypass the sequestered first portion of blood, and exit the outlet port for conveyance to a blood collection device.

20. The blood sequestration device in accordance with aspect 17, 18 or 19, wherein the air permeable blood barrier includes an air permeable material that seals upon contact with blood.

Claims

1. A blood sequestration device (1500) comprising;

   an inlet port (1502);
   a junction (1607) connected with the inlet port (1502);
   a sequestration chamber (1508) having a vent (1510) comprising an air permeable blood barrier (1512);
   a sampling channel (1506) having a proximal end connected with the inlet port (1502) via the junction (1607), and a distal end connected with an outlet port (1504); and
   a housing (1501) that houses and defines the inlet port (1502), the junction (1607), the sequestration chamber (1508), the sampling channel (1506), and the outlet port (1504),
   characterized in that the sequestration chamber (1508) is connected with the
   inlet port (1502) via the junction (1607) which is configured to direct a first portion of blood to the sequestration chamber (1508), and the air permeable blood barrier (1512) includes an air permeable material that seals at least partially upon contact with a portion of the first portion of blood.

2. The blood sequestration device (1500) in accordance with claim 1,
   wherein the sequestration chamber (1508) includes a sequestration channel defined in the housing (1501).

3. The blood sequestration device (1500) in accordance with claim 1 or 2, further comprising a blood sampling pathway connected with the inlet port (1502) opposite the junction (1607), and
   wherein the inlet port (1502) defined by the housing (1501) has a cross-sectional geometry consistent with the blood sampling pathway.

4. The blood sequestration device (1500) in accordance with one of the preceding claims, wherein
   the sampling channel (1506) defined by the housing (1501) has a cross-sectional geometry consistent with the inlet port (1502).

5. The blood sequestration device (1500) in accordance with one of claims 2 to 4, wherein the housing (1501) comprises a bottom member (1522) mated with a top member (1520), each of the bottom member (1522) and the top member (1520) defining a part of each of the inlet port (1502), the outlet port (1504), the sequestration chamber (1508), and the sampling channel (1506).

6. A system of a blood sequestration device (1500), a blood sampling pathway having a patient needle, and a sample collection device, the blood sequestration device (1500) comprising;
   an inlet port (1502) connected with the patient needle;
   a junction (1607) connected with the inlet port (1502) opposite the blood sampling pathway;
   a sequestration chamber (1508) having a vent (1510) comprising an air permeable blood barrier (1512);
   a sampling channel (1506) having a proximal end connected with the inlet port (1502); and
   an outlet port (1504) connected with a distal end of the sampling channel (1506) and with the sample collection device; and
   a housing (1501) that houses and defines the inlet port (1502), the outlet port (1504), the sequestration chamber (1508), and the sampling channel (1506),
   characterized in that the sequestration chamber (1508) is connected with the inlet port (1502) and the air permeable blood barrier (1512) includes an air permeable material that seals at least partially upon contact with blood.

7. The system in accordance with claim 6, wherein the inlet port (1502) is connected with the patient needle via a first portion of the blood sampling pathway.

8. The system in accordance with claim 6 or 7, wherein the outlet port (1504) is connected with the sample collection device via a second portion of the blood sampling pathway.

9. The system in accordance with one of claims 6 to 8,

wherein the sequestration chamber (1508) includes a sequestration channel defined in the housing (1501).

10. The system in accordance with claim 9, wherein the sequestration channel has a proximal end connected with the inlet port (1502), and a distal end having the vent (1510) comprising an air permeable blood barrier (1512).

11. The system in accordance with one of claims 6 to 10, wherein the sequestration chamber (1508) and the sampling channel (1506) are connected with the inlet port (1502) by
the junction (1607) that is configured to direct a first portion of blood to the sequestration chamber (1508).

12. The system in accordance with one of claims 6 to 11, wherein the sampling channel (1506) has a substantially uniform cross-sectional geometry that is consistent with the blood sampling pathway.

13. The system in accordance with claim 12, wherein the sequestration chamber (1506) includes a sequestration chamber that has a cross-sectional area that is larger than the cross-sectional geometry of the sampling channel (1506).

14. The system in accordance with claim 7, member (1520), wherein the housing (1501) comprises a bottom member (1522) mated with a top member (1520), each of the bottom member (1522) and the top member (1520) defining a part of each of the inlet port (1502), the outlet port (1504), the sequestration chamber (1508), and the sampling channel (1506).

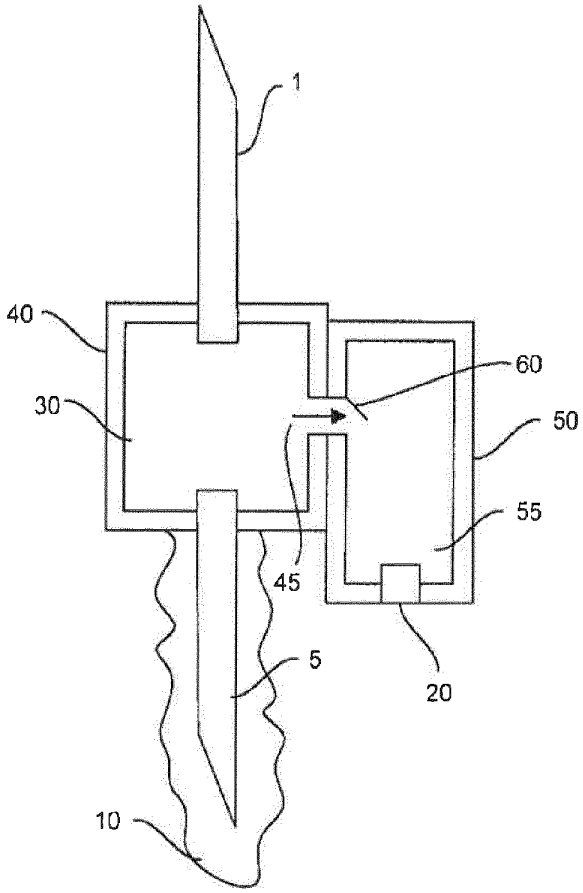


FIG. 1

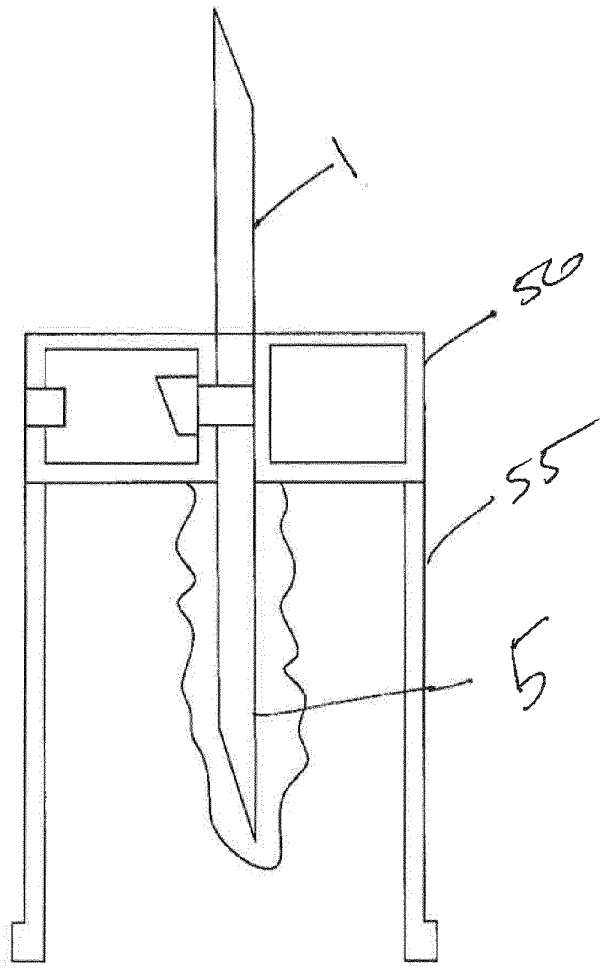


FIG. 2

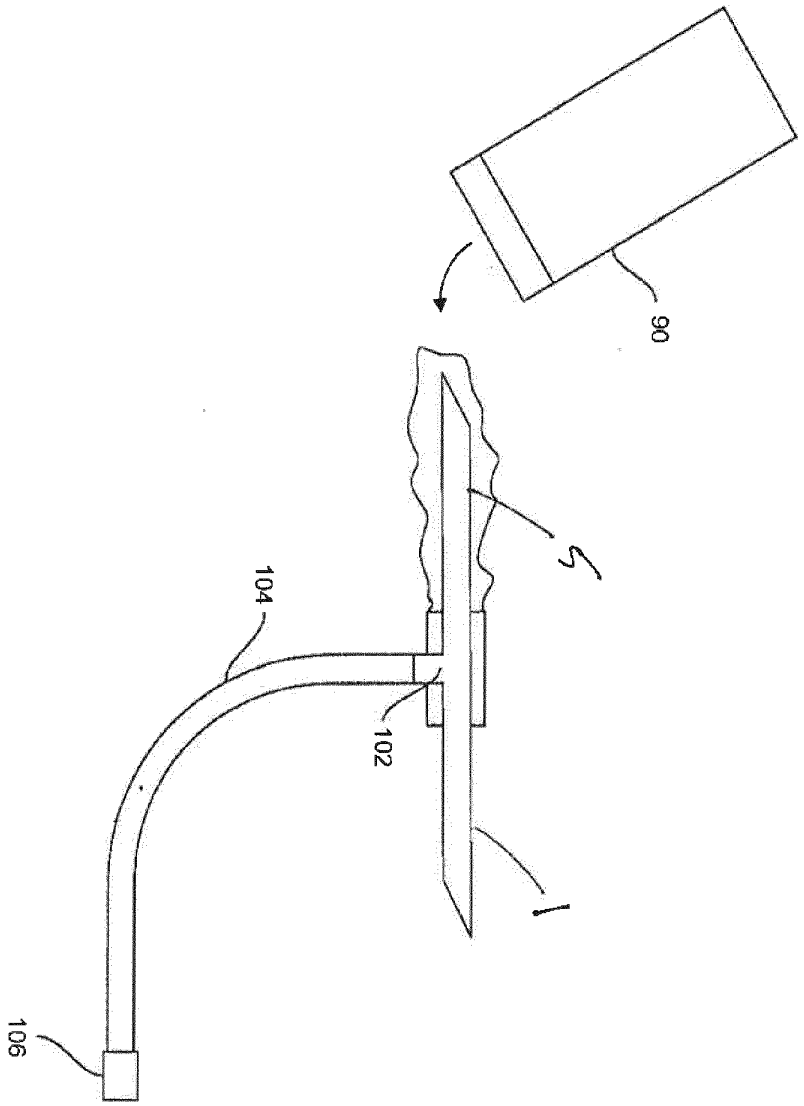


FIG. 3

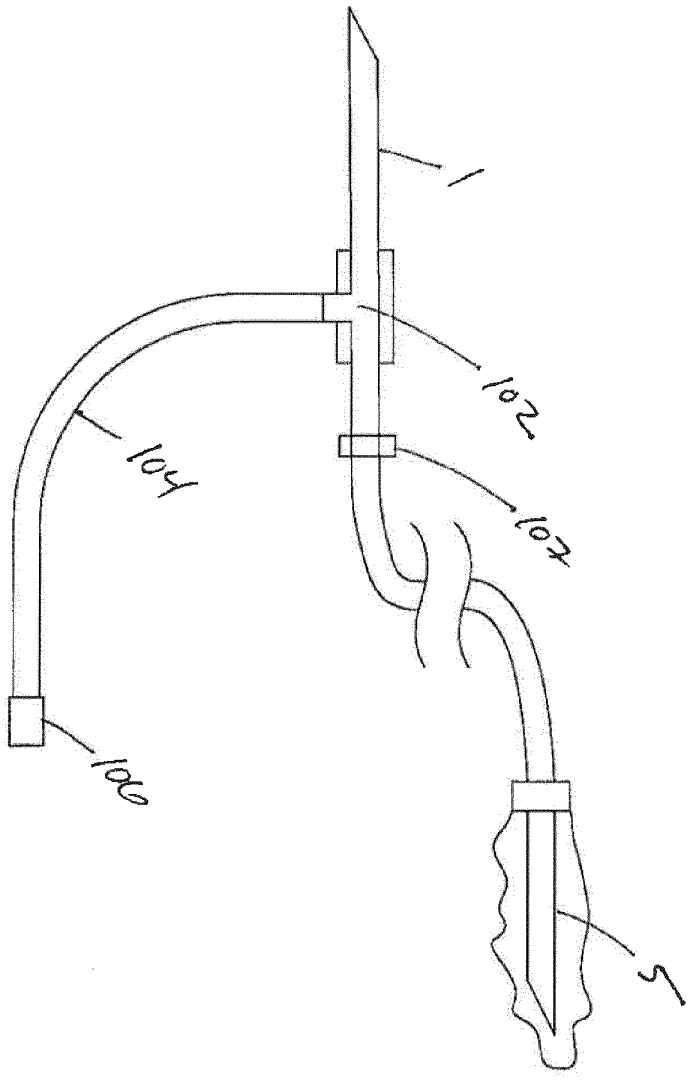


FIG. 4

FIG. 5

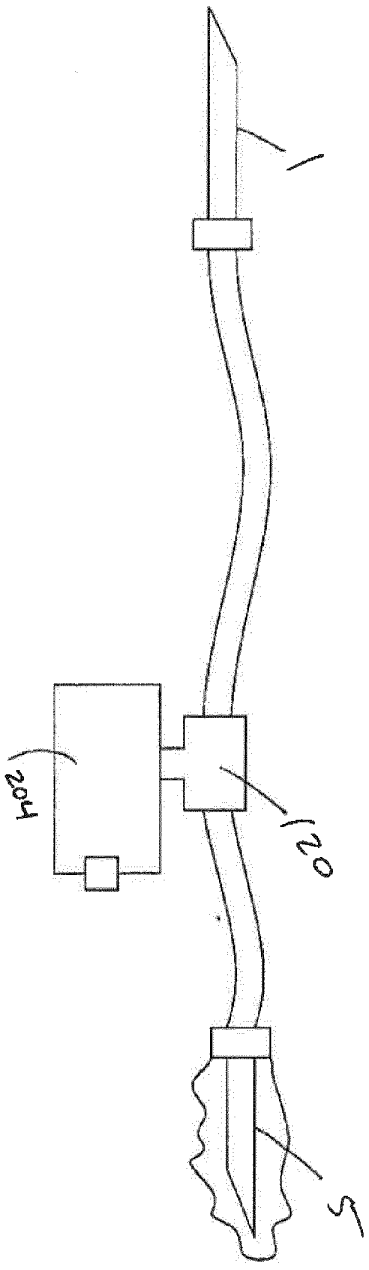
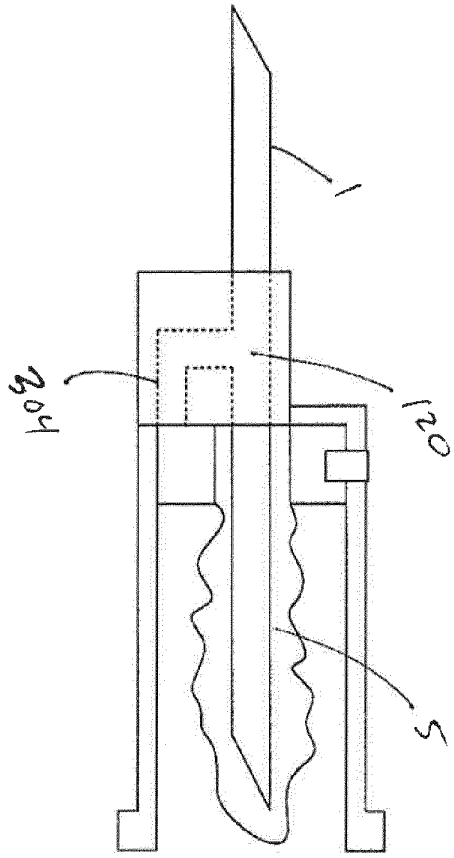


FIG. 6



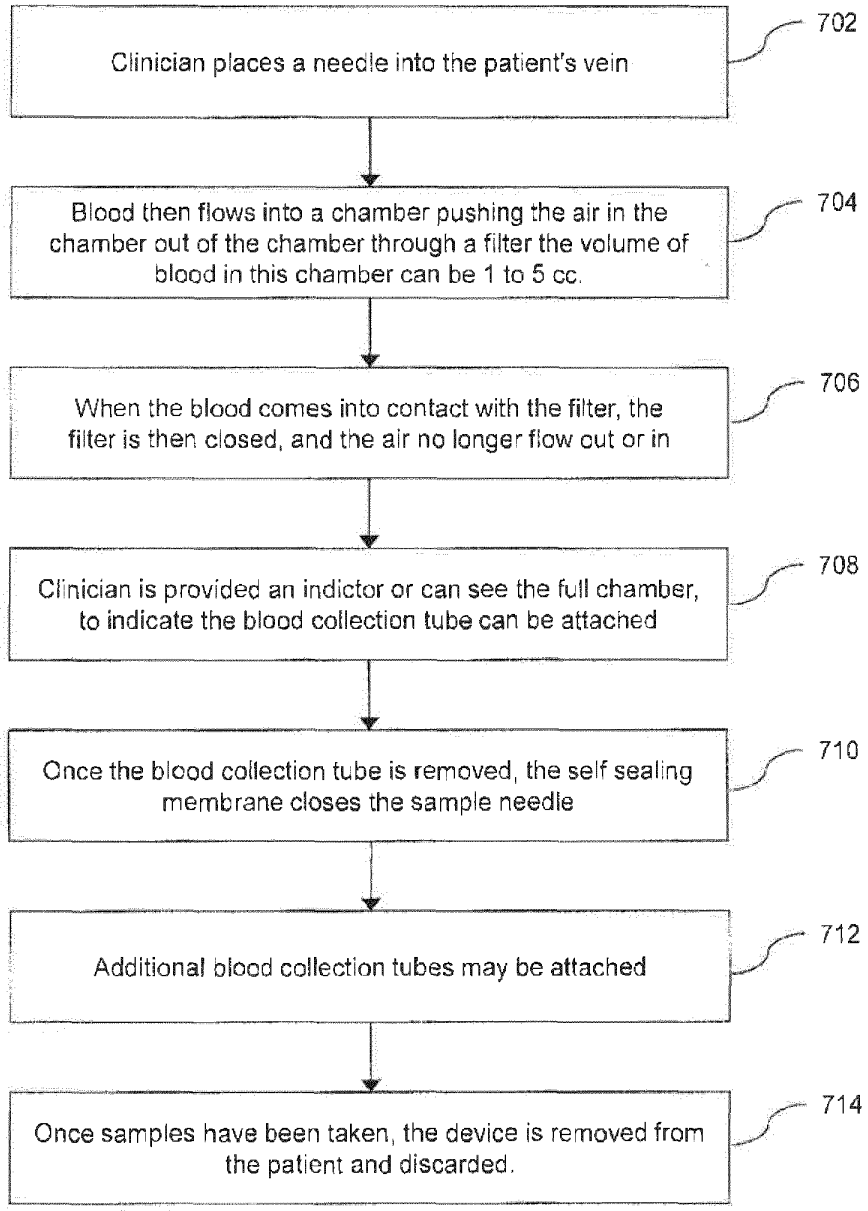

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter, the filter is then closed, and the air no longer flow out or in
706
Clinician is provided an indictor or can see the full chamber, to indicate the blood collection tube can be attached
708
Once the blood collection tube is removed, the self sealing membrane closes the sample needle
710
Additional blood collection tubes may be attached
712
Once samples have been taken, the device is removed from the patient and discarded.
714

FIG. 7

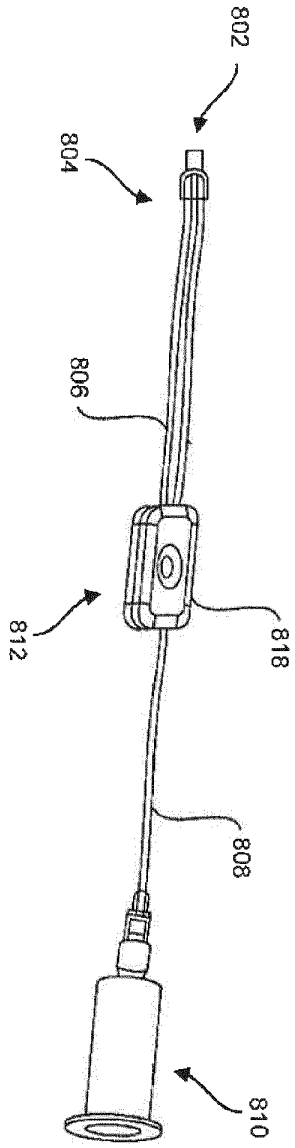


FIG. 8A

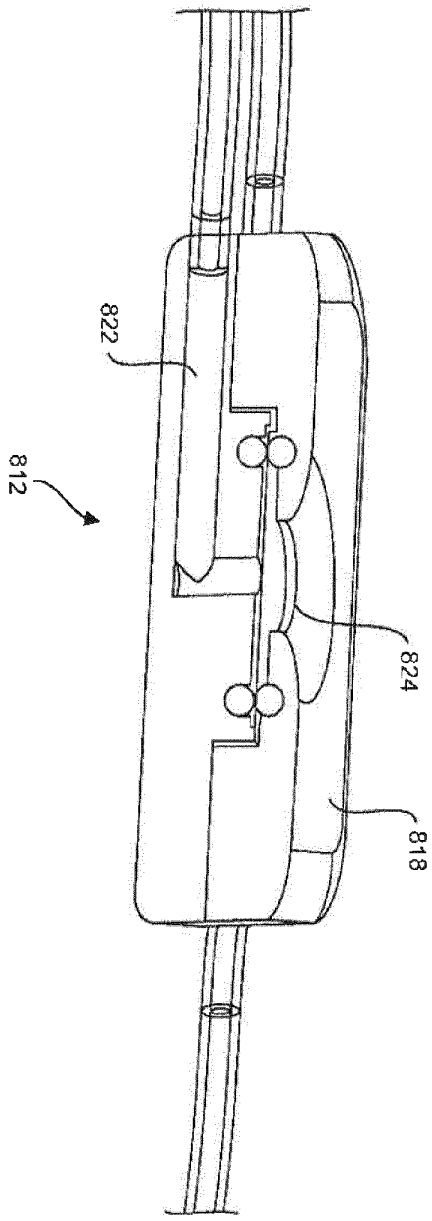


FIG. 8B

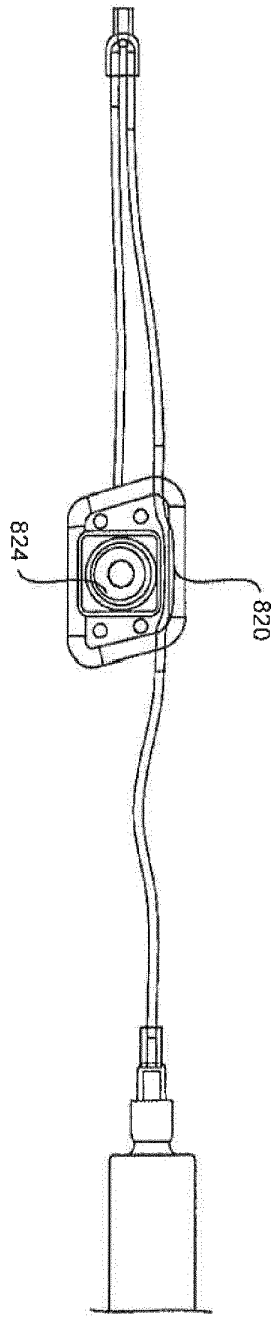


FIG. 8C

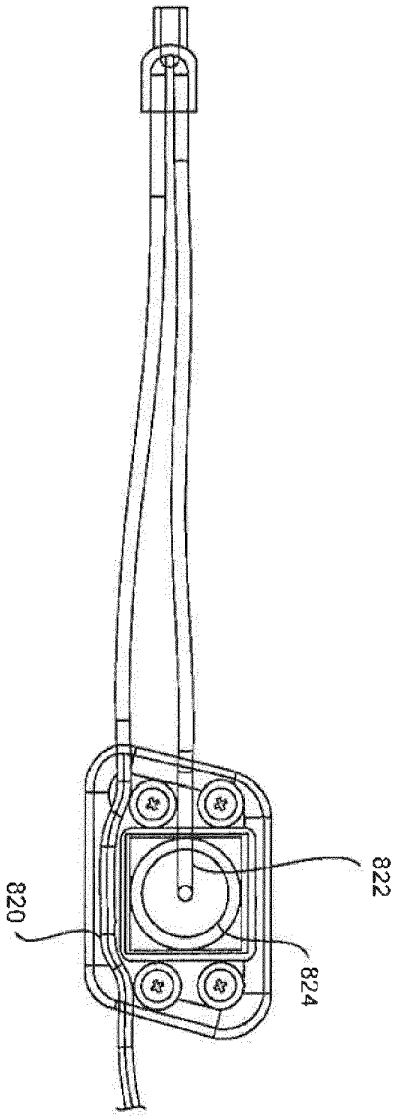


FIG. 8D

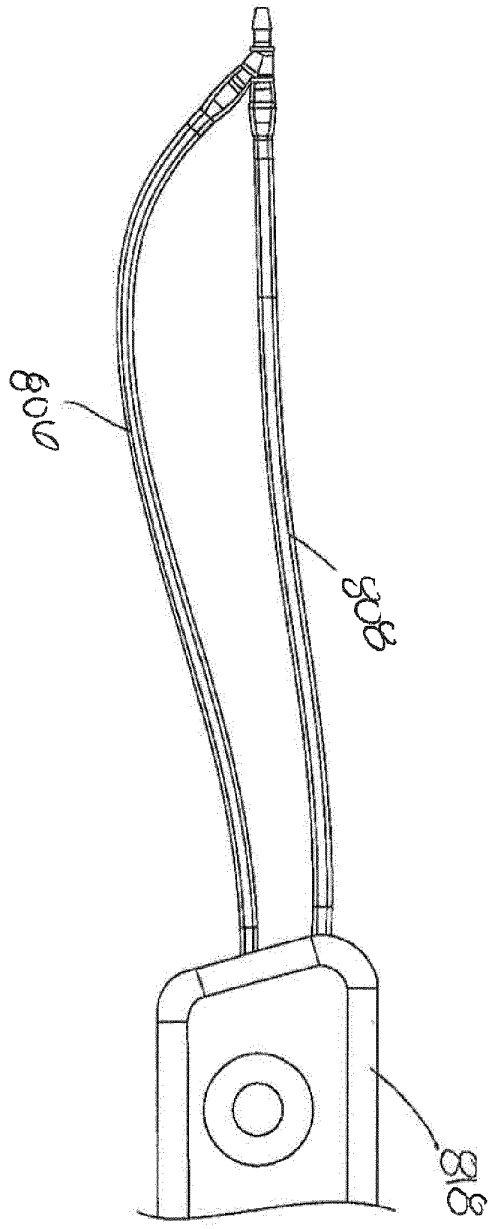


FIG. 8E

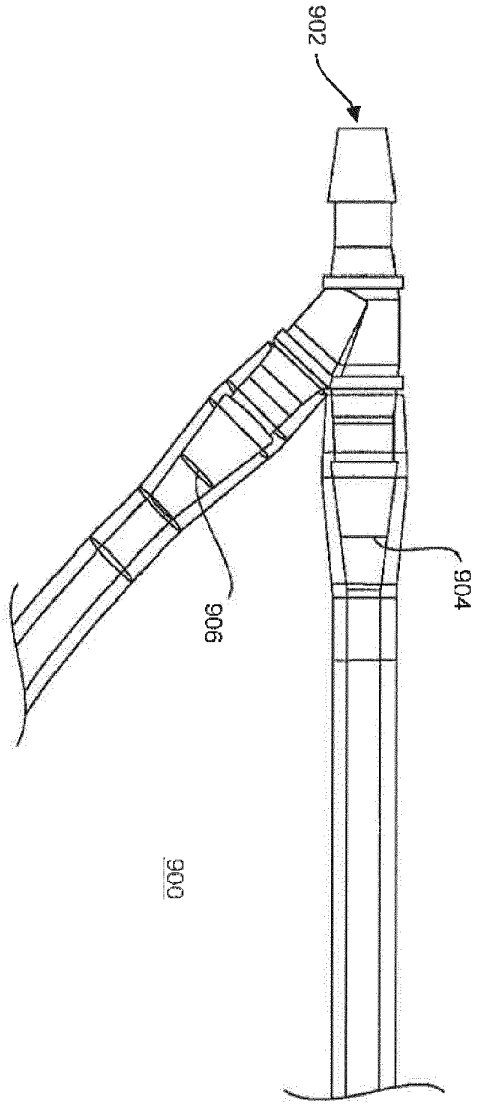


FIG. 9

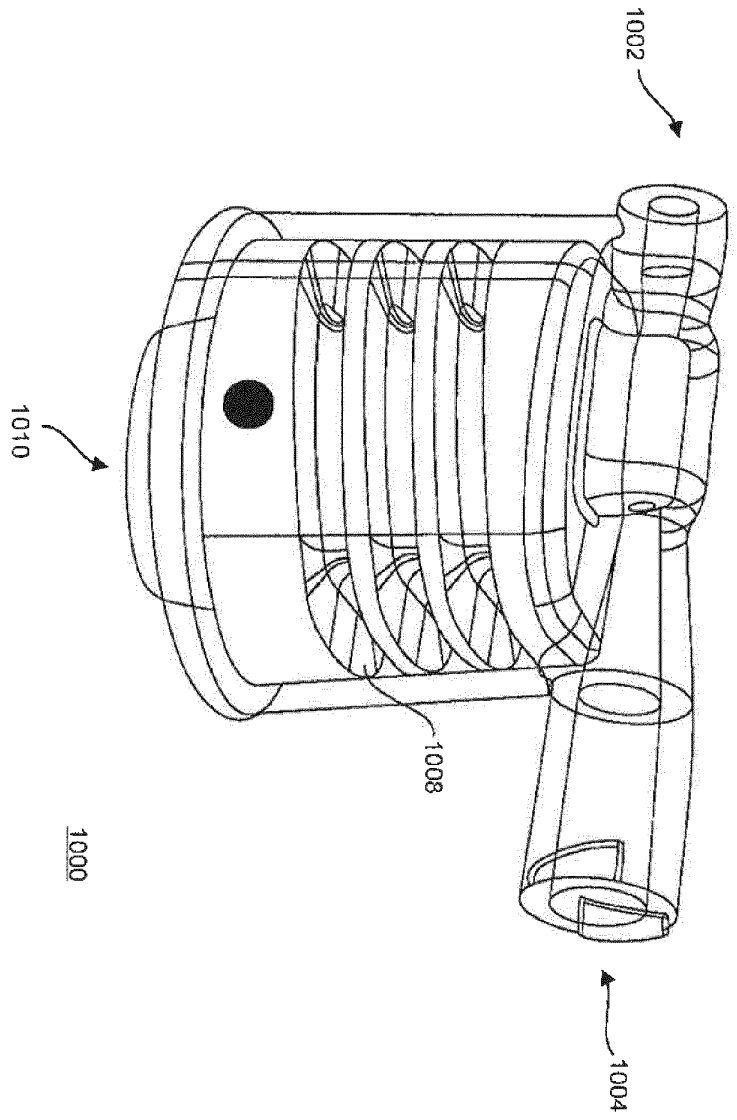


FIG. 10A

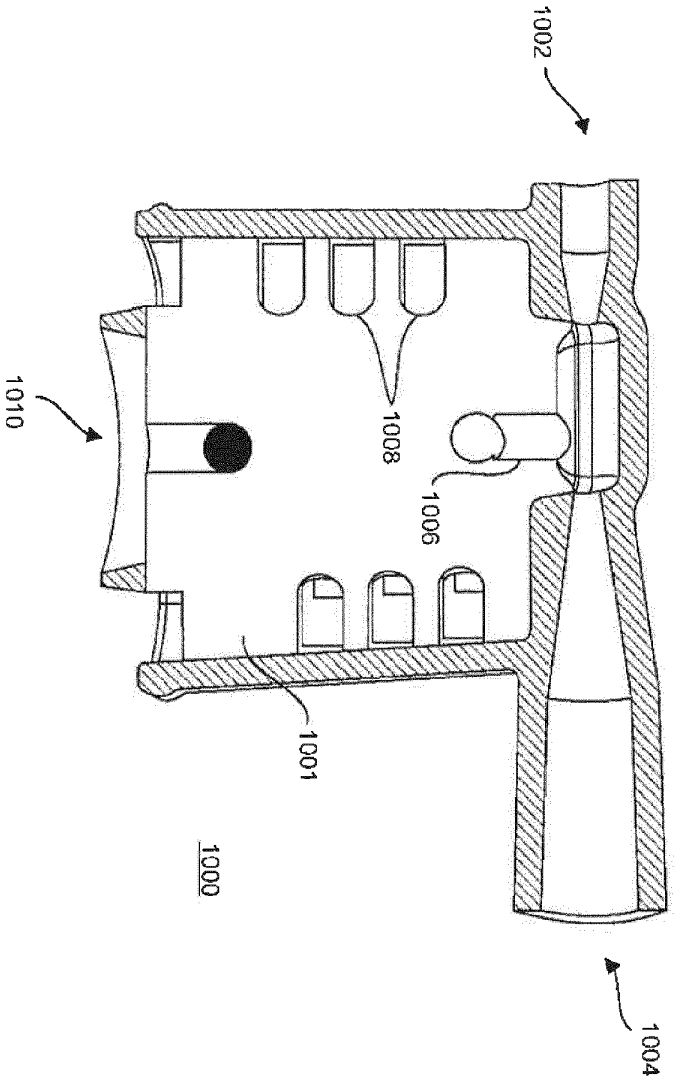


FIG. 10B

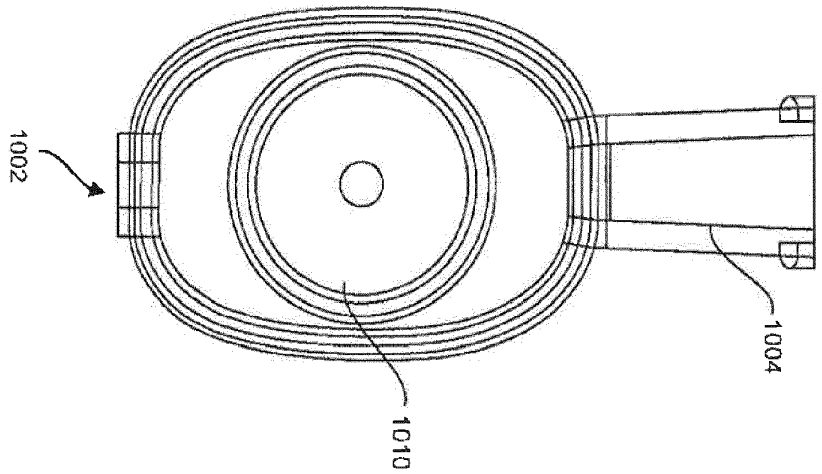


FIG. 10C

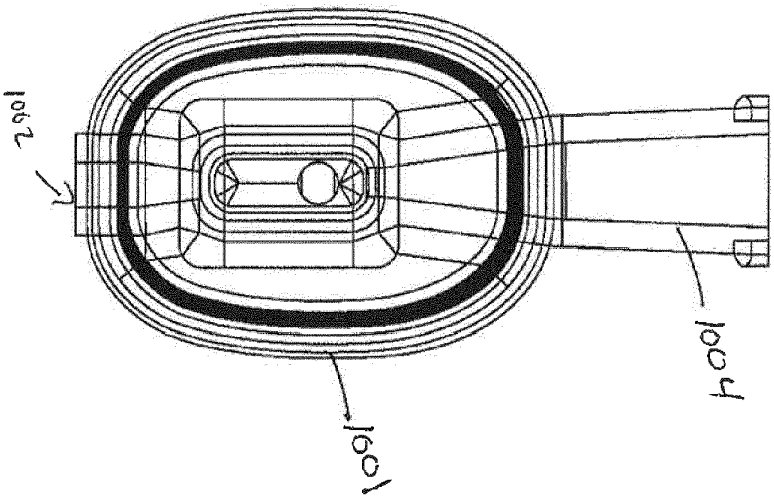
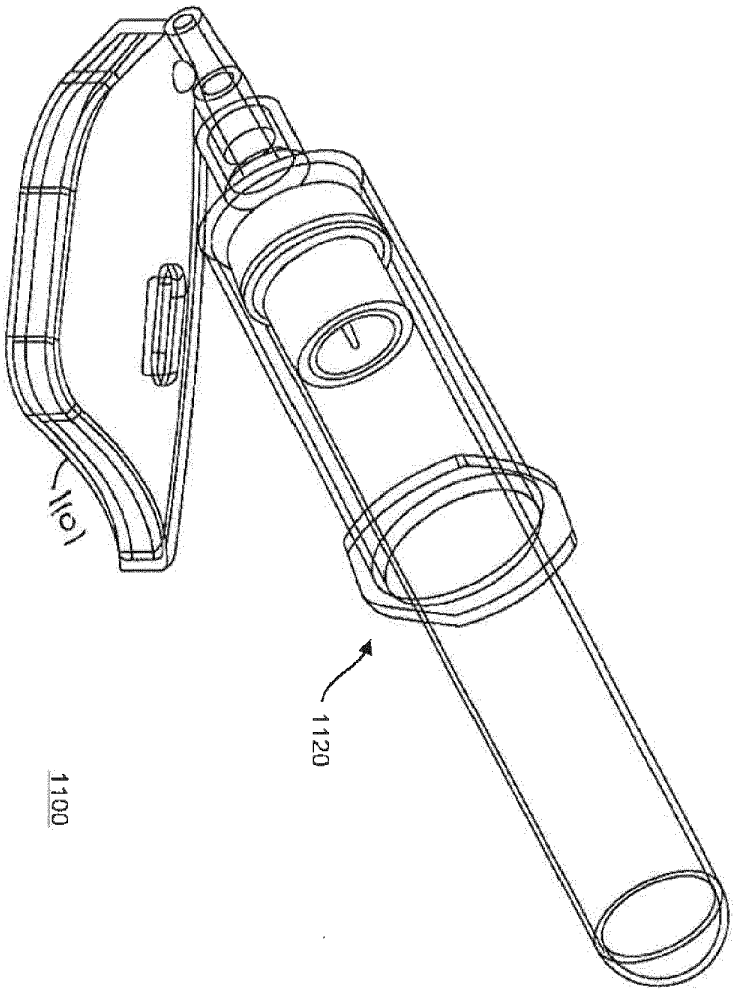


FIG. 10D

FIG. 11A



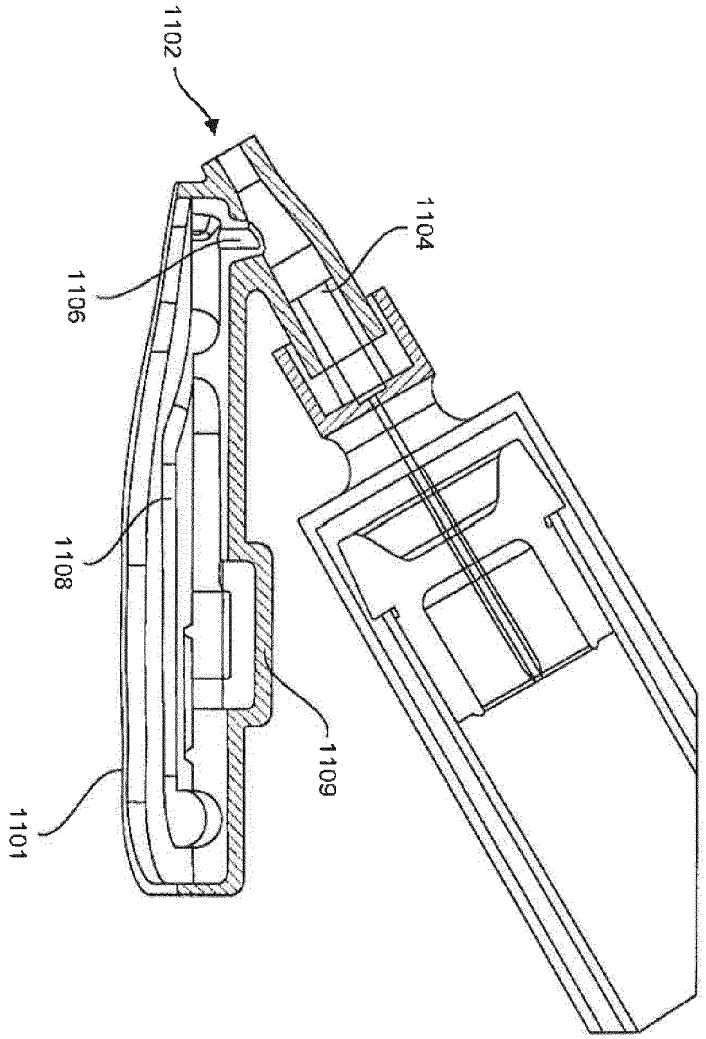


FIG. 11B

FIG. 11C

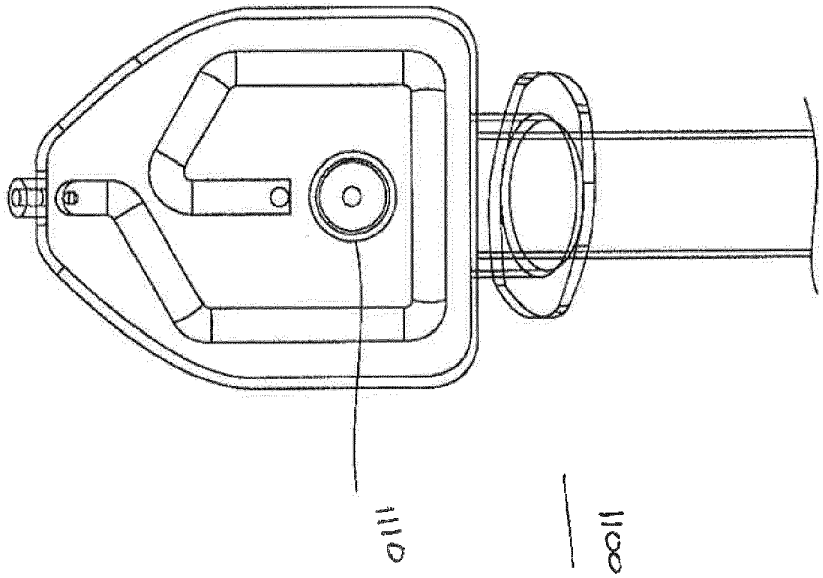
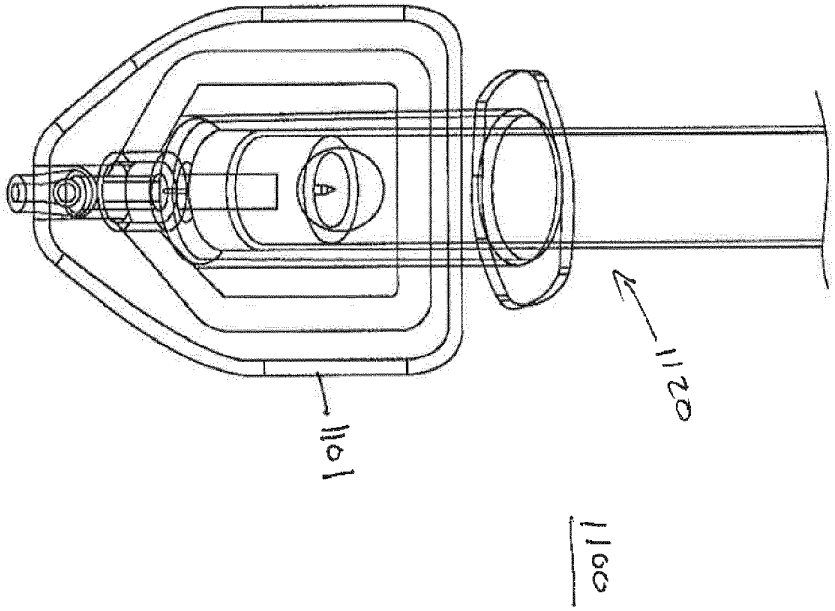


FIG. 11D



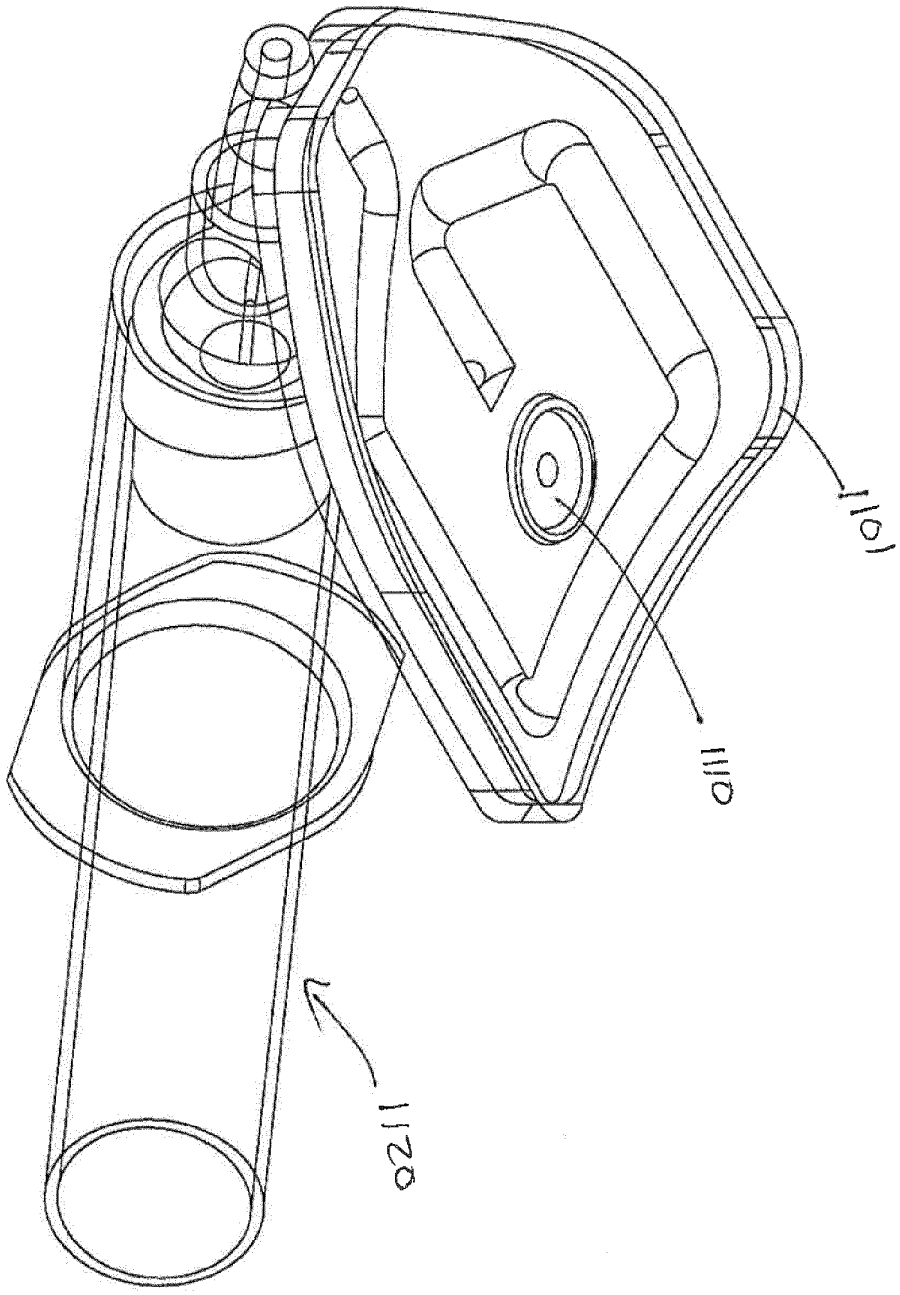


FIG. 11E

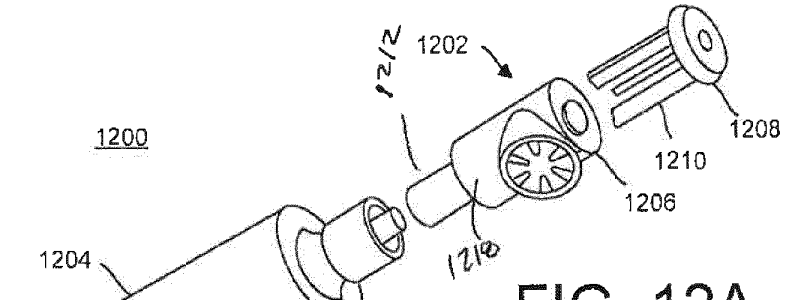


FIG. 12A

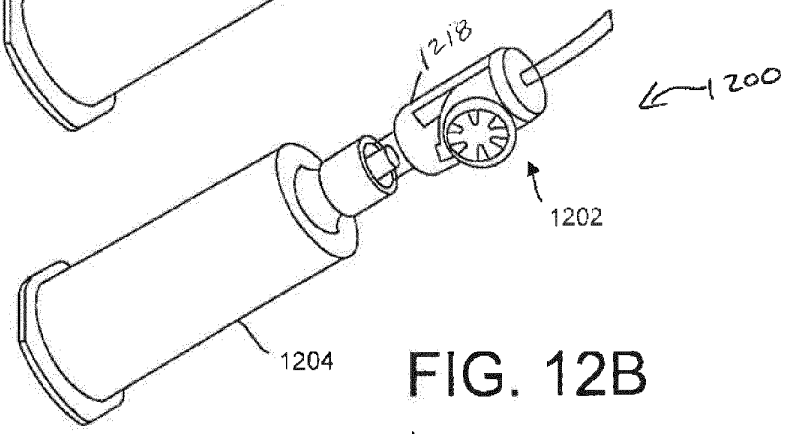


FIG. 12B

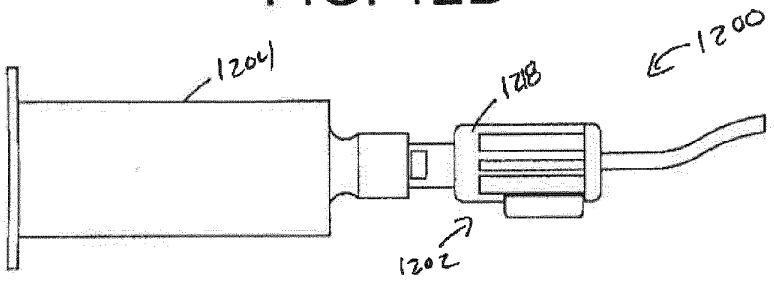


FIG. 12C

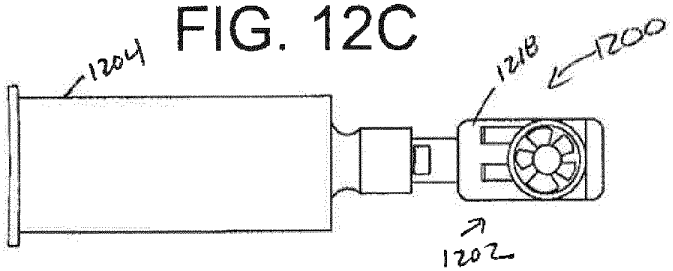


FIG. 12D

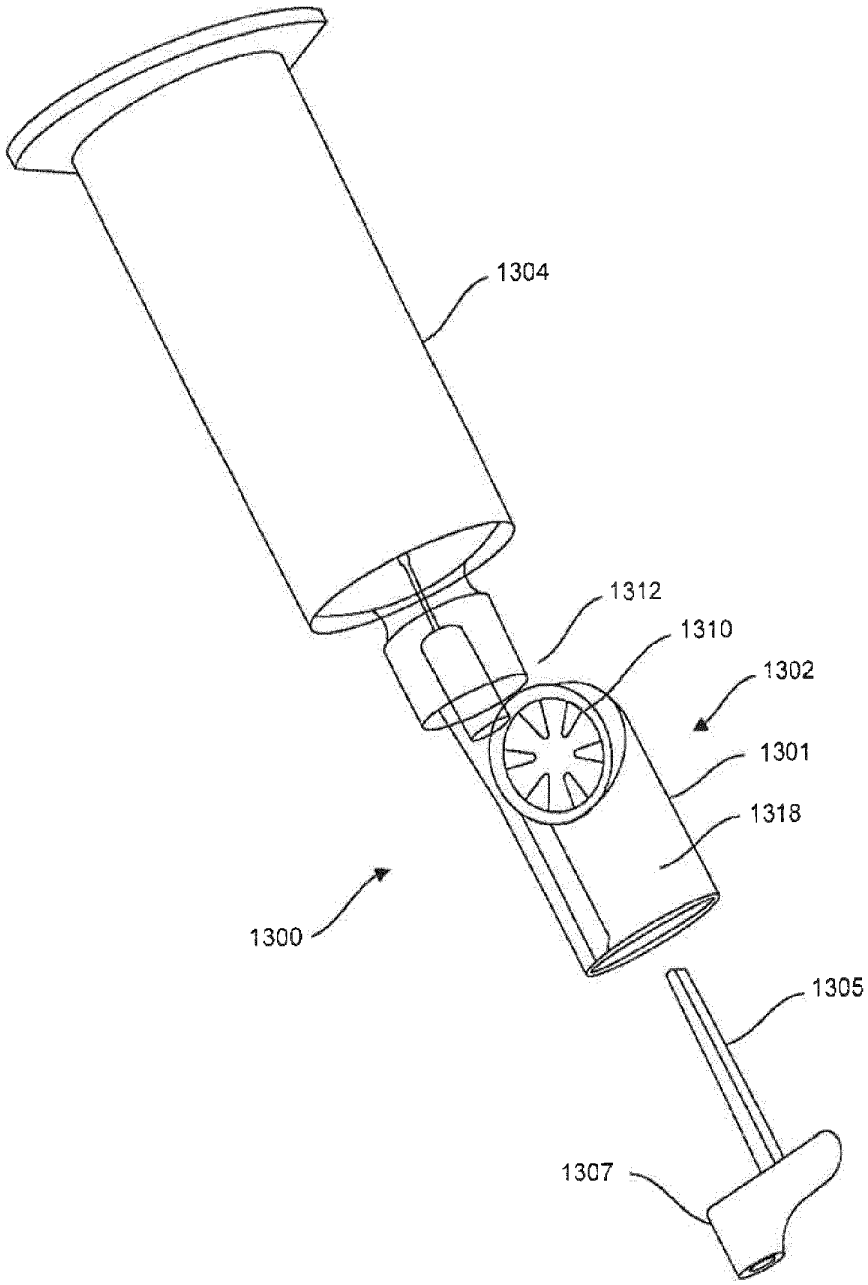


FIG. 13A

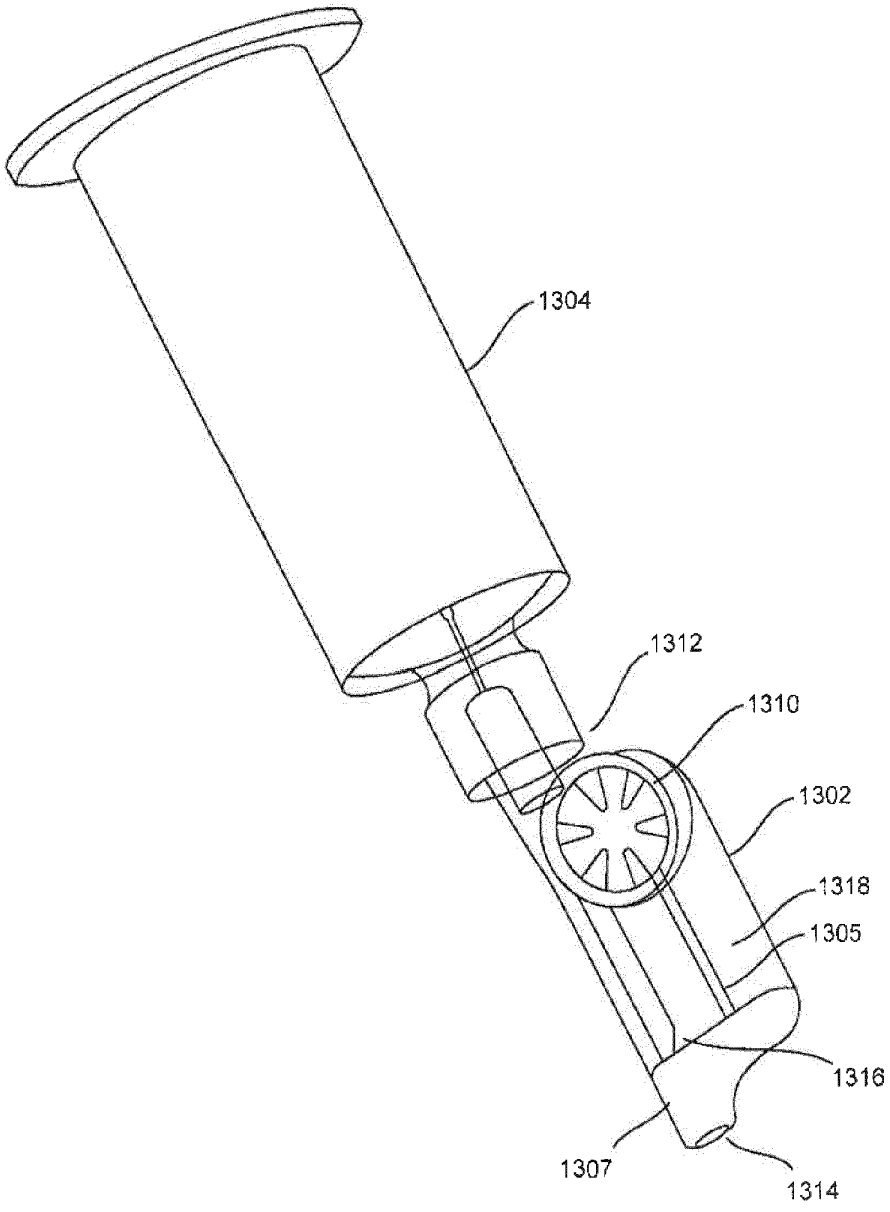


FIG. 13B

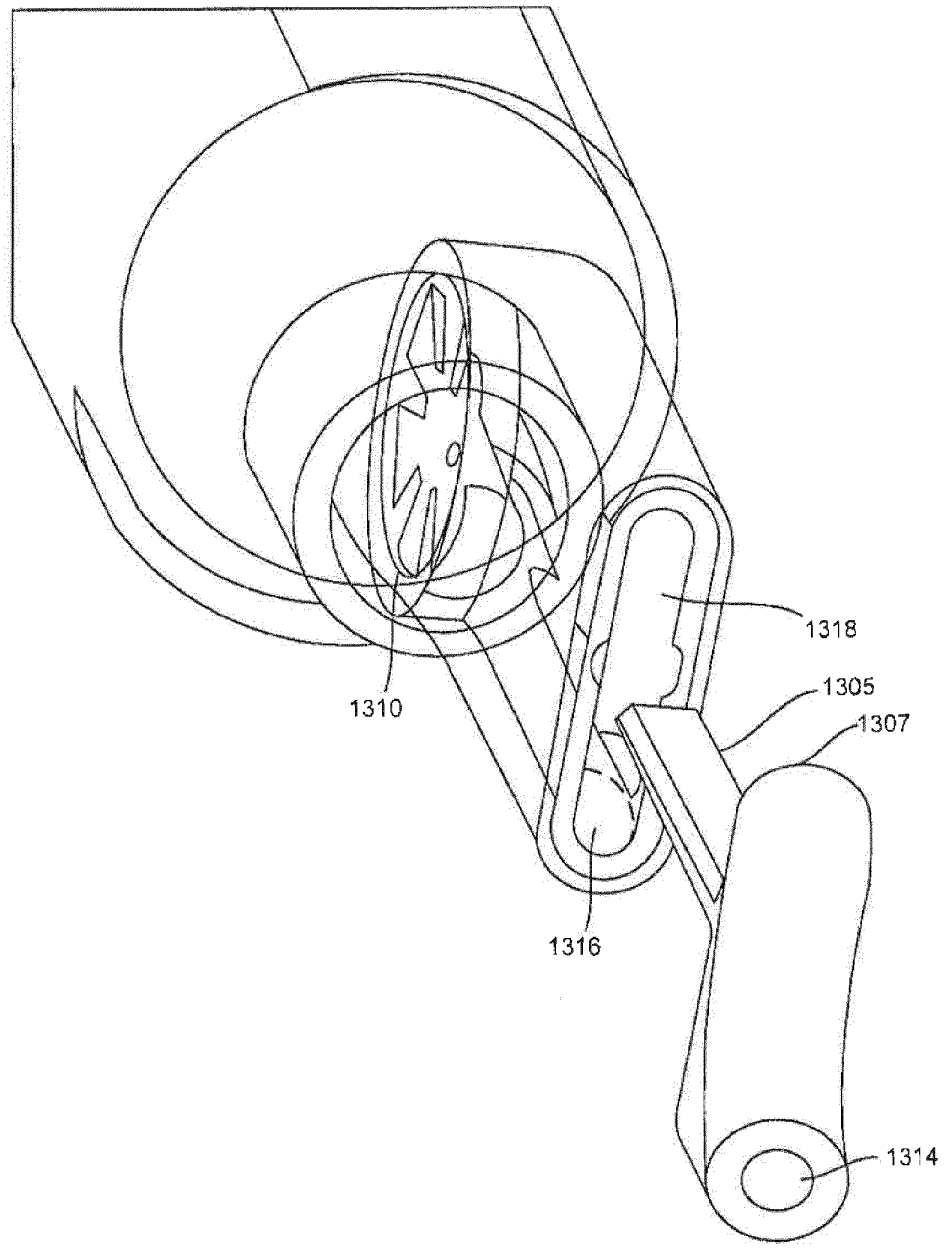


FIG. 13C

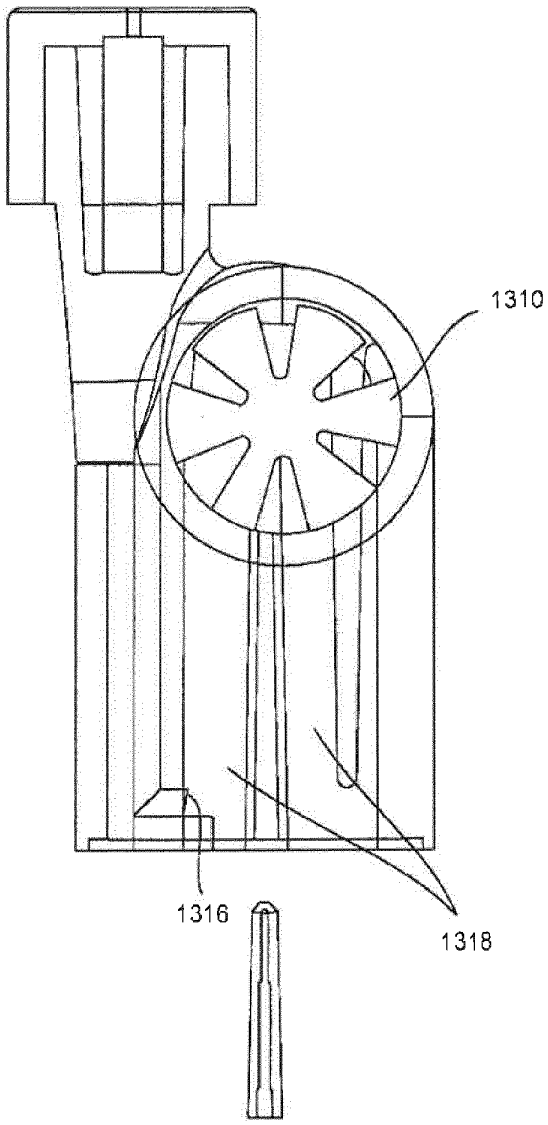


FIG. 13D

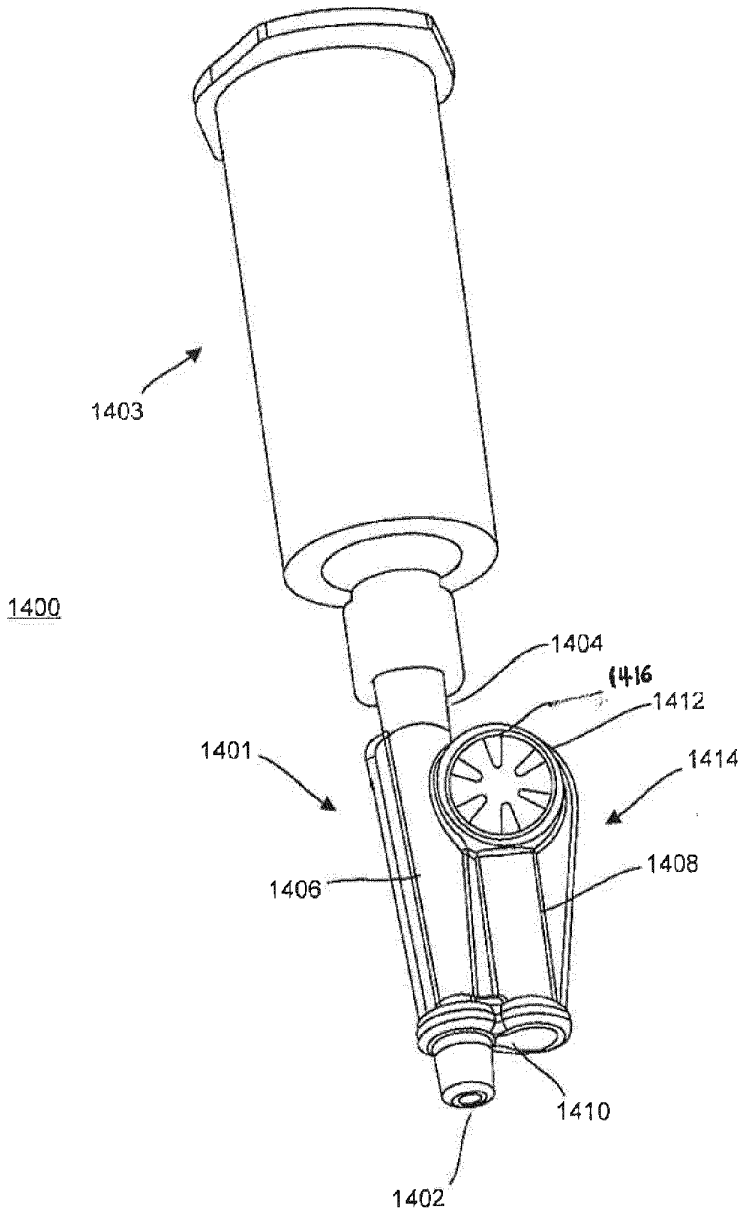


FIG. 14A

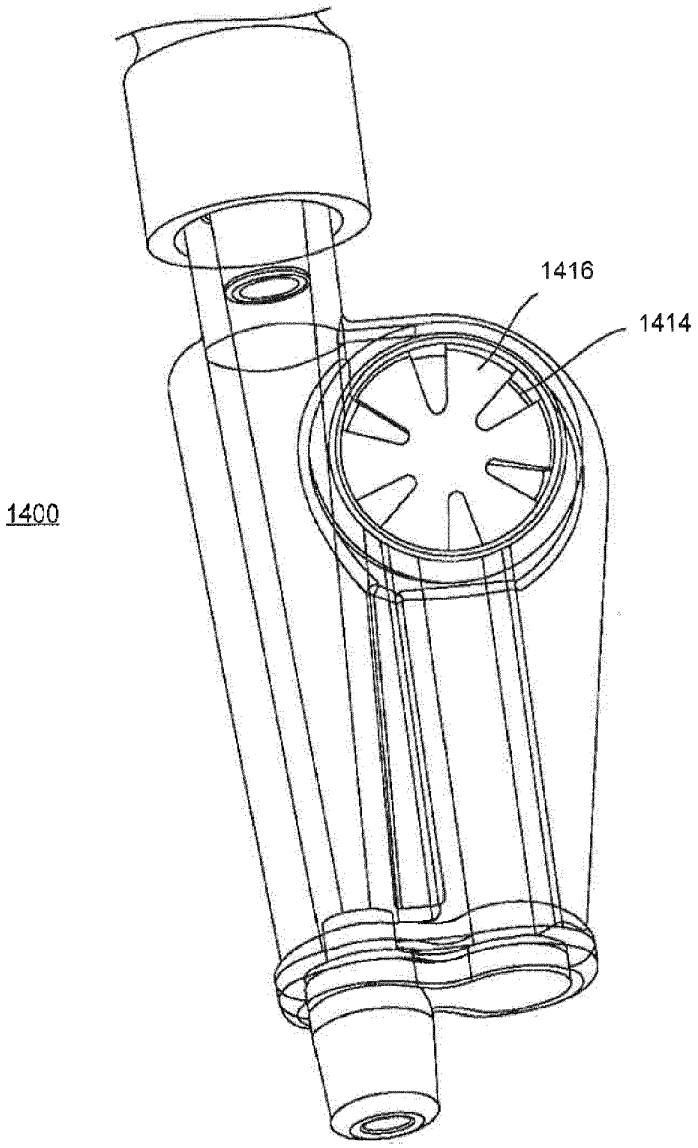


FIG. 14B

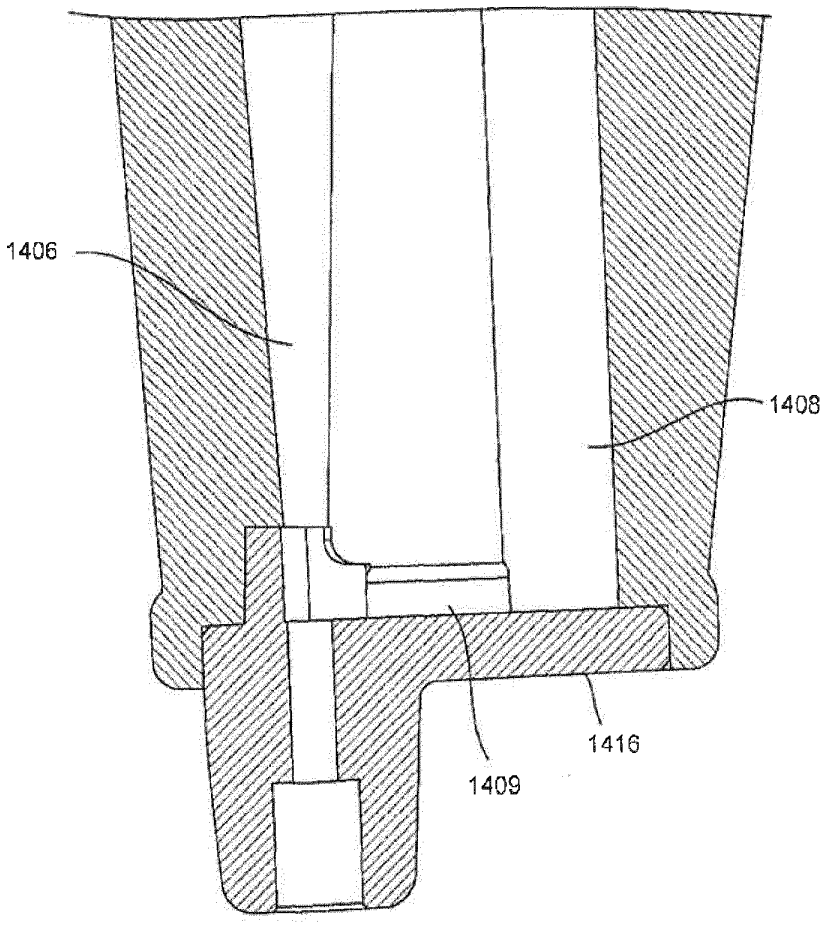


FIG. 14C

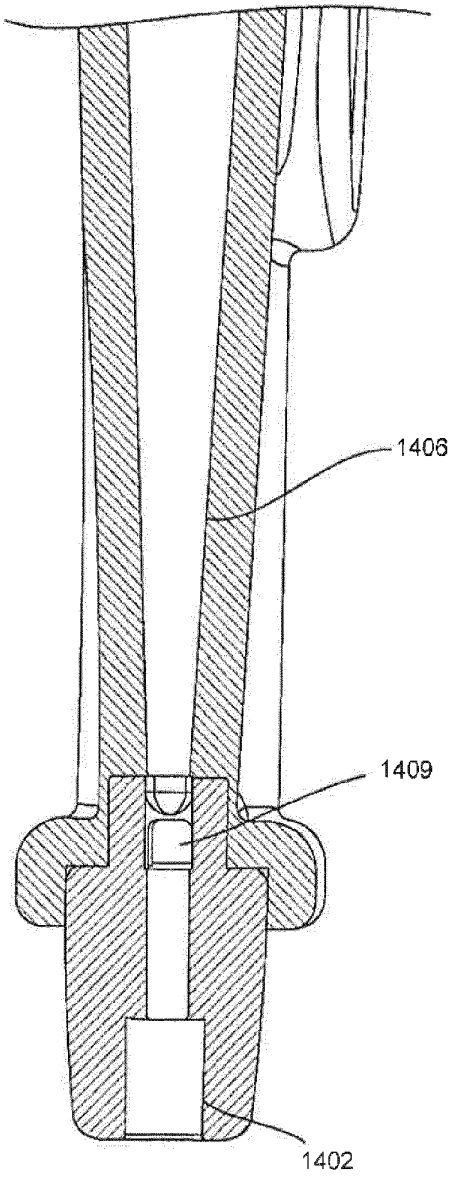


FIG. 14D

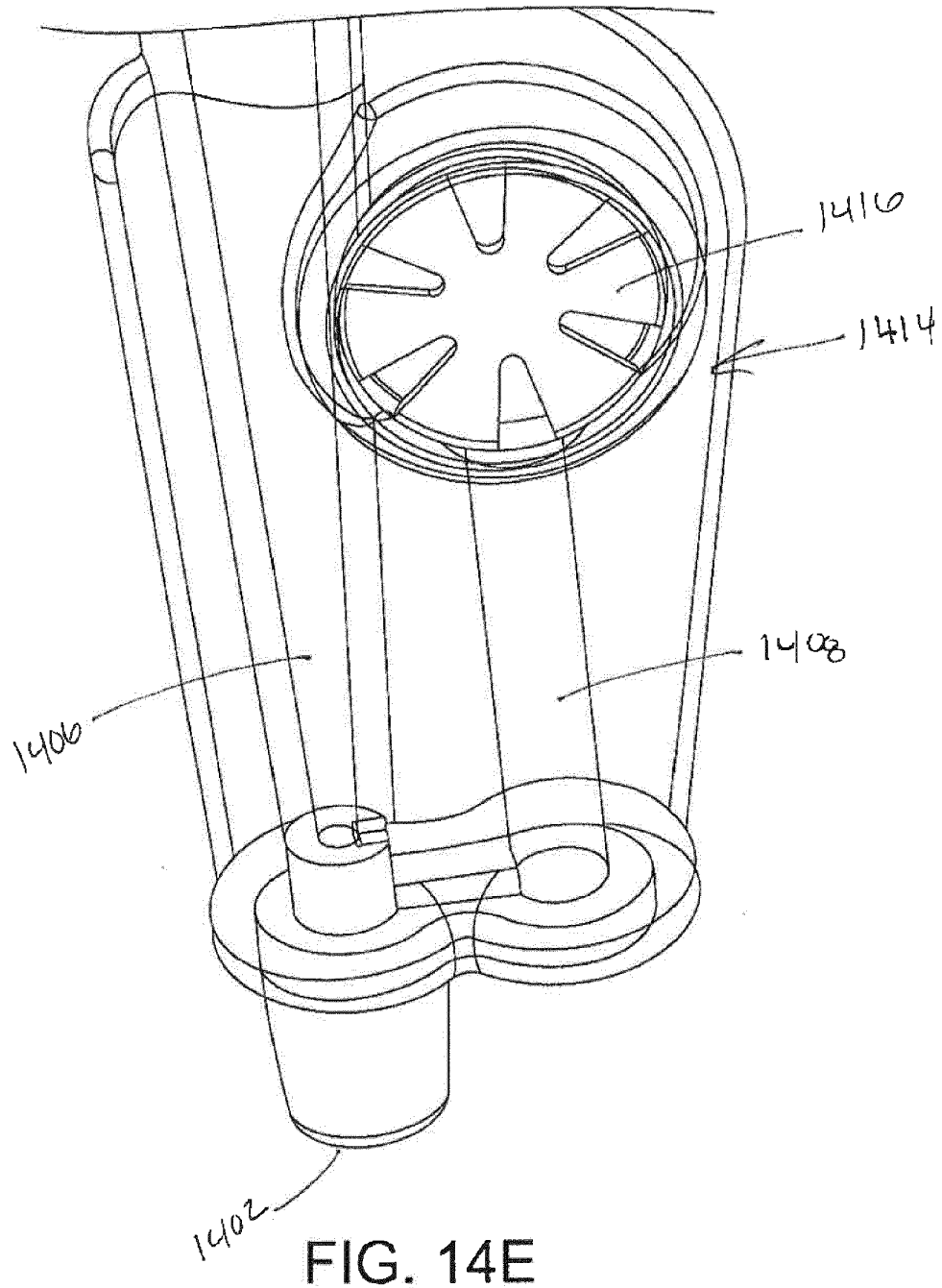


FIG. 14E

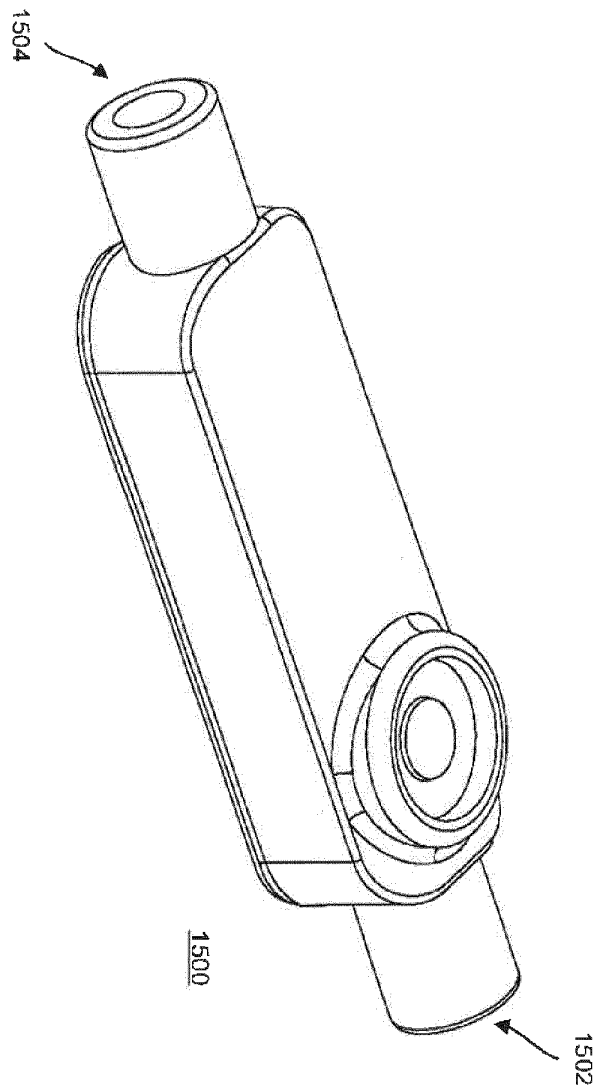


FIG. 15A

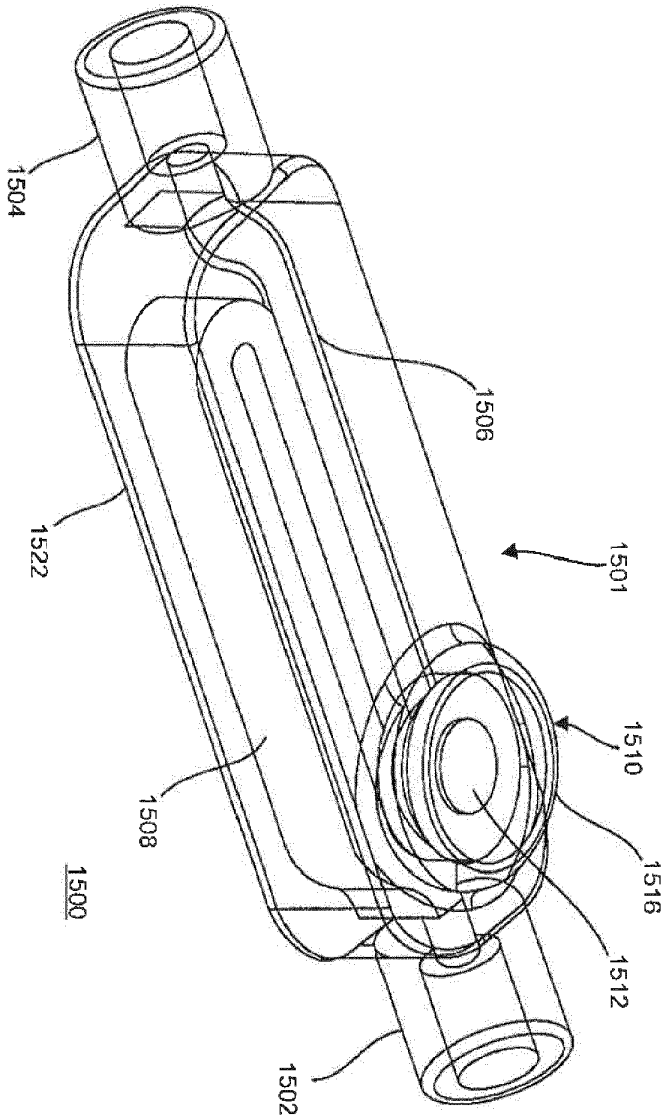


FIG. 15B

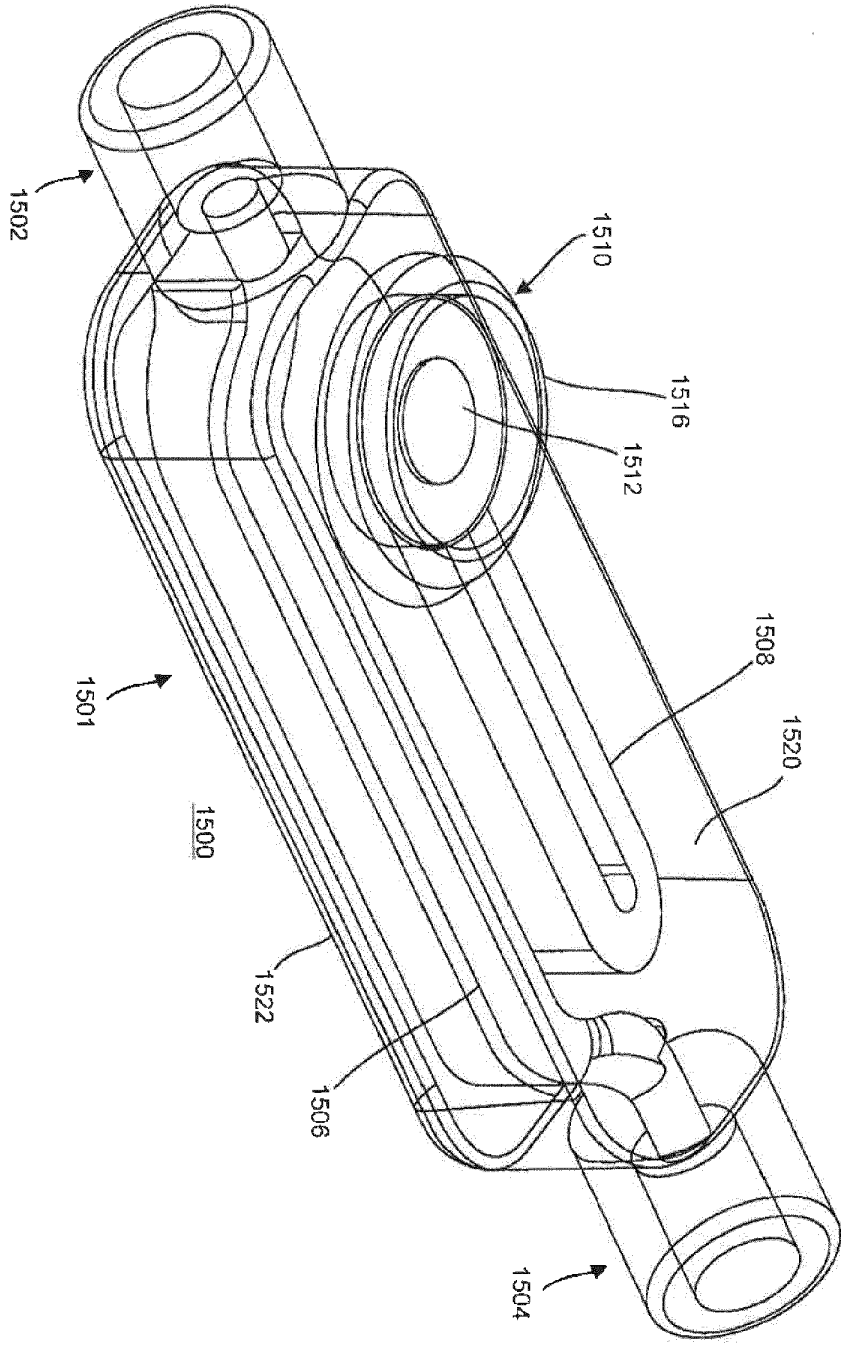


FIG. 15C

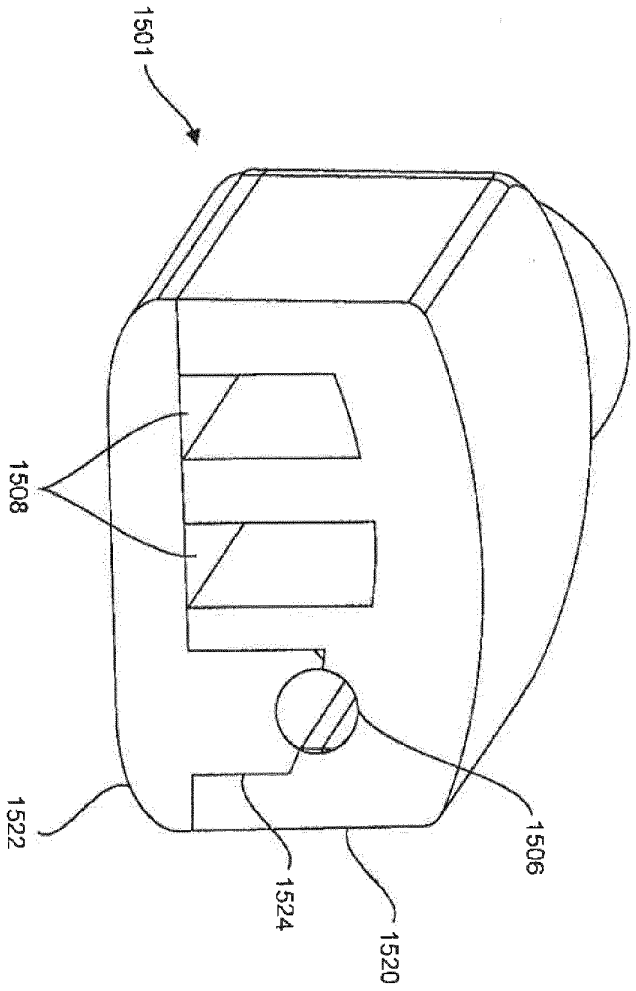


FIG. 15D

FIG. 15E

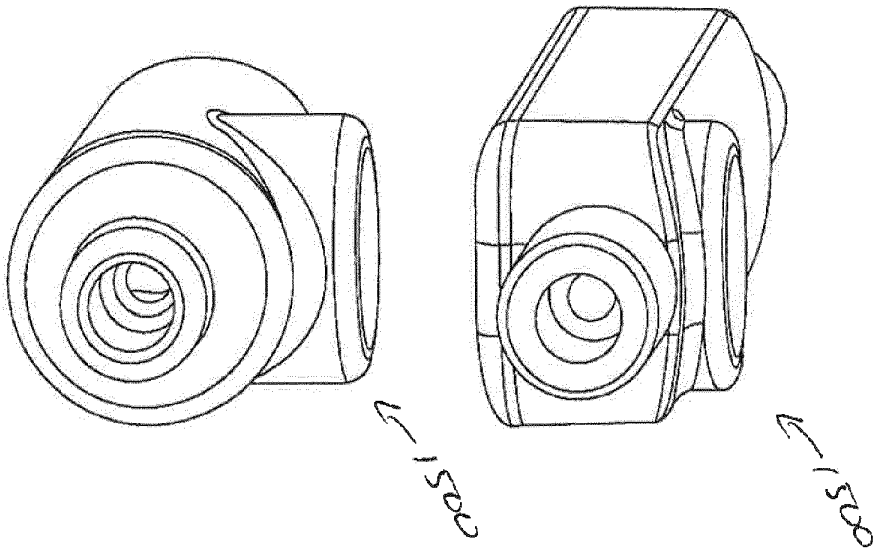
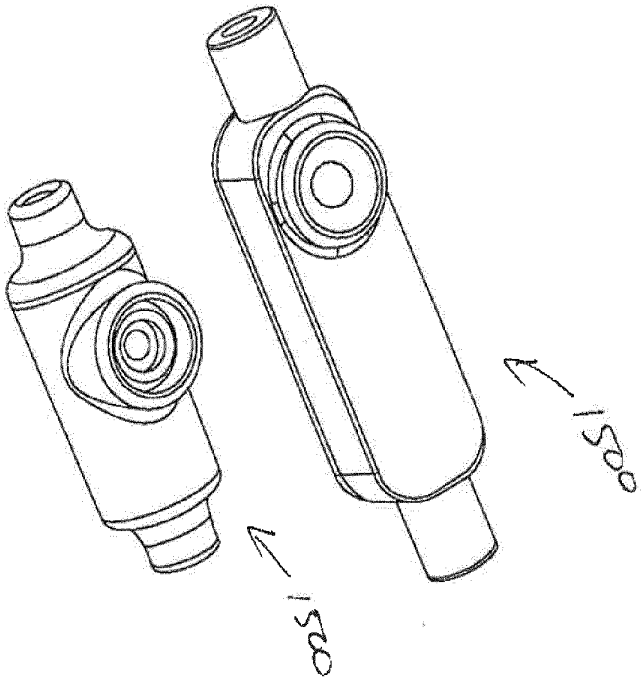


FIG. 15F



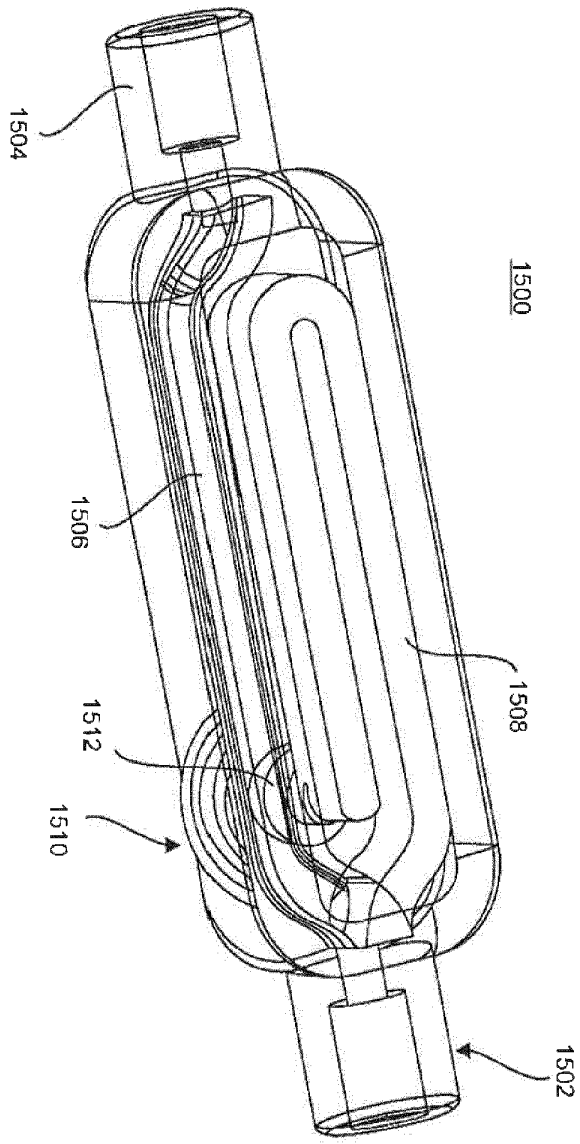


FIG. 15G

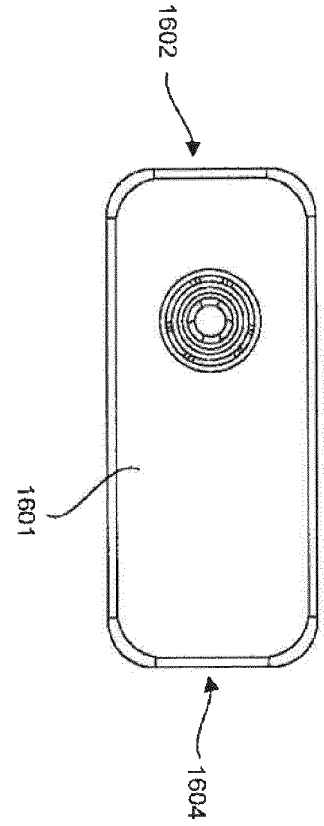


FIG. 16A

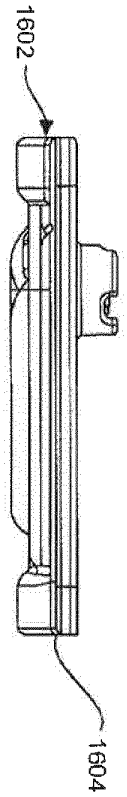


FIG. 16B

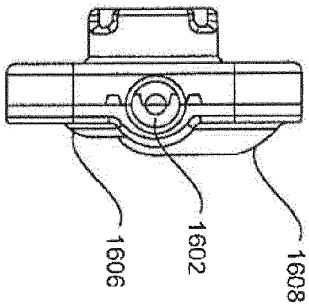


FIG. 16C

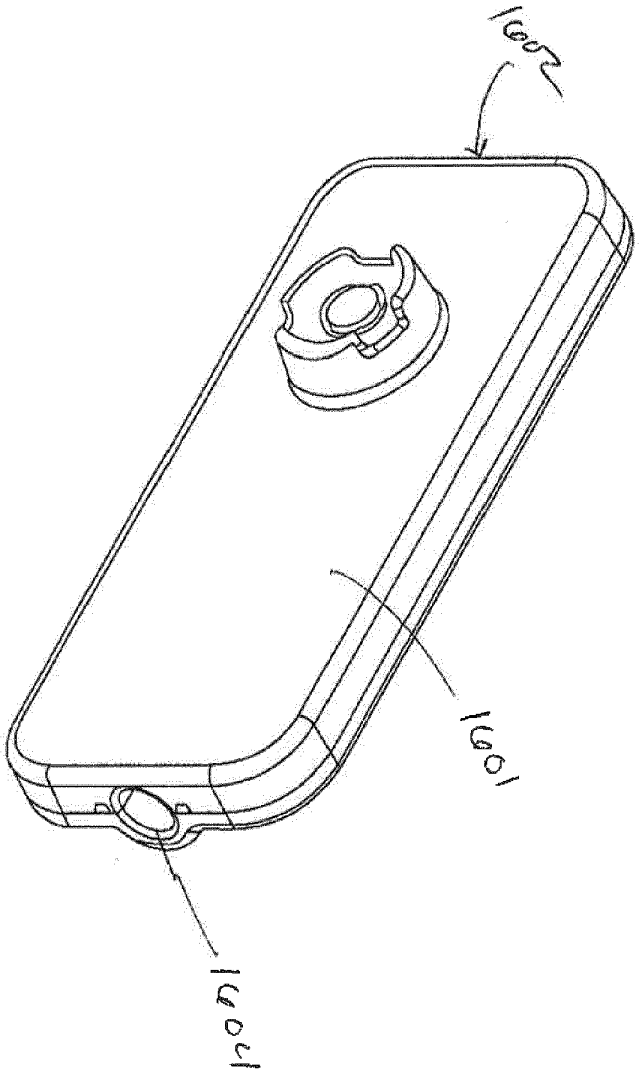


FIG. 16D

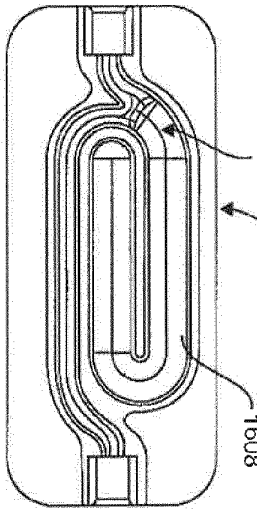


FIG. 17A

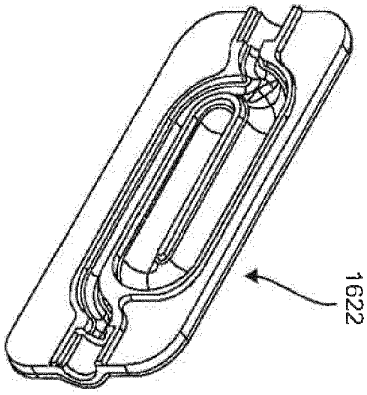


FIG. 17B

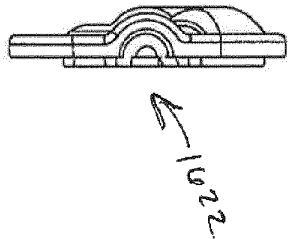


FIG. 17C



FIG. 17D

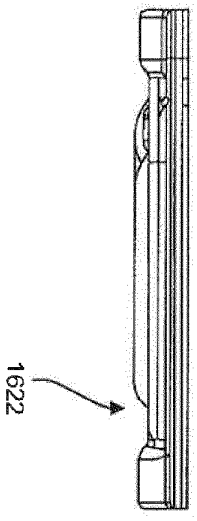


FIG. 17E

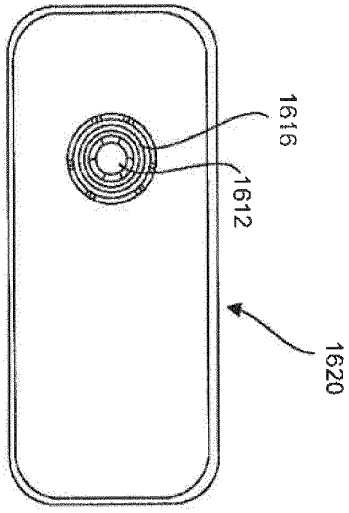


FIG. 18A

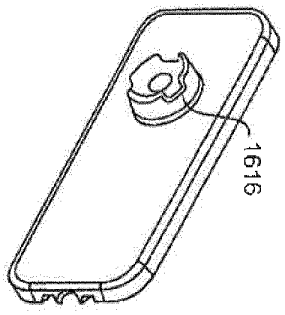


FIG. 18B

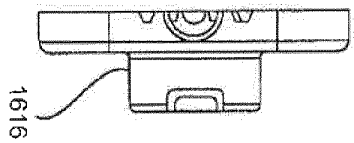


FIG. 18C

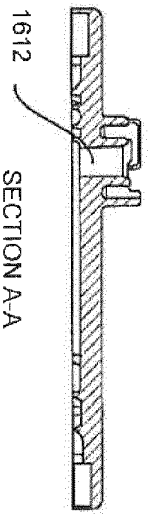


FIG. 18D

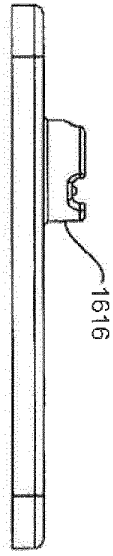


FIG. 18E

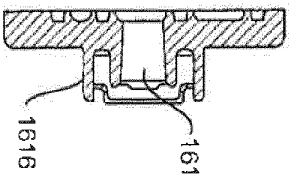


FIG. 18F

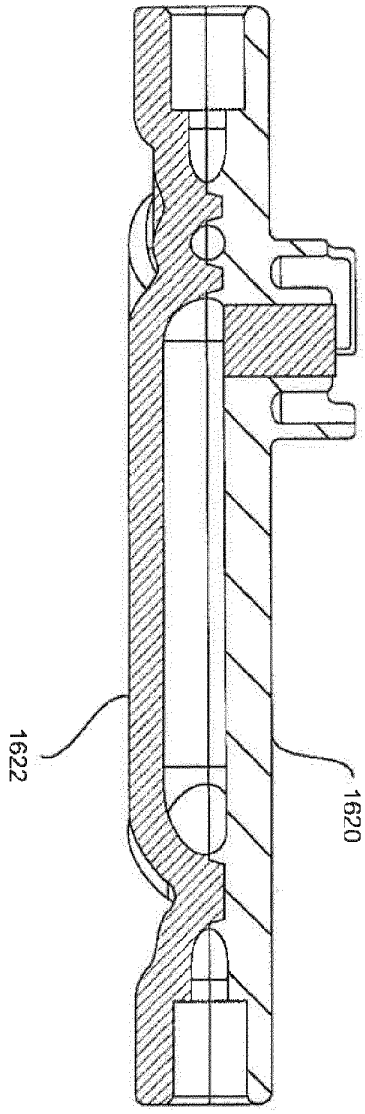


FIG. 19A

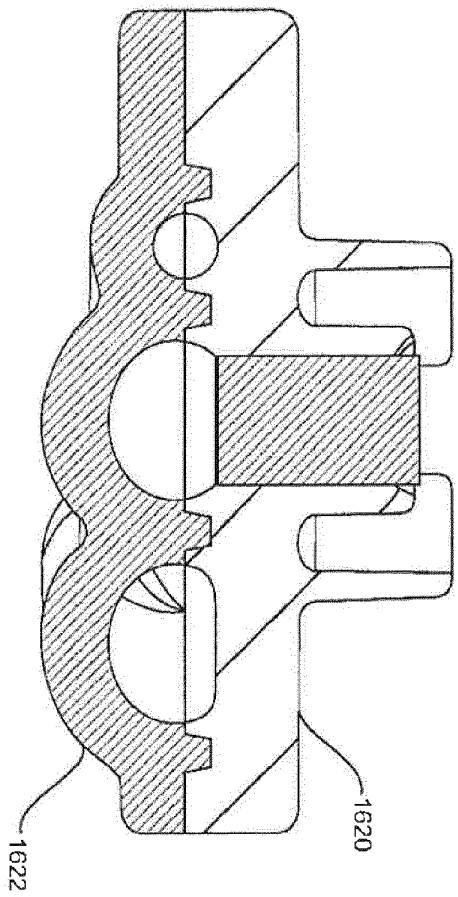


FIG. 19B

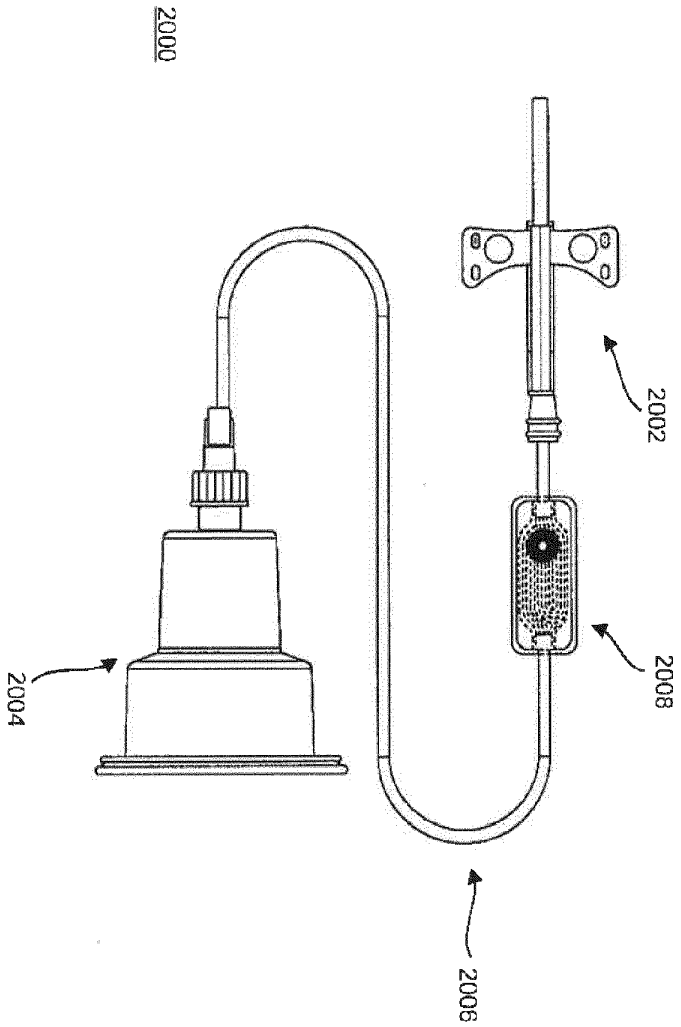


FIG. 20

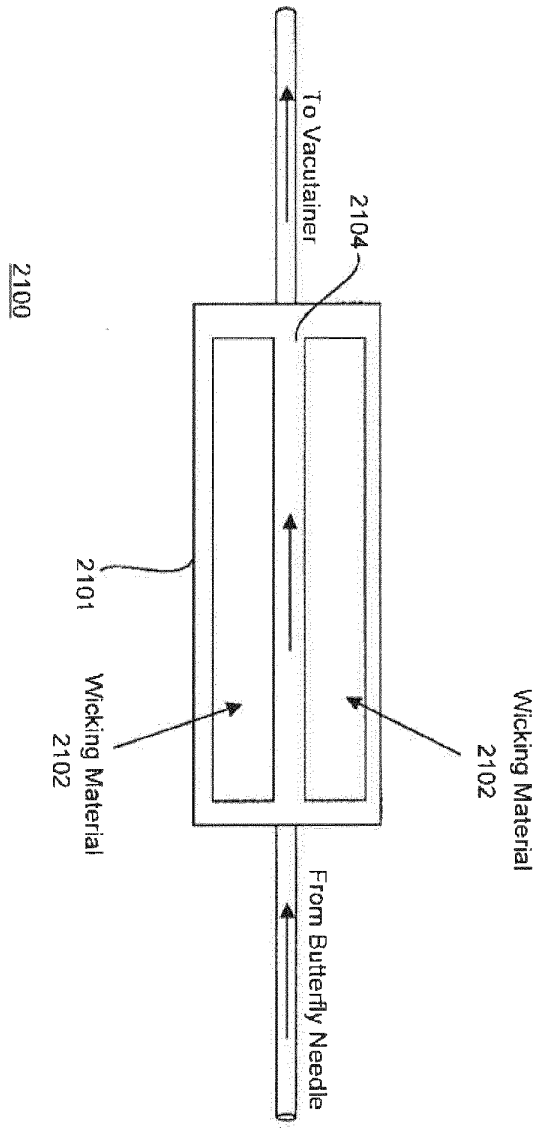

2100
To Vacutainer
2104
2101
Wicking Material
2102
Wicking Material
2102
From Butterfly Needle

FIG. 21

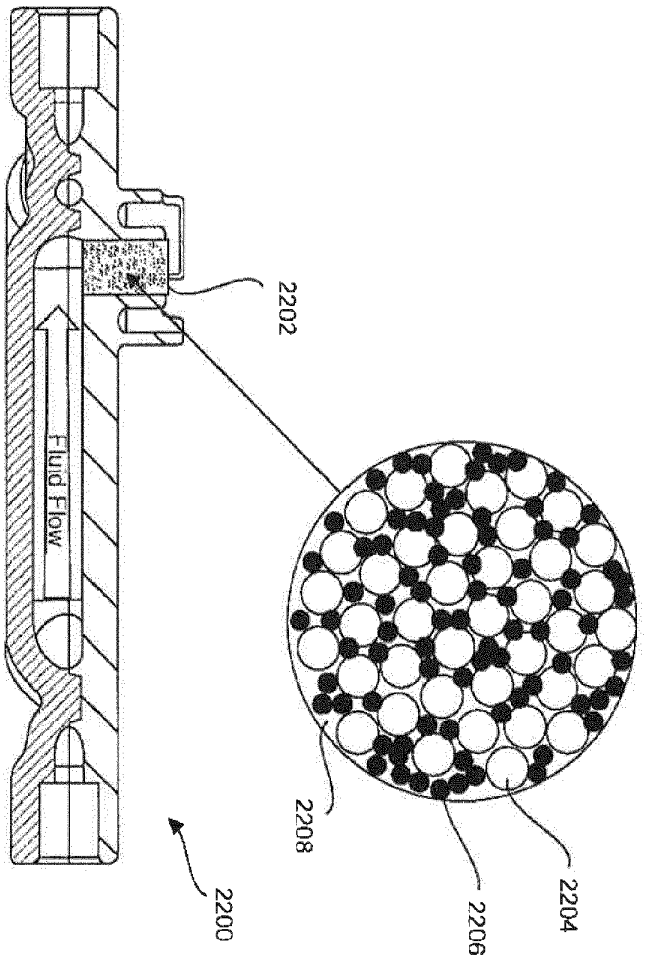


FIG. 22A

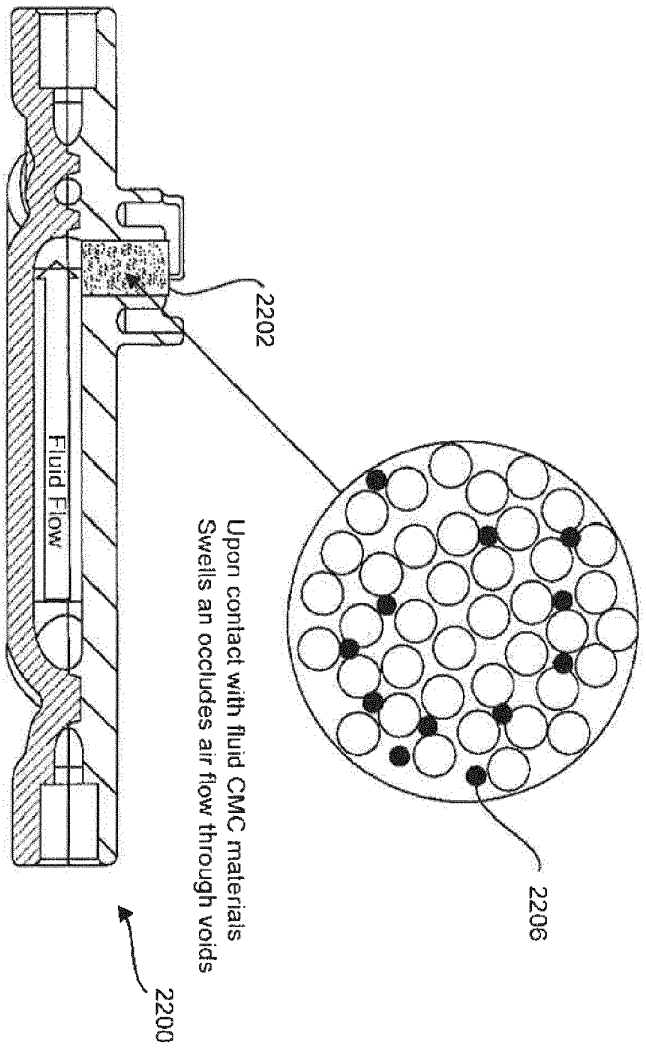

2202
Fluid Flow
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2206
2200

FIG. 22B

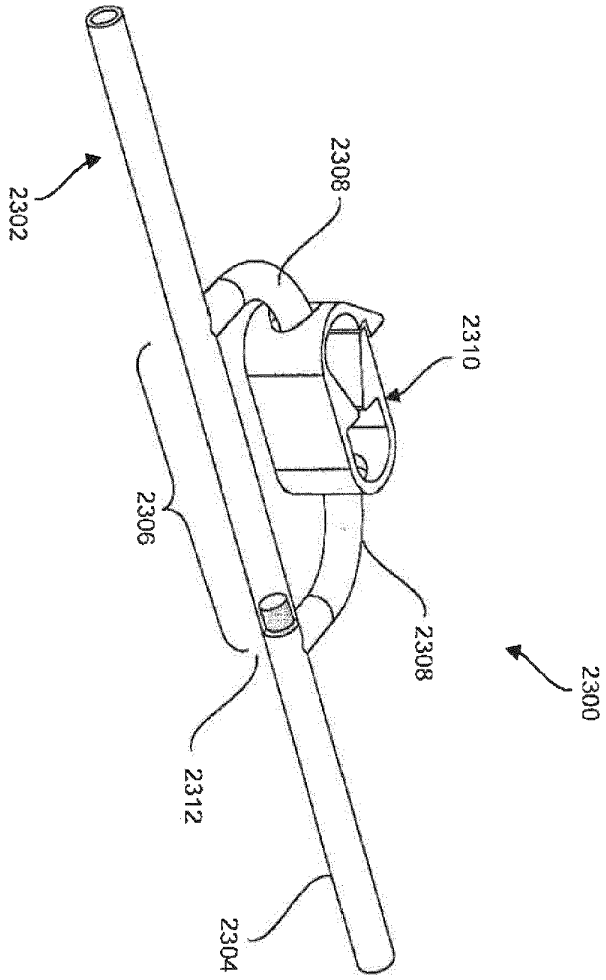


FIG. 23A

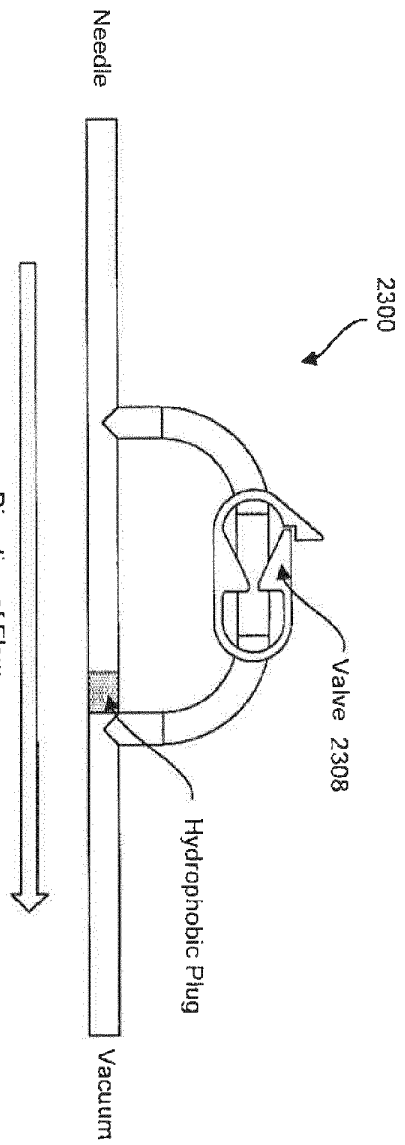

Needle
2300
Direction of Flow
Valve 2308
Hydrophobic Plug
Vacuum

FIG. 23B

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EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) * abstract; figures *	1-14	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	18 November 2019	Schultz, Ottmar

CATEGORY OF CITED DOCUMENTS

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D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

Europäisches Patentamt
European Patent Office
Office européen des brevets

EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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Place of search	Date of completion of the search	Examiner
Berlin	18 November 2019	Schultz, Ottmar

CATEGORY OF CITED DOCUMENTS

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& : member of the same patent family, corresponding document

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 19 20 0766

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18-11-2019

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: FLUID CONTROL DEVICES AND METHODS OF USING THE SAME

(57) Abstract: A fluid control device (200) includes an inlet (212) configured to be placed in fluid communication with a bodily fluid source and an outlet (216) configured to be placed in fluid communication with a fluid collection device, which can produce a negative pressure differential between the outlet and the inlet. A sequestration portion (214) is in fluid communication with the inlet and includes a first flow controller (222) configured to transition from a first state to a second state to place the sequestration portion in fluid communication with the outlet when the negative pressure differential has a first magnitude. A sampling portion (224) is in fluid communication with an outlet and includes a second flow controller (221) configured to transition from a first state to a second state to place the sampling portion in fluid communication with the inlet when the negative pressure differential has a second magnitude greater than the first magnitude.

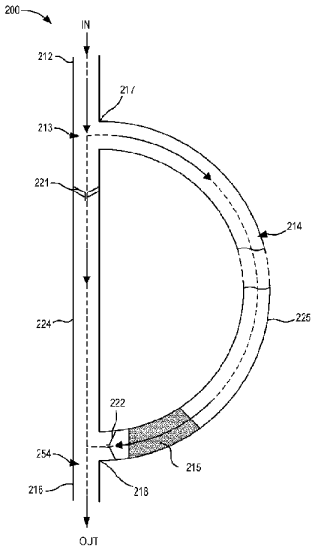


FIG. 2

WO 2019/232196 A1

[Continued on next page]

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

FLUID CONTROL DEVICES AND METHODS OF USING THE SAME

Cross-Reference to Related Applications

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 62/678,637 entitled, "Fluid Control Devices and Methods of Using the Same," filed May 31, 2018, the disclosure of which is incorporated herein by reference in its entirety.

Background

[0002] Embodiments described herein relate generally to the procurement of bodily fluid samples, and more particularly to fluid diversion, sequestration, and/or isolation devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source.

[0003] Health care practitioners routinely perform various types of microbial as well as other broad diagnostic tests on patients using parenterally obtained bodily fluids. As advanced diagnostic technologies evolve and improve, the speed, accuracy (both sensitivity and specificity), and value of information that can be provided to clinicians continues to improve. Maintaining the integrity of the bodily fluid sample during and/or after collection also ensures that analytical diagnostic results are representative of the in vivo conditions of a patient. Examples of diagnostic technologies that are reliant on high quality, non-contaminated, and/or unadulterated bodily fluid samples include but are not limited to microbial detection, molecular diagnostics, genetic sequencing (e.g., deoxyribonucleic acid (DNA), ribonucleic acid (RNA), next-generation sequencing (NGS), etc.), biomarker identification, and/or the like.

[0004] Inaccurate results from such testing can be due to the presence biological matter including cells external to the intended sample source and/or other external contaminants that inadvertently are included in the bodily fluid sample being analyzed. In short, when the purity of the bodily fluid sample is compromised during the specimen procurement process, resultant analytical test results may be inaccurate, distorted, adulterated, falsely positive, falsely negative, and/or otherwise not representative of the actual condition of the patient. In turn, these results can lead to faulty, inaccurate, confused, unsure, low-confidence, and/or otherwise undesired clinical decision making.

[0005] In some instances, devices and/or systems can be used to reduce the likelihood of contamination, adulteration, and/or the like of bodily fluid samples for testing. For example, some known devices can be configured to collect, divert, separate, and/or sequester (e.g., isolate) an initial volume of bodily fluid that may be more likely to contain contaminants such as dermally residing microbes or the like. Some such devices, however, can be cumbersome, non-intuitive, perceived as difficult to use, inappropriate or unusable for a target patient population, etc. In addition, some such devices can require training, user observation, intervention by more than one user, and/or can otherwise present challenges that can lead to limited efficacy. In some instances, these and/or other challenges can complicate the collection of consistently high quality samples that are non-contaminated, sterile, unadulterated, etc., which in turn, can influence the validity of test result outcomes.

[0006] As such, a need exists for fluid control and/or diversion devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source that result in consistent bodily fluid collection (e.g., from a general patient population and/or a challenging patient population). In addition, a need exists for devices and methods that can include, for example, bodily fluid collection with the assistance of various sources of external energy and/or negative pressure.

Summary

[0007] Devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source are described herein. In some embodiments, a fluid control device includes an inlet and an outlet. The inlet is configured to be placed in fluid communication with a bodily fluid source and the outlet is configured to be placed in fluid communication with a fluid collection device. The coupling of the outlet to the fluid collection device can produce a negative pressure differential within the fluid control device between the outlet and the inlet. The fluid control device has a sequestration portion in fluid communication with the inlet and a sampling portion in fluid communication with the outlet. The sequestration portion includes a first flow controller configured to transition from a first state in which the sequestration portion is sequestered from the outlet to a second state in which the sequestration portion is in fluid communication with the outlet when the negative pressure differential has a first magnitude. The sampling portion includes a second flow controller configured to transition from a first

state in which the sampling portion is sequestered from the inlet to a second state in which the sampling portion is in fluid communication with the inlet when the negative pressure differential has a second magnitude greater than the first magnitude.

Brief Description of the Drawings

[0008] FIG. 1 is a schematic illustration of a fluid control device according to an embodiment.

[0009] FIG. 2 is a schematic illustration of a fluid control device according to an embodiment.

[0010] FIG. 3 is a schematic illustration of a fluid control device according to an embodiment.

[0011] FIG. 4 is a schematic illustration of a fluid control device according to an embodiment.

[0012] FIGS. 5-7 are each a schematic illustration of a flow controller included in a fluid control device according to various embodiments.

[0013] FIG. 8 is a schematic illustration of a fluid control device according to an embodiment.

[0014] FIGS. 9 and 10 are schematic cross-sectional illustrations of the fluid control device illustrated in FIG. 8, taken along the line A-A, and shown in a first state and a second state, respectively.

[0015] FIGS. 11 and 12 are schematic cross-sectional illustrations of a fluid control device in a first state and a second state, respectively, according to an embodiment.

[0016] FIGS. 13 and 14 are schematic cross-sectional illustrations of a fluid control device in a first state and a second state, respectively, according to an embodiment.

[0017] FIGS. 15 and 16 are flowcharts, each of which illustrates a method of using a fluid control device to divert an initial volume of bodily fluid to procure bodily fluid samples with reduced contamination, according to different embodiments.

Detailed Description

[0018] Devices and methods for collecting, diverting, sequestering, isolating, etc. an initial volume of bodily fluid to reduce contamination in subsequently procured bodily fluid samples

are described herein. Any of the fluid control devices described herein can be configured to receive, procure, and/or transfer a flow, bolus, volume, etc., of bodily fluid. A first reservoir, channel, flow path, chamber, and/or portion of the device can receive an initial amount of the bodily fluid flow, which then can be substantially or fully sequestered therein (e.g., contained or retained, circumvented, isolated, segregated, vapor-locked, separated, and/or the like). In some instances, contaminants such as dermally residing microbes or the like can be included and/or entrained in the initial amount of the bodily fluid and likewise are sequestered in or by the first reservoir, flow path, or portion of the device. Once the initial amount is sequestered, any subsequent amount of the bodily fluid flow can be diverted, channeled, directed, and/or otherwise allowed to flow to or through a second portion of the device and/or any additional flow path(s) thereof. Based at least in part on the initial amount being sequestered, subsequent amount(s) of bodily fluid can be substantially free from contaminants that may otherwise produce inaccurate, distorted, adulterated, and/or false results in some diagnostics and/or testing. In some instances, the initial amount of bodily fluid also can be used, for example, in other testing such as those less affected by the presence of contaminants, can be discarded as a waste volume, can be infused back into the patient, and/or can be used for any other suitable clinical application.

[0019] In some embodiments, a feature of the fluid control devices and/or methods described herein is the use of an external negative pressure source (e.g., provided by a fluid collection device or any other suitable means) that can (1) overcome physical patient challenges which can limit and/or prevent a sufficient pressure differential to fully engage the sequestration chamber or sequestration portion of the control device and/or to transition fluid flow to the fluid collection device; (2) result in proper filling of the sequestration chamber with a clinically validated and/or desirable volume of bodily fluid; (3) result in efficient, timely, and/or user-accepted consistency with bodily fluid collection process; and/or (4) provide a means of transitioning fluid flow (e.g., automatically or by manipulation to move any number of physical components of the system or by changing, switching, engaging, and/or otherwise providing desired fluid flow dynamics) to enable sequestration and/or isolation of the initial amount (e.g., pre-sample) and collection of a subsequent sample.

[0020] In some embodiments, a fluid control device includes an inlet and an outlet. The inlet is configured to be placed in fluid communication with a bodily fluid source and the outlet is configured to be placed in fluid communication with a fluid collection device. The coupling of the outlet to the fluid collection device can produce a negative pressure differential within

the fluid control device between the outlet and the inlet. The fluid control device has a sequestration portion in fluid communication with the inlet and a sampling portion in fluid communication with the outlet. The sequestration portion includes a first flow controller configured to transition from a first state in which the sequestration portion is sequestered from the outlet to a second state in which the sequestration portion is in fluid communication with the outlet when the negative pressure differential has a first magnitude. The sampling portion includes a second flow controller configured to transition from a first state in which the sampling portion is sequestered from the inlet to a second state in which the sampling portion is in fluid communication with the inlet when the negative pressure differential has a second magnitude greater than the first magnitude.

[0021] In some embodiments, a fluid control device includes a housing, a first flow controller, and a second flow controller. The housing has an inlet configured to establish fluid communication with a bodily fluid source and an outlet configured to be coupled to a fluid collection device. The housing defines a sequestration flow path that is in fluid communication with the inlet and a sampling flow path that is in fluid communication with the outlet. The first flow controller has a flow state in which the sequestration flow path is in fluid communication with the outlet and a non-flow state in which the sequestration flow path is sequestered from the outlet. The second flow controller has a flow state in which sampling flow path is in fluid communication with the inlet and a non-flow state in which the sampling flow path is sequestered from the inlet. The first flow controller configured to be in the flow state when a negative pressure differential generated by coupling the outlet to the fluid collection device has a first magnitude such that an initial volume of bodily fluid flows through the sequestration flow path toward the first flow controller. The first flow controller is configured to transition to the non-flow state when the initial volume of bodily fluid is received in the sequestration flow path such that (1) the sequestration flow path is sequestered from the outlet and (2) the negative pressure differential is increased to a second magnitude operable to transition the second flow controller from the non-flow state to the flow state.

[0022] In some embodiments, a method of using a fluid control device to obtain a bodily fluid sample with reduced contamination includes coupling a fluid collection device to an outlet of the fluid control device. The coupling of the fluid collection device to the outlet is configured to produce a negative pressure differential within at least a portion of the fluid control device. A first flow controller is transitioned from a first state to a second state when the negative pressure differential has a first magnitude. The first flow controller is configured

to sequester a sequestration portion of the fluid control device from the outlet when in the first state and to establish fluid communication between the sequestration portion and the outlet when in the second state. An initial volume of bodily fluid is received from an inlet of the fluid control device into the sequestration portion in response to the negative pressure differential when the first flow controller is in the second state. The first flow controller is configured to transition from the second state to a third state in response to the sequestration portion receiving the initial volume of bodily fluid. When the first flow controller is in the third state, the first flow controller sequesters the sequestration portion from the outlet the negative pressure differential increases from the first magnitude to a second magnitude. A second flow controller is transitioned from a first state to a second state when the negative pressure differential has the second magnitude. The second flow controller is configured to sequester a sampling portion of the fluid control device from the inlet when in the first state and to establish fluid communication between the sampling portion and the inlet when in the second state. A subsequent volume of bodily fluid is transferred from the inlet to the fluid collection device via the sampling portion and the outlet.

[0023] In some embodiments, a fluid control device includes an inlet and an outlet. The inlet is configured to be placed in fluid communication with a bodily fluid source or an intermediary bodily fluid transfer device. The outlet is configured to be placed in fluid communication with a fluid collection device such as, for example, a sample reservoir (bottle, container, dish, vial, etc.), a culture bottle, and evacuated container, a syringe, a lumen-containing device, and/or any other suitable bodily fluid collection and/or transfer device. The fluid control device has a first state in which a negative pressure differential produced from an external source (e.g., the fluid collection device such as a sample reservoir, a syringe, a vessel, and/or any suitable intermediary fluid reservoir) is applied to the fluid control device to draw an initial volume of bodily fluid from the bodily fluid source, through the inlet, and into a sequestration and/or diversion portion of the fluid control device (which can be formed by or in the fluid control device or coupled thereto). The fluid control device has a second state in which (1) the sequestration and/or diversion portion sequesters the initial volume, and (2) the negative pressure differential draws a subsequent volume of bodily fluid, being substantially free of contaminants, from the bodily fluid source, through the fluid control device, and into the fluid collection device.

[0024] Any of the embodiments and/or methods described herein can be used in the procurement of clean or substantially unadulterated bodily fluid samples such as, for example,

blood samples. In some instances, bodily fluid samples (e.g., blood samples) can be tested for the presence of one or more potentially undesirable microbes, such as bacteria (e.g., Gram-Positive bacteria and/or Gram-Negative bacteria), fungi, yeast (e.g., Candida), and/or other undesirable microbes. Various technologies can be employed to assist in the detection of the presence of microbes as well as other types of biological matter, specific types of cells, biomarkers, proteins, antigens, enzymes, blood components, and/or the like during diagnostic testing. Examples include but are not limited to molecular polymerase chain reaction (PCR), magnetic resonance and other magnetic analytical platforms, automated microscopy, spatial clone isolation, flow cytometry, whole blood ("culture free") specimen analysis (e.g., NGS) and associated technologies, morphokinetic cellular analysis, and/or other common or evolving and advanced technologies to characterize patient specimens and/or to detect, identify, type, categorize, and/or characterize specific organisms, antibiotic susceptibilities, and/or the like.

[0025] For example, in some instances, microbial testing and/or detection can include incubating blood samples in one or more vessels that may contain culture media (e.g., a nutrient rich and/or environmentally controlled medium to promote growth and/or any number of other mediums), common additives, and/or other types of solutions conducive to microbial growth. Any of the microbes and/or organisms present in the blood sample flourish and/or grow over time in the culture medium (e.g., a variable amount of time from less than an hour to more than several days – which can be longer or shorter depending on the diagnostic technology employed). The presence of the microbes and/or organisms can be detected by automated, continuous monitoring, and/or other methods specific to the analytical platform and/or technology used for detection, identification, and/or the like (e.g., by observing carbon dioxide levels and/or any other suitable methods of detection).

[0026] The presence of microbes and/or organisms in the culture medium suggests the presence of the same microbes and/or organisms in the blood sample, which in turn, suggests the presence of the same microbes and/or organisms in the bodily fluid of the patient from whom the sample was obtained. In other instances, a bodily fluid sample may be analyzed directed (i.e., not incubated) for the presence of the microbes and/or organisms. Accordingly, when the microbes and/or organisms are determined to be present in the blood sample, the patient may be diagnosed and prescribed one or more antibiotics or other treatments specifically designed to treat or otherwise remove the undesired microbes and/or organisms from the patient.

[0027] Patient samples, however, can become contaminated during procurement and/or otherwise can be susceptible to false results. For example, microbes from a bodily surface (e.g., dermally residing microbes) that are dislodged during the specimen procurement process (e.g., either directly or indirectly via tissue fragments, hair follicles, sweat glands, and other skin adnexal structures) can be subsequently transferred to a culture medium, test vial, or other suitable specimen collection or transfer vessel with the patient sample and/or otherwise included in the specimen that is to be analyzed. Another possible source of contamination is from the person drawing the patient sample (e.g., a doctor, phlebotomist, nurse, technician, etc.) and/or the equipment used for drawing the patient sample. For example, equipment, supplies, and/or devices used during a patient sample procurement process often include multiple fluidic interfaces (e.g., patient to needle, needle to transfer adapter, transfer adapter to sample vessel, catheter hub to syringe, syringe to transfer adapter, needle/tubing to sample vessels, and/or any other fluidic interface or any combination(s) thereof) that can each introduce points of potential contamination. In some instances, such contaminants may thrive in a culture medium and/or may be otherwise identified, thereby increasing a risk or likelihood of false, compromised, and/or erroneous microbial test results, which may inaccurately reflect the presence or lack of such microbes within the patient (i.e., in vivo).

[0028] Such inaccurate results because of contamination and/or any other sources of adulteration are a concern when attempting to diagnose or treat a wide range of suspected illnesses, diseases, infections, patient conditions, and/or other maladies. For example, false results from microbial tests may result in a misdiagnosis and/or delayed treatment of a patient illness (which could result in the harm to and/or death of the patient or, on the other hand, may result in the patient being unnecessarily subjected to one or more anti-microbial therapies, which may cause serious side effects to and/or consequences for the patient including, for example, death. As such, false results produce an unnecessary burden and expense on the health care system due to extended length of patient stay and/or other complications associated with erroneous treatments. The use of diagnostic imaging equipment to arrive at these false results is also a concern from both a cost perspective and a patient safety perspective as unnecessary exposure to concentrated radiation associated with a variety of imaging procedures (e.g., CT scans) has many known adverse effects on long-term patient health.

[0029] As used in this specification and/or any of the claims included herein, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

Thus, for example, the term "a member" is intended to mean a single member or a combination of members, "a material" is intended to mean one or more materials, or a combination thereof.

[0030] As used herein, the terms "about," "approximately," and/or "substantially" when used in connection with a stated value(s) and/or a geometric structure(s) or relationship(s) is intended to convey that the value or characteristic so defined is nominally the value stated and/or characteristic described. In some instances, the terms "about," "approximately," and/or "substantially" can generally mean and/or can generally contemplate a value or characteristic stated within a desirable tolerance (e.g., plus or minus 10% of the value or characteristic stated). For example, a value of about 0.01 would include 0.009 and 0.011, a value of about 0.5 would include 0.45 and 0.55, a value of about 10 would include 9 to 11, and a value of about 1000 would include 900 to 1100. While a value, structure, and/or relationship stated may be desirable, it should be understood that some variance may occur as a result of, for example, manufacturing tolerances or other practical considerations (such as, for example, the pressure or force applied through a portion of a device, conduit, lumen, etc.). Accordingly, the terms "about," "approximately," and/or "substantially" can be used herein to account for such tolerances and/or considerations.

[0031] As used herein, "bodily fluid" can include any fluid obtained directly or indirectly from a body of a patient. For example, "bodily fluid" includes, but is not limited to, blood, cerebrospinal fluid, urine, bile, lymph, saliva, synovial fluid, serous fluid, pleural fluid, amniotic fluid, mucus, sputum, vitreous, air, and the like, or any combination thereof.

[0032] As used herein, the words "proximal" and "distal" refer to the direction closer to and away from, respectively, a user who would place the device into contact with a patient. Thus, for example, the end of a device first touching the body of the patient would be the distal end, while the opposite end of the device (e.g., the end of the device being manipulated by the user) would be the proximal end of the device.

[0033] As used herein, the terms "pre-sample," "first," and/or "initial," can be used interchangeably to describe an amount, portion, or volume of bodily fluid that is collected and/or sequestered prior to procuring the "sample" volume. A "pre-sample," "first," and/or "initial" volume can refer to a predetermined, defined, desired, and/or given volume of bodily fluid. For example, a predetermined and/or desired pre-sample volume of bodily fluid can be a drop of bodily fluid, a few drops of bodily fluid, and/or a volume of bodily fluid equal to about 0.1 milliliter (mL), about 0.2 mL, about 0.3 mL, about 0.4 mL, about 0.5 mL, about 1.0

mL, about 2.0 mL, about 3.0 mL, about 4.0 mL, about 5.0 mL, about 10.0 mL, about 20.0 mL, about 50.0 mL, and/or any volume or fraction of a volume therebetween. Alternatively, a pre-sample volume can be greater than 50.0 mL or less than 0.1 mL. In some specific embodiments, a predetermined and/or desired pre-sample volume can be between about 0.1 mL and about 5.0 mL. In other embodiments, a pre-sample volume can be, for example, a combined volume of any number of lumen (e.g., lumen that form at least a portion of a flow path from the bodily fluid source to an initial collection chamber, portion, reservoir, etc...

[0034] As used herein, the terms "sample," "second," and/or "subsequent" can be used interchangeably to describe a volume, portion, or amount of bodily fluid that is used, for example, in one or more sample or diagnostic tests. A "sample" volume can be either a random volume or a predetermined or desired volume of bodily fluid collected after collecting, sequestering, and/or isolating a pre-sample volume of bodily fluid. A desired sample volume of bodily fluid can be, for example, between about 10.0 mL to about 60.0 mL. Alternatively, a desired sample volume of bodily fluid can be less than 10.0 mL or greater than 60.0 mL. In some embodiments, for example, a sample volume can be at least partially based on one or more tests, assays, analyses, and/or processes to be performed on the sample volume.

[0035] The embodiments described herein can be configured to transfer bodily fluid with reduced contamination and/or substantially free from contamination to one or more fluid collection device(s). In some embodiments, a fluid collection device can include, but is not limited to, any suitable vessel, container, reservoir, bottle, adapter, dish, vial, syringe, device, diagnostic and/or testing machine, and/or the like. In some embodiments, a fluid collection device can be substantially similar to or the same as known sample containers such as, for example, a Vacutainer ® (manufactured by Becton Dickinson and Company (BD)), a BacT/ALERT ® SN or BacT/ALERT ® FA (manufactured by Biomerieux, Inc.), and/or any suitable reservoir, vial, microvial, microliter vial, nanoliter vial, container, microcontainer, nanocontainer, and/or the like. In some embodiments, a fluid collection device can be similar to and/or substantially the same as any of those described in U.S. Patent No. 8,197,420 entitled, "Systems and Methods for Parenterally Procuring Bodily-Fluid Samples with Reduced Contamination," filed December 13, 2007 ("the '420 Patent"), the disclosure of which is incorporated herein by reference in its entirety.

[0036] In some embodiments, a fluid collection device can be devoid of contents prior to receiving a sample volume of bodily fluid. For example, in some embodiments, a fluid collection device or reservoir can define and/or can be configured to define or produce a

vacuum or suction such as, for example, a vacuum-based collection tube (e.g., a Vacutainer ®), a syringe, and/or the like. In some embodiments, a sample reservoir can include, for example, any suitable additives, substances, enzymes, oils, fluids, compounds, chemicals, etc. (e.g., heparin, citrate, acid citrate dextrose (ACD), ethylenediaminetetraacetic acid (EDTA), oxalate, sodium polyanethol sulfonate (SPS), and/or the like). In other embodiments, a sample reservoir can contain, for example, an aerobic culture medium or an anaerobic culture medium. The sample reservoir (e.g., culture bottle) can receive a bodily fluid sample, which can then be tested (e.g., after incubation via in vitro diagnostic (IVD) tests and/or any other suitable test) for the presence of, for example, Gram-Positive bacteria, Gram-Negative bacteria, yeast, fungi, and/or any other organism. If testing of the culture medium yields a positive result, the culture medium can be subsequently tested using, for example, a PCR-based system to identify a specific organism.

[0037] While the term "culture medium" can be used to describe a substance configured to react with organisms in a bodily fluid (e.g., microorganisms such as bacteria) and the term "additive" can be used to describe a substance configured to react with portions of the bodily fluid (e.g., constituent cells of blood, serum, synovial fluid, etc.), it should be understood that a sample reservoir can include any suitable substance, liquid, solid, powder, lyophilized compound, gas, etc. Moreover, when referring to an "additive" within a sample reservoir, it should be understood that the additive could be a culture medium, an additive, and/or any other suitable substance, and/or any combination(s) thereof. That is to say, the embodiments described herein can be used with any suitable fluid collection device, reservoir, and/or the like containing any suitable substance.

[0038] While some of the embodiments are described herein as being used for procuring bodily fluid for one or more culture sample testing, it should be understood that the embodiments are not limited to such a use. Any of the embodiments and/or methods described herein can be used to transfer a flow of bodily fluid to any suitable device that is placed in fluid communication therewith. Thus, while specific examples are described herein, the devices, methods, and/or concepts are not intended to be limited to such specific examples.

[0039] The embodiments described herein and/or portions thereof can be formed or constructed of one or more biocompatible materials. In some embodiments, the biocompatible materials can be selected based on one or more properties of the constituent material such as, for example, stiffness, toughness, durometer, bioreactivity, etc. Examples of suitable biocompatible materials include metals, glasses, ceramics, or polymers. Examples of suitable

metals include pharmaceutical grade stainless steel, gold, titanium, nickel, iron, platinum, tin, chromium, copper, and/or alloys thereof. A polymer material may be biodegradable or non-biodegradable. Examples of suitable biodegradable polymers include polylactides, polyglycolides, polylactide-co-glycolides (PLGA), polyanhydrides, polyorthoesters, polyetheresters, polycaprolactones, polyesteramides, poly(butyric acid), poly(valeric acid), polyurethanes, and/or blends and copolymers thereof. Examples of non-biodegradable polymers include nylons, polyesters, polycarbonates, polyacrylates, polysiloxanes (silicones), polymers of ethylene-vinyl acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, and/or blends and copolymers thereof.

[0040] The embodiments described herein and/or portions thereof can include components formed of one or more parts, features, structures, etc. When referring to such components it should be understood that the components can be formed by a singular part having any number of sections, regions, portions, and/or characteristics, or can be formed by multiple parts or features. For example, when referring to a structure such as a wall or chamber, the structure can be considered as a single structure with multiple portions, or multiple, distinct substructures or the like coupled to form the structure. Thus, a monolithically constructed structure can include, for example, a set of substructures. Such a set of substructures may include multiple portions that are either continuous or discontinuous from each other. A set of substructures can also be fabricated from multiple items or components that are produced separately and are later joined together (e.g., via a weld, an adhesive, and/or any other suitable method).

[0041] Referring now to the drawings, FIG. 1 is a schematic illustration of a fluid control device 100 according to an embodiment. Generally, the fluid control device 100 (also referred to herein as "control device" or "device") is configured to withdrawal bodily fluid from a patient. A first portion or amount (e.g., an initial amount) of the withdrawn bodily fluid is sequestered from a second portion or amount (e.g., a subsequent amount) of the withdrawn bodily fluid which can be subsequently used for additional testing, discarded, and/or reinfused into the patient. In this manner, contaminants or the like can be sequestered within the first portion or amount, leaving the second portion or amount substantially free of contaminants. The second portion or amount of bodily fluid can then be used as a biological sample in one or more tests for the purpose of medical diagnosis and/or treatment (e.g., a blood culture test or the like), as described in more detail herein. The first portion or amount of bodily fluid can be

discarded as waste or can be used in any suitable test that is less likely to produce false, inaccurate, distorted, inconsistent, and unreliable results as a result of potential contaminants contained therein. In some circumstances, for example in patients with limited supply of the bodily fluid such as blood, the first portion or amount of bodily fluid can be reinfused back into the patient via any suitable method.

[0042] The control device 100 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the control device 100 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in a sequestration, diversion, isolation, and/or storage portion of the control device 100. As described in further detail herein, the control device 100 can be configured to transition between operating modes such that (1) the first portion or amount of bodily fluid selectively flows through at least a first portion of the fluid control device and is subsequently sequestered therein, and (2) the second portion or amount of bodily fluid selectively flows through at least a second portion of the fluid control device and into a fluid collection device or the like. In some embodiments, the control device 100 can be configured to transition between operating modes automatically (e.g., based on pressure differential, time, electronic signal or instruction, saturation of a membrane or member, an absorbent and/or barrier material, etc.) or via and/or in response to intervention (e.g., user intervention, mechanical intervention, or the like).

[0043] The control device 100 includes an inlet 112, at least one outlet 116, and a sequestration chamber 114. In addition, the control device 100 defines one or more fluid flow paths 113 between the inlet 112 and at least the sequestration chamber 114 and/or one or more fluid flow paths 154 between the inlet 112 and the outlet(s) 116.

[0044] The inlet 112 of the control device 100 is configured to be placed in fluid communication with a bodily fluid source such as, for example, the vasculature of a patient. In some embodiments, the inlet 112 can be coupled to and/or can include an inlet device such as, for example, an intravenous (IV) catheter, a needle, a peripherally inserted central catheter (PICC), a syringe, one or more pieces of sterile tubing, and/or any other suitable lumen-containing device and/or intermediary transfer device. In some embodiments, the inlet 112 can be a port, a valve, and/or the like such as, for example, a Luer Lok ® or any other suitable coupler. In such embodiments, the inlet 112 (e.g., port or coupler) can be configured to couple to an access or inlet device in fluid communication with a patient (e.g., a placed or indwelling IV catheter or needle). In some embodiments, the inlet 112 can be physically and fluidically coupled to the access or inlet device via a lock, coupler, port, etc. In other embodiments, the

inlet 112 can be in fluid communication with the access or inlet device via an intermediate lumen-containing device such as, for example, sterile tubing or the like. In still other embodiments, the inlet 112 of the control device 100 can form and/or can be integrally or monolithically formed with the access or inlet device.

[0045] The sequestration chamber 114 is at least temporarily placed in fluid communication with the inlet 112 via the fluid flow path(s) 113. As described in further detail herein, the sequestration chamber 114 is configured to (1) receive a flow and/or volume of bodily fluid from the inlet 112 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein.

[0046] Although not shown in FIG.1, in some embodiments, the fluid control device 100 can have one or more flow path(s) 113 that include one or more flow modulating features (e.g., flow restrictors, fluid flow retardants, etc.) that selectively modulate the flow of bodily fluid drawn therethrough. In some embodiments, the flow modulating features can be structural and built into the fluid control device 100. In other embodiments, the flow modulating features can be separately formed or can be a material that can be introduced within the fluid control device 100, for example within the sequestration chamber 114, as described in further detail herein.

[0047] The sequestration chamber 114 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 114 can be at least partially formed by a body portion of the control device 100 (not shown in FIG. 1). In other embodiments, the sequestration chamber 114 can be a reservoir placed and/or disposed within a portion of the control device 100. In other embodiments, the sequestration chamber 114 can be formed and/or defined by a portion of the fluid flow path 113. That is to say, the control device 100 can define one or more lumen and/or can include one or more lumen-defining device(s) configured to receive a flow of bodily fluid from the inlet 112, thereby defining the fluid flow path 113. In such embodiments, at least a portion of the lumen and/or a portion of the lumen-defining device(s) can form and/or can define the sequestration chamber 114.

[0048] The sequestration chamber 114 can have any suitable volume and/or fluid capacity. For example, in some embodiments, the sequestration chamber 114 can have a volume and/or fluid capacity between about 0.25 milliliters (mL) and about 5.0 mL. In some embodiments, the sequestration chamber 114 can have a volume measured in volumes as small as a microliter or less of bodily fluid (e.g., a volume as small as 20 drops of bodily fluid, 10 drops of bodily

fluid, 5 drops of bodily fluid, a single drop of bodily fluid, or any suitable volume therebetween). In other embodiments, the sequestration chamber 114 can have a volume up to, for example, about 5.0 mL, 10.0 mL, 15.0 mL, 20.0 mL, 30.0 mL, 40.0 mL, 50.0 mL, or more. In some embodiments, the sequestration chamber 114 can have a volume that is equal to and/or that is based at least in part on the volumes of a lumen of the inlet device coupled to and/or included in the control device 100, the lumen of the inlet 112, and a portion of the fluid flow path 113 defined between the inlet 112 and the sequestration chamber 114 and/or any combination thereof. In other embodiments, the sequestration chamber 114 can have a volume that is equal to and/or that is based at least in part on the individual and/or combined volumes of a portion of the inlet device, the inlet 112 of the control device 100, and the portion of the fluid flow path 113 defined between the inlet 112 and the sequestration chamber 114.

[0049] Although not shown in FIG. 1, in some embodiments, the fluid control device 100 and/or the sequestration chamber 114 can include and/or can be formed of one or more features or materials configured to interact with a portion of the bodily fluid transferred into the sequestration chamber 114. For example, in some embodiments, the fluid control device 100 and/or the sequestration chamber 114 can include and/or define a valve, a membrane, a diaphragm, a restrictor, a vent, a selectively permeable member (e.g., a fluid impermeable barrier or seal that at least selectively allows the passage of air or gas therethrough), a port, a junction, an actuator, and/or the like, or any suitable combination thereof (collectively referred to herein as a "flow controller"). Such flow controllers can be configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 114 and/or any other suitable portion of the fluid control device 100. In this context, the flow of fluids, for example, can be a liquid such as water, oil, dampening fluid, bodily fluid, and/or any other suitable liquid, and/or can be a gas such as air, oxygen, carbon dioxide, helium, nitrogen, ethylene oxide, and/or any other suitable gas.

[0050] In some embodiments, one or more openings and/or one or more flow controllers can be configured to facilitate air displacement into or out of the sequestration chamber 114. In some embodiments, the air displacement from the sequestration chamber 114 as an initial portion of the bodily fluid is transferred into the sequestration chamber 114 can allow for a redistribution of pressure in the sequestration chamber 114 and/or between the sequestration chamber 114 and, for example, the fluid source and/or a portion of the fluid flow path outside of the sequestration chamber 114, or a pressure of an ambient environment into which the sequestration chamber 114 is vented. In some embodiments, the redistribution of pressure can

be a factor in determining and/or defining how bodily fluid flows through the control device 100 and/or the amount or volume of bodily fluid to be transferred into the sequestration chamber 114.

[0051] In other embodiments, the sequestration chamber 114 and/or control device 100 can include a flow controller operable to selectively control a flow of bodily fluid through the fluid flow paths 113 in any suitable manner. For example, in some embodiments, the control device 100 can be configured to selectively transfer a volume of bodily fluid to the sequestration chamber 114 or to the outlet 116 based at least in part on a pressure differential between two or more portions of the control device 100. In some embodiments, the pressure differential can result from fluidically coupling the outlet 116 to an evacuated fluid collection device 160 (e.g., a sample reservoir, a syringe, a pressure charged canister, and/or other source or potential energy to create a vacuum or pressure differential). In other embodiments, the pressure differential can result from a change in volume and/or temperature. In still other embodiments, the pressure differential can result from at least a portion of the control device 100, and/or other portions of the flow paths 113 and/or 154 being evacuated and/or charged (e.g., the sequestration chamber 114 and/or any other suitable portion). In some embodiments, the pressure differential can be established automatically or via direct or indirect intervention and/or manipulation (e.g., by the user). Moreover, a flow of a fluid (e.g., gas and/or liquid) resulting from a pressure differential can be selectively controlled via one or more flow controllers that can, for example, transition between one or more operating conditions to control the fluid flow. It should be understood that the flow controllers included in the embodiments described herein are presented by way of example and not limitation. Thus, while specific flow controllers are described herein, it should be understood that fluid flow can be controlled through the control device 100 by any suitable means.

[0052] In some embodiments, a wall or structure of the fluid control device 100 can define an opening, aperture, port, orifice, and/or the like that is in fluid communication with the sequestration chamber 114. In some embodiments, the control device 100 can include a semi-permeable member, film, membrane, or material such as a hydrophobic or hydrophilic membrane disposed in or about the opening or elsewhere in the flow paths 113 to selectively allow a flow of air or gas through the opening while limiting or substantially preventing a flow of fluid (e.g., bodily fluid such as blood) through the opening.

[0053] In some embodiments, for example, the control device 100 can include an absorbent and/or hydrophilic material disposed within the sequestration chamber 114. Accordingly,

when bodily fluid is transferred into the sequestration chamber 114, the absorbent and/or hydrophilic material can absorb, attract, retain, expand, and/or otherwise interact with at least a portion of the bodily fluid, which in turn, can sequester and/or retain at least an initial portion of the bodily fluid within the sequestration chamber 114, as described in further detail herein.

[0054] In some embodiments, the fluid control device 100 can include one or more self-sealing vent materials that permit the flow of air or air pressure (e.g., vacuum) but not the flow of fluid (i.e., liquid). For example, the self-sealing material when wetted or when in contact with a fluid may absorb or otherwise become saturated and transition to a sealed configuration such that the self-sealing material does not permit air or liquid therethrough. The transitioning of the self-sealing material (e.g., vent) may be associated with the fluid control device 100 moving from a first state (e.g., wherein an initial portion of the bodily fluid is being transferred into the sequestration chamber 114) to a second state (e.g., after the initial portion of the bodily fluid is transferred into the sequestration chamber 114).

[0055] In some embodiments, the sequestration chamber 114 or any other portion of the fluid control device 100 can include and/or can be formed of an expandable or collapsible material configured to transition between a first state (e.g., while an initial portion of the bodily fluid is being transferred into the sequestration chamber 114) to a second state (e.g., after the initial portion of the bodily fluid is transferred into the sequestration chamber 114). For example, the collapsible material can be in the form of a dissolvable substance that initially blocks the flow path 113 within which it is present and does not permit the flow of fluid (e.g., gas or liquid) therethrough. Upon coming into contact with a predetermined amount of fluid, however, the material can be dissolved or otherwise transitioned to a dissolved configuration to release the obstruction of the fluid flow path 113 in which the material is disposed. In some embodiments, the change in configuration resulting from such a material expanding, collapsing, dissolving, etc. can be operable to transition the control device 100 and/or any suitable portion of the control device 100 from a first state, mode, position, configuration, etc., to a second state, mode, position, configuration, etc., as described in further detail herein.

[0056] In some embodiments, the control device 100 and/or the sequestration chamber 114 can include a valve such as, for example, a duckbill valve, a butterfly valve, a one-way check valve, etc. and can be made from any suitable material with any suitable cracking pressure (e.g., an amount of pressure or force sufficient to open the valve) to be used to direct fluid flow as desired. For example, the fluid control device 100 can include two or more valves with varying cracking pressure such that they open sequentially with increasing pressure. Such a

configuration can be used, for example, in conjunction with a suitable source of negative pressure and suitable flow controllers to direct fluid flow.

[0057] The outlet(s) 116 is/are in fluid communication with and/or is/are configured to be placed in fluid communication with the fluid flow paths 113 and/or 154. The outlet 116 can be any suitable outlet, opening, port, stopcock, lock, seal, coupler, valve (e.g., a one-way check valve, duckbill valve, umbrella valve, and/or the like), etc. and is configured to be fluidically coupled to the fluid collection device 160. In some embodiments, the outlet 116 can be monolithically formed with the collection device 160, a syringe, and/or other intermediary bodily-fluid transfer device. In other embodiments, the outlet 116 can be at least temporarily coupled to the collection device 160 via an adhesive, a resistance fit, a mechanical fastener, a threaded coupling, a piercing or puncturing arrangement, any number of mating recesses, and/or any other suitable coupling or combination thereof. Similarly stated, the outlet 116 can be physically (e.g., mechanically) and/or fluidically coupled to the collection device 160 such that an interior volume defined by the collection device 160 is in fluid communication with the outlet 116. In still other embodiments, the outlet 116 can be operably coupled to the collection device 160 via an intervening structure (not shown in FIG. 1), such as a flexible sterile tubing. In still other embodiments, the outlet 116 can be fluidically coupled to a downstream source of negative pressure that suitably directs the flow of fluid into the collection device 160.

[0058] In some embodiments, the arrangement of the outlet 116 can be such that the outlet 116 is physically and/or fluidically sealed prior to coupling to the collection device 160. In some embodiments, the outlet 116 can be transitioned from a sealed configuration to an unsealed configuration in response to being coupled to the collection device 160 and/or in response to a negative pressure differential between an environment within the outlet 116 and/or control device 100 and an environment within the collection device 160.

[0059] The fluid collection device 160 can be any suitable device for at least temporarily containing a bodily fluid, such as, for example, those described above. For example, in some embodiments, the fluid collection device 160 can be a single-use disposable collection tube(s), a syringe, a vacuum-based collection tube(s), an intermediary bodily-fluid transfer device, and/or the like. In some embodiments, the fluid collection device 160 can be substantially similar to or the same as known sample containers such as, for example, a Vacutainer ®, a BacT/ALERT ® SN or BacT/ALERT ® FA, and/or any other suitable reservoir, vial, microvial, microliter vial, nanoliter vial, container, microcontainer, nanocontainer, and/or the like. In some embodiments, the collection device 160 can be a sample reservoir that includes

a vacuum seal that maintains negative pressure conditions (vacuum conditions) inside the sample reservoir, which in turn, can facilitate withdrawal of bodily fluid from the patient, through the fluid control device 100, and into the sample reservoir, via a vacuum or suction force, as described in further detail herein. In embodiments in which the fluid collection device 160 is an evacuated container or the like, the user can couple the collection device 160 to the outlet 116 to initiate a flow of bodily fluid from the patient such that a first or initial portion of the bodily fluid is transferred into and sequestered by the sequestration chamber 114 and such that any subsequent portion or volume of bodily fluid bypasses and/or is otherwise diverted away from the sequestration chamber 114 and flows into the fluid collection device 160.

[0060] Although the outlet 116 of the control device 100 is described above as being fluidically coupled to and/or otherwise placed in fluid communication with the fluid collection device 160 (e.g., a sample reservoir, syringe, etc.), in other embodiments, the control device 100 can be used in conjunction with any suitable bodily fluid collection device, system, and/or the like. For example, in some embodiments, the fluid control device 100 can be used in any suitable fluid transfer device such as those described in U.S. Patent Publication No. 2015/0342510 entitled, "Sterile Bodily-Fluid Collection Device and Methods," filed June 2, 2015 (referred to herein as the "'510 publication"), the disclosure of which is incorporated herein by reference in its entirety. More particularly, the control device 100 can be used in an "all-in-one" or pre-assembled device (e.g., such as those described in the '510 publication) to receive and sequester an initial volume of bodily fluid such that contaminants in subsequent volumes of bodily fluid are reduced and/or eliminated. In other embodiments, the outlet 116 can include and/or can be coupled to an adapter, outlet needle, and/or the like. For example, in some embodiments, the outlet 116 can be coupled to and/or can include a transfer adapter and/or the like such as, for example, the transfer adapters described in U.S. Patent Publication No. 2015/0246352 entitled, "Apparatus and Methods for Disinfection of a Specimen Container," filed March 3, 2015 (referred to henceforth as the "'352 publication"), the disclosure of which is incorporated herein by reference in its entirety.

[0061] As described above, the device 100 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 100 to establish fluid communication between the inlet 112 and the bodily fluid source (e.g., a vein of a patient, cerebral spinal fluid (CSF) from the spinal cavity, urine collection, and/or the like). As a specific example, in some

instances, the inlet 112 can be coupled to and/or can include a needle or the like that can be manipulated to puncture the skin of the patient and to insert at least a portion of the needle in the vein of the patient, thereby placing the inlet 112 in fluid communication with the bodily fluid source (e.g., the vein, an IV catheter, a PICC, etc.).

[0062] In some embodiments, once the inlet 112 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 116 can be fluidically coupled to the collection device 160. As described above, the collection device 160 can be any suitable reservoir, container, and/or collection system configured to receive a volume of bodily fluid. More particularly, the collection device 160 can be, for example, an evacuated reservoir or container that defines a negative pressure and/or can be a syringe that can be manipulated to produce a negative pressure. In some instances, coupling the outlet 116 to the collection device 160 selectively exposes at least a portion of the fluid flow paths 113 and/or 154 to the negative pressure, thereby resulting in a negative pressure differential operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 112, and into the fluid control device 100.

[0063] In some embodiments, the arrangement of the control device 100 is such that when a volume of bodily fluid is transferred to and/or through the inlet 112, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 112, through at least a portion of the fluid flow path 113, and into the sequestration chamber 114. That is to say, in some embodiments, the control device 100 can be in first or initial state in which the initial portion or volume of bodily fluid can flow in or through at least a portion the fluid flow path 113 and into the sequestration chamber 114. For example, in some embodiments, the initial state of the control device 100 can be one in which one or more flow controllers (e.g., valves, membranes, diaphragms, restrictors, vents, air permeable and fluid impermeable barriers, ports, and/or the like) are in a first state in which the fluid flow path 113 is exposed to the negative pressure differential via the sequestration chamber 114. In other words, the negative pressure within the sample reservoir 160 (or created by a syringe or other source of negative pressure) can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 114 that is operable in drawing an initial flow of bodily fluid into the sequestration chamber 114 when one or more flow controllers is in a first or initial state.

[0064] For example, in some embodiments, the control device 100 can include one or more flow controller(s) such as those described above that is at least temporarily fluidically coupled

to a flow path between the fluid collection device 160 and the sequestration chamber 114. In some embodiments, the flow controller(s) can be at least temporarily fluidically coupled to a flow path between the fluid collection device 160 and the inlet 112. While in some embodiments the flow controller examples noted above can be, for example, known off-the-shelf components that are used in medical devices to control the flow of fluids and air, in other embodiments, the flow controller can be a custom, proprietary, and/or specifically tailored component integrated into the device 100. When the flow controller is in the first or initial state, the flow controller can allow a flow of fluid therethrough in response to the negative pressure of the collection device 160. In some embodiments, the flow controller is configured to allow only a flow of air or gas through the flow controller and is configured to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) through the flow controller. As such, the collection device 160 can produce a negative pressure differential that is operable to draw an initial portion and/or amount of bodily fluid into the sequestration chamber 114 when the flow controller is in a first or initial state without allowing the initial portion of bodily fluid to flow into the fluid flow path 154 and/or otherwise out of the sequestration chamber 114.

[0065] Although not shown in FIG. 1, in some embodiments, the control device 100 can include a member, device, mechanism, etc. configured to modulate a magnitude of the negative pressure to which the sequestration chamber 114 is exposed. For example, in some embodiments, the control device 100 can include a valve, a membrane, a porous material, a restrictor, and/or any other suitable member and/or device configured to modulate pressure. In some embodiments, modulating and/or controlling a magnitude of the pressure to which the sequestration chamber 114 is exposed can, in turn, modulate a magnitude of pressure exerted on the bodily fluid and/or within a vein of a patient. In some instances, such pressure modulation can reduce, for example, hemolysis of a blood sample and/or a likelihood of collapsing a vein (e.g., which is particularly important in fragile patients needing microbial and/or other diagnostic testing associated with use of the control device 100). In addition, the modulation of the negative pressure can, for example, at least partially control a rate at which the fluid control device 100 transitions between a first configuration or state and a second configuration or state. In some embodiments, modulating the negative pressure can act like a timer. For example, a time between the introduction of the negative pressure differential and the transitioning of the diverter from the first state to the second state can be known, predetermined, calculated, and/or controlled. As such, in some instances, modulating the negative pressure can at least partially control an amount or volume of bodily fluid transferred

into the sequestration chamber 114 (e.g., can control a volume of the initial amount of bodily fluid).

[0066] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described above. For example, in some instances, the control device 100 can remain in the first state until a predetermined and/or desired volume (e.g., the initial volume) of bodily fluid is transferred to the sequestration chamber 134. In some embodiments, the initial volume can be associated with and/or at least partially based on a volume of the sequestration chamber 114. In other embodiments, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that can be transferred into the device prior to one or more portions of the control device 100 transitioning from a first operating state or mode to a second operating state or more (e.g., an amount of bodily fluid that can be absorbed by an absorbent, expandable, hydrophilic, and/or a wicking material, an amount of bodily fluid sufficient to fully wet or saturate a vent material or semi-permeable member or membrane, an amount sufficient to equalize one or more pressure differentials within the control device 100, an amount sufficient to transition a valve or actuator, and/or the like).

[0067] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 114, the initial volume is sequestered, segregated, retained, contained, isolated, etc. in the sequestration chamber 114. For example, in some embodiments, the transitioning of the one or more flow controllers from a first state to a second state can be operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 114. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, other external sources of contamination, colonization of catheters and PICC lines that are used to collect samples, and/or the like can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 114 when the initial volume is sequestered therein.

[0068] With the initial volume transferred and/or diverted into the sequestration chamber 114, the device 100 can transition to the second state in which a subsequent volume(s) of bodily fluid can flow through at least a portion the fluid flow paths 113 and/or 154 from the inlet 112 to the outlet 116. In some embodiments, the control device 100 can passively and/or automatically transition (e.g., without user intervention) from the first state to the second state once the initial volume of bodily fluid is sequestered in the sequestration chamber 114. For

example, in some embodiments, filling the sequestration chamber 114 to capacity and/or fully saturating, wetting, and/or impregnating an absorbent or similar material disposed between the sequestration chamber 114 and the sample reservoir 160 can be such that further transfer of bodily fluid into the sequestration chamber 114 is limited and/or substantially prevented due to a removal or diversion of the negative pressure. In other embodiments, the control device 100 can be manually transitioned or transitioned in response to at least an indirect interaction by a user. For example, in some embodiments, a user can at least partially obstruct the opening and/or vent. In other embodiments, the user can actuate an actuator or the like (not shown in FIG. 1) to transition the control device 100 from the first state to the second state. In still other embodiments, at least a portion of the initial volume of bodily fluid can transition the control device 100 from the first state to the second state. For example, the control device 100 can include a bodily fluid activated switch, valve, port, and/or the like. In other embodiments, a volume of bodily fluid can move and/or displace one or more actuators or the like that can, for example, open a port, flow path, and/or outlet. In still other embodiments, a user can manipulate such a switch, valve, port, actuator, etc. to transition the control device 100 from the first state to the second state.

[0069] With the collection device 160 fluidically coupled to the outlet 116 and with the control device 100 being in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 134), any subsequent volume(s) of the bodily fluid can flow from the inlet 112, through at least one of the fluid flow paths 113 and/or 154, through the outlet 116, and into the collection device 160. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 114 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates and amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 100 can be such that the control device 100 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 114.

[0070] FIG. 2 illustrates a cross-sectional side-view of a fluid control device 200 according to an embodiment. The fluid control device 200 can be similar in at least form and/or function to the fluid control device 100 described above with reference to FIG. 1. Accordingly, portions of the fluid control device 200 that can be similar to portions of the fluid control device 100 are not described in further detail herein.

[0071] As shown in FIG. 2, the fluid control device 200 (also referred to herein as "control device" or "device") includes an inlet 212, an outlet 216, and a sequestration chamber 214. As described above with reference to the control device 100, the inlet 212 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, PICC line, or the like). The outlet 216 is configured to be fluidically coupled to a fluid collection device, a syringe, and/or other intermediary bodily fluid transfer device or vessel (not shown in FIG. 2) such as, for example, a transfer device similar to those described in the '510 publication.

[0072] As described above with reference to the fluid control device 100, the control device 200 includes one or more fluid flow paths 213 between the inlet 212 and a sequestration chamber 214 and/or one or more fluid flow paths 254 between the inlet 212 and the outlet 216. The device 200 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the device 200 can be substantially similar in at least form and/or function to the device 100 described above with reference to FIG. 1. In some embodiments, the device 200 can include a first portion 224 and a second portion 225. As shown in FIG. 2, in some embodiments, the second portion 225 can be, for example, a bypass and/or diversion portion that is physically coupled to and selectively in fluid communication with the first portion 224. Moreover, the device 200 includes and/or forms a first junction 217 at a position where a first end (e.g., an inlet end) of the second portion 225 is coupled to the first portion 224 and includes and/or forms a second junction 218 at a position where a second end (e.g., an outlet end) of the second portion 225 is coupled to the first portion 224. That is to say, the device 200 can be configured to have and/or form a bifurcation (e.g., the second portion 225) at the first junction 217 which is rejoined at, for example, the second junction 218. In some embodiments, the second portion 225 can form and/or can have a D-shaped configuration and/or arrangement. In other embodiments, the first portion 224 and/or the second portion 225 can form and/or can have any suitable configuration and/or arrangement (e.g., a serpentine configuration, a looping configuration, a spiraled configuration, any suitable geometric configuration, and/or the like). In some embodiments, the first portion 224 and/or the second portion 225 of the device 200 can include and/or can be formed by flexible tubing or the like having any suitable shape and/or size and being reconfigurable or movable to be placed in any suitable configuration and/or arrangement.

[0073] In some embodiments, the sequestration chamber 214 of the device 200 can be formed by and/or included in the second portion 225 of the device 200. The coupling of the

second portion 225 to the first portion 224 (e.g., at the first junction 217) is such that the sequestration chamber 214 can be selectively placed in fluid communication with the inlet 212 via the fluid flow path 213 and the first junction 217. Similarly, the coupling of the second portion 225 to the first portion 224 (e.g., at the second junction 218) is such that the sequestration chamber 214 can be selectively placed in fluid communication with the outlet 216 and/or a fluid collection device coupled to the outlet 216 via the fluid flow path 254 and the second junction 218,.

[0074] As described in further detail herein, the sequestration chamber 214 is configured to (1) selectively receive a flow and/or volume of bodily fluid from the inlet 212 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein. The sequestration chamber 214 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 214 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 114. In some embodiments, at least a portion of the fluid flow path 213 can extend through a portion of the device 200 and/or the first junction 217 to form and/or define at least a portion of the sequestration chamber 214. In other embodiments, the first junction 217 and/or the sequestration chamber 214 can include a flow control mechanism and/or the like that can at least temporarily separate the fluid flow path 213 from the sequestration chamber 214. In some embodiments, the device 200 can include, form, and/or define one or more flow controllers such as flow controllers 221, 222, and/or 215. The flow controllers 221, 222, and/or 215 can be, for example, a valve, membrane, diaphragm, restrictor, vent, a selectively permeable member (e.g., a fluid impermeable barrier or seal that allows at least selective passage of gas or air such as, for example, a blood barrier like Porex ®, and/or the like), port, etc. (collectively referred to herein as a "flow controller") placed in one or more desired positions and configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 214 and/or any other suitable portion of the device 200.

[0075] More particularly, in the embodiment shown in FIG. 2, the flow controllers 221 and 222 each can be a valve configured to have a specific, desired, and/or predetermined cracking pressure or the like. The valves 221 and/or 222 can be, for example, inline or Lined Pipe Insert (LP) valves that can configured to be suitably placed in any position along pipe or tubing systems. In some embodiments, the valves 221 and/or 222 can be configured to stay in a closed state, limiting or substantially preventing the flow of air or liquid, until a specific amount of

pressure greater than the cracking pressure is applied on the valves 221 and/or 222 to transition the valve 221 and/or 222, respectively, from a closed state to an open state.

[0076] In some embodiments, the valves 221 and/or 222 and other additional valves (not shown) each can be configured to have a variable cracking pressure and to be placed in any suitable position in and/or along the device 200. For example, in some embodiments, as shown in FIG.2, the valve 221 can be disposed in the first portion 224 of the device 200 and downstream of the first junction 217 and the valve 222 can be disposed in the second portion 225 of the device 200 upstream and/or before the second junction 218. In some embodiments, the device 200 can be configured such that the valve 221 has a greater cracking pressure than the valve 222 such that an applied vacuum source may be used to result in a sequential opening of the valves 221 and 222. For example, the cracking pressure of each of the valves 221 and 222 and the pressure exerted by the source of negative pressure can be collectively configured to achieve a sequential and/or otherwise desired first flow of bodily fluid towards and/or into the sequestration chamber 214 and then a desired second flow of bodily fluid towards the outlet 216 and the fluid collection device.

[0077] By way of specific example, in some embodiments, a source of negative pressure (e.g., a fluid collection device and/or the like) can define a vacuum having a magnitude of approximately 8 pounds per square inch (psi). Thus, when the source of negative pressure is coupled to the outlet 216, the pressure is communicated to both valves 221 and 222. In some embodiments, the valve 221 may have, for example, a cracking pressure of 3.4 psi and the valve 222 may have, for example, a cracking pressure of 0.017 psi. As such, the negative pressure differential produced as a result of coupling the negative pressure source to the outlet 216, in turn, can transition the valve 222 (having the lower cracking pressure) from a substantially closed configuration or state to a substantially open configuration or state prior to transitioning the valve 221 (having the higher cracking pressure) from a substantially closed configuration or state to a substantially open configuration or state. In some instances, this sequential opening of the valves (i.e., valve 222 before valve 221), can be operable to direct a flow of fluid (e.g., a first flow) towards the sequestration chamber 214 and then direct the flow of fluid (e.g., a second flow) towards the fluid collection device and/or negative pressure source coupled to the outlet 216, as described further below.

[0078] The device 200, can in some embodiments, include one or more flow controllers in the form of materials that are selectively permeable to air but impermeable or at least selectively permeable to fluid (e.g., liquid). For example, the device 200 can include one or

more membranes made of material that permit the flow of air or convey a vacuum from a source of negative pressure but do not permit or convey a flow of bodily fluid (e.g., hydrophobic). In some embodiment, the device 200 can include flow controllers that can be in a first or initial state or configuration before interaction with a bodily fluid or any other suitable form of actuation, and then transition and/or be transitioned to a second state or configuration upon interaction with the bodily fluid or a suitable form of actuation. For example, in some embodiments, such flow controllers can be in an initial or first state that selectively permits a flow of air therethrough while substantially limiting and/or preventing a flow of bodily fluid therethrough. Upon interaction with a bodily fluid (or any other suitable fluid), the flow controller can transition to a second state, in which the flow controller can be substantially impermeable to the flow of air and the flow of bodily fluid therethrough.

[0079] As shown in the embodiment illustrated in FIG.2, the device 200 can include a flow controller 215 in the form of a membrane, porous material, absorbent material, etc. The flow controller 215 can be any suitable shape, size, and/or configuration. In some embodiments, the flow controller 215 can be formed of a porous material having any suitable pore size to, for example, permit a flow of air therethrough while limiting and/or substantially preventing a flow of liquid therethrough. For example, in some embodiments, the flow controller 215 can be a membrane or the like having a diameter of about 17 mm and having a pore size of about 0.45 micrometers (μm). In other embodiments, the flow controller 215 can be a membrane and/or the like having any suitable diameter (e.g., 1 mm, 2 mm, 3 mm ,4 mm, 5 mm, 10 mm, 15 mm, 20 mm, 30 mm, or more, and/or any diameter therebetween). Likewise, in other embodiments, the flow controller 215 can be a membrane and/or the like having any suitable pore size. In some embodiments, a pore size for a flow controller, membrane, and/or the like can be based on, for example, the type of fluid (e.g., bodily fluid) to be withdrawn, collected, and/or sequestered, the amount or type of particulate matter expected in the fluid flow (e.g., in the flow of the bodily fluid and/or the flow of air), the vacuum source to be used and/or a magnitude of an expected negative pressure differential, and/or any other suitable factor or consideration.

[0080] As shown, the flow controller 215 is positioned within the device 200 to selectively establish fluid communication between the second portion 225 and/or the sequestration chamber 214 and the outlet 216 via the junction 218. Thus, with the flow controller 215 being configured as a semi-permeable member, the flow controller 215 can be configured to at least temporarily allow a gas or air to transfer from the second portion 225 of the device 200 and/or the sequestration chamber 214, through the flow controller 215 and the junction 218, and into

the fluid flow path 254 and can be configured to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) between the second portion 225 and/or the sequestration chamber and the fluid flow path 254 (e.g., via the junction 218), as described in further detail herein. Although not shown, in some embodiments, the device 200 can include one or more actuators or the like configured to control and/or transition the state of the flow controller 215. The outlet 216 of the device 200 is in fluid communication with and/or is configured to be placed in fluid communication with the fluid flow paths 213 and/or 254. The outlet 216 can be any suitable outlet, opening, port, lock, seal, coupler, etc. and is configured to be fluidically coupled to a fluid collection device, such as a sample reservoir, a syringe, container, and/or other sample vessel. In some embodiments, the outlet 216 can be monolithically formed with the fluid collection device or can be at least temporarily coupled to the fluid collection device, as described above with reference to the outlet 116 of the device 100. The fluid collection device can be any suitable collection system for containing a bodily fluid, such as, for example, any of those described in detail above with reference to the collection device 160. More particularly, in some embodiments, the outlet 216 can be configured to couple to an evacuated sample reservoir. In some other embodiments, the outlet 216 can be configured to couple to a source of negative pressure downstream of the outlet 216, while also coupled to the fluid collection device. As such, the user can couple the fluid collection device to the outlet 216 to initiate a flow of bodily fluid from the patient such that a first or initial portion of the bodily fluid is transferred into and sequestered by the sequestration chamber 214 and such that any subsequent portion or volume of bodily fluid bypasses and/or is otherwise diverted away from the sequestration chamber 214 and flows into the fluid collection device.

[0081] In operation, the device 200 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 200 to establish fluid communication between the inlet 212 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 212 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 216 can be fluidically coupled to the fluid collection device. As described above, in the embodiment shown in FIG. 2, the fluid collection device can be a negative pressure source and/or can be configured to produce a negative pressure differential. For example, the fluid collection device can be an evacuated reservoir or container that defines a negative pressure, a syringe, a pump, and/or any other negative pressure source. In other embodiments, the fluid

collection device can be a container, reservoir, or device configured to be coupled to a separate negative pressure source.

[0082] Coupling the outlet 216 to the fluid collection device and/or the source of negative pressure selectively exposes at least a portion of the fluid flow path 254 to the negative pressure within or passing through the fluid collection device. As described above, the flow controller 215 and/or the valves 221 and 222 can be configured to selectively control the flow of fluid through the device 200. More particularly, coupling the outlet 216 to the fluid collection device and/or source of negative pressure results in a negative pressure differential within the fluid flow path 254, which in turn, exposes the valves 221 and 222 to the negative pressure. As described above, in some embodiments, the valve 221 can have a greater cracking pressure (e.g., 3.4 psi) compared to that of the valve 222 (e.g., 0.017 psi). Furthermore, the flow controller 215 upstream of the valve 222 can be a membrane in an initial or first state, in which the flow controller 215 is permeable to a flow of air or gas. In some instances, such an arrangement results in the valve 222 being transitioned from a closed state to an open state such that the negative pressure is communicated through the valve 222 and the flow controller 215 and into the sequestration chamber 214.

[0083] Accordingly, a negative pressure differential is produced that is operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 212, and into the fluid flow path 213. Moreover, with the valve 222 in the open state and the valve 221 in the closed state, the bodily fluid can flow through the fluid flow path 213 and into the sequestration chamber 214 (e.g., via the junction 217). As described above with reference to the control device 100, the arrangement of the device 200 is such that when a volume of bodily fluid is transferred to and/or through the inlet 212, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 212, through at least a portion of the fluid flow path 213 and/or the junction 217, and into the sequestration chamber 214. That is to say, in some embodiments, the control device 200 can be in first or initial state in which the initial portion or volume of bodily fluid can flow in or through at least a portion the fluid flow path 213 and/or junction 217 and into the sequestration chamber 214. When the device 200 is in the first or initial state, the valve 221 is in a closed state and as such, the bodily fluid does not pass through the valve 221 nor substantially enter the fluid flow path 254.

[0084] As described above, the control device 200 can be in the initial state when the flow controller 222 (valve) is in an open state, which in turn, allows the negative pressure differential

to draw the initial amount of bodily fluid into the sequestration chamber 214. In some instances, the bodily fluid can flow through the second portion 225 (e.g., the sequestration chamber 214) until the flow reaches the flow controller 215 (e.g., a selectively permeable membrane or member, as described above). The membrane 215 can be in its initial or first state and therefore can be permeable to air but impermeable to liquids. As such, the membrane 215 isolates, separates, segregates, sequesters and/or otherwise prevents direct liquid communication between the fluid flow paths 213 and the sequestration chamber 214. In addition, the inlet 212 is exposed to the negative pressure differential via the sequestration chamber 214. In other words, the negative pressure within the fluid collection device can result in a negative pressure (or negative pressure differential) within at least the second portion 225 of the device 200 (e.g., the sequestration chamber 214) that is operable in drawing an initial flow of bodily fluid from the inlet 212, through at least a portion of the fluid flow path 213 and/or the junction 217, and into the sequestration chamber 214 when the control device 200 is in the first or initial state.

[0085] When the flow controller 215 is in the first or initial state, the flow controller 215 can allow a flow of fluid (e.g., a gas or air) therethrough in response to the negative pressure of the sample reservoir (or a syringe or other source of potential energy used to create negative pressure), as described above with reference to the device 100. The flow controller 215 (e.g., selectively permeable membrane or member) can be configured to transition from the first state of being permeable to air and impermeable to liquid, to a second state of being impermeable to air and liquid in response to the flow of the initial amount of bodily fluid into the sequestration chamber 214. For example, the filling of the sequestration chamber 214 to capacity can correspond to and/or otherwise result in the bodily fluid saturating, wetting, and/or impregnating the flow controller 215 (e.g., membrane material), which can transition the flow controller 215 from the first state to the second state. In the second state the flow controller 215 is impermeable to air and liquid, thereby limiting and/or substantially preventing fluid communication between the sequestration chamber 214 and the source of negative pressure (e.g., the fluid collection device). In other words, the sequestration chamber 214 can be sequestered from the negative pressure source in response to initial volume of bodily fluid filling the sequestration chamber 214.

[0086] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control device 100. For example, in some instances, the initial volume can be associated with and/or at least partially based on

an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 215 (e.g., selectively permeable membrane or member). In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition the flow controller 215 to a second state (e.g., a saturated or fully wetted state). In some embodiments, the flow controller 215 is placed in a sealed configuration when transitioned to the second state. That is to say, saturating and/or fully wetting the flow controller 215 (e.g., the semi-permeable material) places the flow controller 215 in a sealed configuration in which the flow controller 215 substantially prevents a flow of a liquid and a gas therethrough.

[0087] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 214, the control device 200 can be transitioned to its second state or operating mode to sequester, segregate, retain, contain, isolate, etc. the initial volume in the sequestration chamber 214. For example, as described above, the flow controller 215 is placed in the sealed configuration, which fluidically isolates the sequestration chamber 214 from the fluid flow path 254. In addition, the transitioning of the flow controller 215 can be in response to the initial amount of bodily fluid filling the sequestration chamber 214. Accordingly, the initial amount of bodily fluid in the sequestration chamber 214 can limit and/or substantially prevent further amounts of bodily fluid from being transferred into the sequestration chamber 214. Thus, the initial amount and/or portion of bodily fluid is sequestered and/or retained within the sequestration chamber 214. As described above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 214 when the initial volume of bodily fluid is sequestered therein.

[0088] With the flow controller 215 in the second state (e.g., an impermeable or sealed state), the negative pressure otherwise exerted on or through the sequestration chamber 214 is now exerted on or through the fluid flow path 254 and thus, on the flow controller 221. In some instances, a magnitude of the negative pressure can build and/or increase within the fluid flow path 254 until the negative pressure becomes sufficient to transition the flow controller 221 from its first state to its second state. More specifically, when the flow controller 221 is a valve, the negative pressure can increase until it becomes sufficient to overcome the cracking pressure of the valve 221. As such, when the valve is placed in its open state (and/or when the flow controller 221 is otherwise in its second state), the inlet 212 is exposed to the negative pressure differential via the fluid flow path 213. With the fluid collection device fluidically

coupled to the outlet 216 and with the control device 200 being in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 214), any subsequent volume(s) of the bodily fluid can flow from the inlet 212, through the fluid flow paths 213 and 254, through the flow controller 221 (e.g., valve), through the outlet 216, and into the fluid collection device. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 214 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates and amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 200 can be such that the control device 200 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 214.

[0089] Although not shown in FIG. 2, in some embodiments, the control device 200 can include an actuator and/or the like configured to be moved (e.g., via a force applied by a user) between a first state and a second state. In other embodiments, a control device can include any suitable member, device, mechanism, etc. configured to selectively establish fluid communication between two or more fluid flow paths (e.g., the fluid flow paths 213 and 254).

[0090] In some instances, it may be desirable to modulate and/or control a magnitude of the negative pressure differential to which the sequestration chamber 214 is exposed. Although not shown in FIG. 2, the device 200 can include one or more means for reducing and/or controlling a magnitude of the negative pressure differential. For example, in some embodiments, the device 200 can include a restricted flow path path(s) or portions of flow path(s) having a smaller diameter than the fluid flow paths 213 and/or 254. For example, in some embodiments, the one or more restricted flow paths can have a diameter of about 1.0 micrometers (μm), about 10.0 μm, about 100.0 μm, about 1000.0 μm, about 10,000.0 μm, about 100,000.0 μm, and/or any suitable diameter therebetween. In other embodiments, the restricted flow path(s) can have a diameter smaller than 1.0 μm or larger than 100,000.0 μm. In such embodiments, a restricted flow path having a smaller diameter may result in a lower magnitude of negative pressure being applied through the sequestration chamber 214 than a magnitude of negative pressure when the restricted flow path has a larger diameter. Moreover, in some such embodiments, the one or more restricted flow paths can be, for example, gas flow path(s) configured to receive a flow of gas or air but not a flow of a liquid (e.g., bodily fluid). In some embodiments, the diameter of the restricted flow path can be sufficiently small to limit and/or prevent a flow of a liquid therethrough.

[0091] In some embodiments, the restricted flow path can be, for example, disposed between the junction 218 and the flow controller 215, such that a flow of bodily fluid and/or any other liquid is substantially prevented by the flow controller 215 (e.g., a selectively permeable barrier or seal). More specifically, in some embodiments, the restricted flow path can be disposed between, for example, the flow controller 222 (e.g., valve) and the flow controller 215 (e.g., selectively permeable membrane or member). Accordingly, the flow controller 222 can be exposed to a greater magnitude of negative pressure than the magnitude of negative pressure to which the flow controller 215 is exposed. In such embodiments, the greater magnitude of negative pressure can facilitate the transition of the flow controller 222 from its first state to its second state. For example, in some embodiments, when the flow controller 222 is a valve, this arrangement can allow for the valve to be exposed to a negative pressure differential that is sufficient to overcome the cracking pressure of the valve.

[0092] Although the pressure modulation is described above as being based on a diameter of a restricted flow path, it should be understood that this is presented by way of example only and not limitation. For example, in some embodiments, a control device can include any suitable number of restricted flow paths, each of which can have substantially the same diameter or can have varied diameters. For example, in some embodiments, a control device can include up to 100 restricted flow paths or more. In such embodiments, each of the restricted flow paths can have a diameter of between about 1.0 μm and about 100.0 μm, between about 1.0 μm and about 10.0 μm, or between about 1.0 μm and about 5.0 μm. In some embodiments, multiple restricted flow paths can be configured to (1) selectively provide a flow path between the outlet 216 and the sequestration chamber 214 that exposes the sequestration chamber 214 to the negative pressure differential, and (2) act as a flow controller configured to selectively allow the passage of a gas and/or air while substantially preventing the passage of a liquid (e.g., bodily fluid). Other means of modulating the magnitude of negative pressure to which the sequestration chamber is exposed can include, for example, a porous material, a valve, a membrane, a diaphragm, a specific restriction, a vent, a deformable member or flow path, and/or any other suitable means. In some embodiments, the flow controller 215 can be a selectively permeable membrane or member having a predetermined and/or desired porosity to provide the desired amount of negative pressure modulation.

[0093] In some embodiments, modulating and/or controlling a magnitude of the pressure to which the sequestration chamber 214 is exposed can, in turn, modulate a magnitude of pressure exerted on the bodily fluid and/or within a vein of a patient. In some instances, such

pressure modulation can reduce, for example, hemolysis of a blood sample and/or a likelihood of collapsing a vein. In some instances, the ability to modulate and/or control an amount or magnitude of negative pressure can allow the control device 200 to be used across a large spectrum of patients that may have physiological challenges whereby negative pressure is often needed to facilitate collection of bodily fluid such as, for example, blood (e.g., a pressure differential between atmospheric pressure and a patient's vascular pressure may not be sufficient to facilitate consistent and sufficiently forceful flow) but not so much pressure that a rapid force flattens, collapses, caves-in, and/or otherwise inhibits patency and ability to collect blood.

[0094] FIG. 3 illustrates a fluid control device 300 according to another embodiment. The fluid control device 300 (also referred to herein as "control device" or "device") can be of any suitable shape, size, and/or configuration. For example, in some embodiments, the fluid control device 300 can be similar in at least form and/or function to the fluid control device 100 described above with reference to FIG. 1 and/or the fluid control device 200 described above with reference to FIG. 2. Accordingly, portions of the fluid control device 300 that can be similar to portions of the fluid control devices 100 and/or 200 are not described in further detail herein.

[0095] As described above with reference to the fluid control device 200 shown in FIG. 2, the fluid control device 300 shown in FIG. 3 includes an inlet 312, an outlet 316, and a sequestration chamber 314. The inlet 312 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, PICC line, or the like). The outlet 316 is configured to be fluidically coupled to a fluid collection device, a syringe, an evacuated container, and/or other intermediary bodily fluid transfer device or vessel (not shown in FIG. 3) such as, for example, a transfer device similar to those described in the '510 publication. Furthermore, the control device 300 includes and/or defines one or more fluid flow paths 313 between the inlet 312 and the sequestration chamber 314 and/or one or more fluid flow paths 354 between the inlet 312 and the outlet 316.

[0096] In some embodiments, the device 300 can include a first portion 324 and a second portion 325. As shown in FIG. 3, in some embodiments, the second portion 325 can be, for example, a bypass and/or diversion portion that is physically coupled to and selectively in fluid communication with the first portion 324. Moreover, the device 300 includes and/or forms a first junction 317 at a position where a first end (e.g., an inlet end) of the second portion 325 is

coupled to the first portion 324 and includes and/or forms a second junction 318 at a position where a second end (e.g., an outlet end) of the second portion 325 is coupled to the first portion 324. That is to say, the device 300 can be configured to have and/or form a bifurcation (e.g., the second portion 325) at the first junction 317 which is rejoined at, for example, the second junction 318. In some embodiments, the first portion 324 and/or the second portion 325 of the device 300 can include and/or can be formed by flexible tubing or the like having any suitable shape and/or size and being reconfigurable or movable to be placed in any suitable configuration and/or arrangement.

[0097] As described in further detail herein, the sequestration chamber 314 is configured to (1) receive a flow and/or volume of bodily fluid from the inlet 312 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein. The sequestration chamber 314 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 314 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 114 and/or 214. In some embodiments, at least a portion of the fluid flow path 313 can extend through a portion of the device 300 to form and/or define at least a portion of the sequestration chamber 314. In some embodiments, the sequestration chamber 314 of the device 300 can be substantially similar in form and/or function to one or more of the sequestration chambers 114 and/or 214. Accordingly, portions of the sequestration chamber 314 may not be described in further detail herein.

[0098] As shown in FIG. 3, the sequestration chamber 314 can be formed by and/or included in the second portion 325 of the device 300 and can be selectively placed in fluid communication with (1) the inlet 312 via the fluid flow path 313 and the first junction 317, and (2) the outlet 316 via the fluid flow path 354 and the second junction 318. As such, the sequestration chamber 314 can be configured to (1) selectively receive a flow and/or volume of bodily fluid from the inlet 312 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein.

[0099] In some embodiment, the fluid control device 300 can include and/or define one or more flow controllers. Flow controllers can include for example, valves, membranes, diaphragms, restrictors, vents, selectively permeable members (e.g., a fluid impermeable barrier or seal that allows at least selective passage of gas or air such as, for example, a blood barrier like Porex ®, and/or the like), ports, etc. (collectively referred to herein as a "flow controller") placed suitably and configured to selectively control (at least in part) a flow of

fluids into and/or out of the sequestration chamber 314 and/or any other suitable portion of the device 300. Some embodiments of the device 300, as shown in FIG. 3, can include flow controllers such as a selectively permeable member 315, a check valve 322, and a dissolvable member 323 that are arranged to, under certain states of function and/or under certain conditions, permit, direct, control, and/or obstruct the flow of fluid in one or more specific directions.

[0100] As shown in FIG. 3, the second portion 325 of the device 300 can include the check valve 322 and the selectively permeable member 315. For example, in some embodiments, the check valve 322 and/or the selectively permeable member 315 can be disposed on, at, or near a proximal or second end of the sequestration chamber 314. In other words, the check valve 322 and the selectively permeable member 315 can be positioned at, on, or near an outlet or outlet portion of the sequestration chamber 314. Said another way, the check valve 322 and/or the selectively permeable member can be positioned at, on, or near an end portion of the sequestration chamber 314 that is closer to the second junction 318 than it is to the first junction 317. In some embodiments, the check valve 322 and/or the selectively permeable member 315 can be integrated into at least a portion of the second junction 318. In some embodiments, the check valve 322 can be substantially similar to the valve 222 described above with reference to the device 200. For example, in some embodiments, the check valve 322 can be configured to have a desired cracking pressure such as those described above with reference to the valve 222. Accordingly, the check valve 322 can be configured to selectively control a flow of fluid between, for example, the fluid flow path 354 and the sequestration chamber 314, as described above with reference to the device 200. As such, the check valve 322 is not described in further detail herein. Moreover, in some embodiments, the device 300 need not include a check valve and/or any other suitable valve.

[0101] The selectively permeable member can be any suitable shape, size, and/or configuration. For example, in some embodiments, the selectively permeable member 315 can be, for example, a membrane, a porous material, an absorbent material, a hydrophilic or hydrophobic material, a selectively permeable barrier, etc. In some embodiments, the selectively permeable member 315 can be substantially similar to the flow controller 215 (e.g., selectively permeable member and/or membrane) and thus, aspects of the selectively permeable member 315 are not described in further detail herein. The selectively permeable member 315 can be configured to at least temporarily allow a gas or air to transfer from the second portion 325 of the device 300 and/or the sequestration chamber 314, through the

selectively permeable member 315 and the junction 318, and into the fluid flow path 354 and can be configured to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) between the second portion 325 and/or the sequestration chamber and the fluid flow path 354 (e.g., via the junction 318). In some embodiments, the selectively permeable member 315 can be in a first or initial state, in which the selectively permeable member 315 allows a flow of air or gas to transfer therethrough, when the device 300 is in its first state and/or configuration. As described in further detail herein, the selectively permeable member 315 can be transitioned to and/or otherwise can be in a second state or configuration, in which the selectively permeable member 315 is substantially impermeable to all fluids (gasses and/or liquids), when the device 300 is in its second state and/or configuration.

[0102] In some embodiments, the dissolvable member 323 can be situated at a suitable position within the first portion of the device 300. For example, in some embodiments, the dissolvable member 323 can be positioned at and/or near the first junction 317, as shown in FIG. 3. In some embodiments, the dissolvable member 323 can be integrated into the junction 317 and/or at least a portion of the junction 317. As such, the dissolvable member 323 can be, for example, upstream of the selectively permeable member 315.

[0103] As described in further detail herein, the dissolvable member 323 can be configured to transition from a first or initial state to a second state in response to contact with a fluid such as, for example, bodily fluid. In some embodiments, for example, the dissolvable member 323 can be disposed within and/or near the first junction 317 to isolate the inlet 312 from the fluid flow path 354 when the device 300 is in the first or initial state. In response to and/or after transferring an initial volume of bodily fluid to the sequestration chamber 314, the device 300 can be transitioned from the first or initial state to the second state. In some embodiments, when the device 300 is in the second state, the dissolvable member 323 can be substantially dissolved, which in turn, can allow fluid communication to be established between the inlet 312 and the fluid flow path 354. In some instances, for example, a portion of the bodily fluid can contact the dissolvable member 323 as the initial volume of bodily fluid flows into the sequestration chamber 314. The contact with the bodily fluid can, in turn, begin to dissolve the dissolvable member 323 such that when the device 300 is transitioned to its second state and/or configuration, the dissolvable member 323 is at least substantially dissolved, thereby placing the inlet 312 in fluid communication with the fluid flow path 354, as described in further detail herein.

[0104] As described above, the device 300 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 300 to establish fluid communication between the inlet 312 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 312 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 316 can be fluidically coupled to the fluid collection device. As described above, in the embodiment shown in FIG. 3, the fluid collection device can be, for example, an evacuated reservoir, a syringe, and/or any container that defines a negative pressure, or is coupled to a downstream source of negative pressure.

[0105] Coupling the outlet 316 to the fluid collection device selectively exposes at least a portion of the fluid flow path 354 to the negative pressure within the fluid collection device. The arrangement of the device 300 when in its first or initial state includes one or more flow controllers in their first state or configuration. For example, the selectively permeable member 315, the check valve 322, and the dissolvable member 323 can each be in their first states and/or configurations when the outlet 316 is coupled to the fluid collection device. In response to the negative pressure, the check valve 322 can be configured to transition from a substantially closed state (e.g., its first configuration or state) to a substantially open state (e.g., its second configuration and/or state). For example, in some instances, establishing fluid communication between the outlet 316 and the fluid collection device can expose the check valve 322 to a negative pressure differential that exceeds, for example, a cracking pressure of the check valve 322. Thus, the check valve 322 can be placed in its second state and/or configuration. In other embodiments, the device 300 need not include a check valve and/or other suitable valve. In such embodiments, the negative pressure differential otherwise operable to transition the check valve 322 would instead be exerted on the selectively permeable member 315, which is substantially similar to when the check valve 322 is in the second or opened state.

[0106] As described above, the selectively permeable member 315 and the dissolvable member 323 are each in their first state or configuration when the outlet 316 is coupled to the fluid collection device. As such, the selectively permeable member 315 can be configured to permit a flow of air, gas, and/or negative pressure therethrough while blocking and/or preventing a flow of liquid therethrough, as described above with reference to the flow controller 215. Furthermore, with the dissolvable member 323 in its first state or configuration, the dissolvable member 323 can be configured to block, isolate, and/or obstruct fluid

communication between, for example, the inlet 312 and the fluid flow path 354 such that it does not permit any flow of fluid (air or liquid or negative pressure) therethrough. Thus, coupling the outlet 316 to the fluid collection device exposes the sequestration chamber 314 to the negative pressure of the fluid collection device, thereby resulting in a negative pressure differential operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 312, and into the sequestration chamber 314.

[0107] As described above with reference to the control devices 100 and 200, the arrangement of the device 300 is such that when a volume of bodily fluid is transferred to and/or through the inlet 312, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 312 and into the sequestration chamber 314. That is to say, in some embodiments, the device 300 is in its first or initial state in which the initial portion or volume of bodily fluid can flow from the inlet 312 and into the sequestration chamber 314 in response to the negative pressure differential associated with the fluid collection device. In other words, the negative pressure within the fluid collection device can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 314 that is operable in drawing an initial flow of bodily fluid from the inlet 312 into the sequestration chamber 314 when the control device 300 is in the first or initial state. As described in detail above, in some instances, it may be desirable to modulate and/or control a magnitude of the negative pressure differential by any suitable means such as those described herein.

[0108] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control devices 100 and/or 200. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the membrane 315. In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition the selectively permeable member 315 to a second state (e.g., a saturated or fully wetted state). As described above with reference to the flow controller 215, the selectively permeable member 315 is placed in a sealed configuration when transitioned to the second state. Thus, transitioning the selectively permeable member 315 to the second state sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents flow through the selectively permeable member 315.

[0109] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 314, the control device 300 can be transitioned to its second state or

operating mode to sequester, segregate, retain, contain, isolate, etc. the initial volume in the sequestration chamber 314. As described above, the selectively permeable member 315 is placed in the sealed configuration and thus, substantially prevents a flow of fluid therethrough. In this embodiment, the arrangement of the control device 300 is such that when the selectively permeable member 315 is placed in the sealed configuration, at least a portion of the negative pressure otherwise being exerted through the selectively permeable member 315 is instead exerted on and/or in the fluid flow path 354. The negative pressure, however, can be isolated within the fluid flow path 354 until the dissolvable member 323 is transitioned from its first state and/or configuration to its second state and/or configuration (e.g., until it is at least partially dissolved).

[0110] With the selectively permeable member 315 sealed in its second state and the filling of the sequestration chamber 314 to capacity by the initial volume of bodily fluid drawn, the amount of bodily fluid held at least temporarily at and/or near the junction 317 can place a sufficient amount of bodily fluid in contact with the dissolvable member 323 to transition the dissolvable member 323 from its first state to its second state. In other words, filing the sequestration chamber 314 can place a sufficient volume or amount of bodily fluid into contact with the dissolvable member 323 to substantially dissolve the dissolvable member 323, thereby transitioning it to its second state or configuration. The transition of the dissolvable member 323, in turn, is sufficient to transition the fluid control device 300 from its first state to its second state.

[0111] With the dissolvable member 323 in its second state and/or configuration (e.g., at least partially dissolved), the negative pressure within the fluid flow path 354 can be exerted on the fluid flow path 313 and/or the inlet 312. In some embodiments, the arrangement of the dissolvable member 323 can be such that as the dissolvable member 323 is dissolved, the inlet 312 is exposed to a greater amount and/or magnitude of negative pressure. In other words, the dissolvable member 323 can be configured to dissolve of a predetermined and/or desired period of time, which in turn, can modulate and/or control an amount of negative pressure to which the inlet 312 is exposed. In some embodiments, the dissolvable member 323 can include one or more characteristics that can be tuned, adjusted, and/or the like configured to adjust (e.g., increase or decrease) a rate at which the dissolvable member 323 transitions to its second state (e.g., dissolves). As the dissolvable member 323 is transitioned to its second state and/or configuration, the negative pressure within the fluid flow path 354, urges, draws, and/or induces a flow of bodily fluid from the inlet 312 and the first junction 317, through the fluid

flow path 354 and the outlet 316, and into the fluid collection device. Moreover, the sealed state of the selectively permeable member 315 and the presence of check valves 322 (or other suitable flow controller) can limit and/or substantially prevent flow of bodily fluid from the fluid flow path 354, through the second junction 318, and toward the sequestration chamber 314. In some embodiments, the transitioning of the selectively permeable member 315 and the dissolvable member 323 from their respective first states to their respective second states is operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 314. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 314 when the initial volume is sequestered therein.

[0112] With the fluid collection device fluidically coupled to the outlet 316 and with the control device 300 in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 314), any subsequent volume(s) of the bodily fluid can flow from the inlet 312, through the fluid flow paths 313 and 354, through the outlet 316, and into the fluid collection device. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 314 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates and amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the fluid control device 300 can be such that the device 300 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 314.

[0113] FIG. 4 illustrates a fluid control device 400 according to an embodiment. The fluid control device 400 can be of any suitable shape, size, and/or configuration. For example, in some embodiments, the fluid control device 400 can be similar in at least form and/or function to one or more of the devices 100, 200, and/or 300 described above with reference to FIG. 1, FIG. 2, and FIG. 3, respectively. Accordingly, portions of the fluid control device 400 that can be similar to portions of the fluid control devices 100, 200, and/or 300 are not described in further detail herein.

[0114] As shown in FIG. 4, the fluid control device 400 (also referred to herein as "control device" or "device") includes an inlet 412, an outlet 416, and a sequestration chamber 414. As described above with reference to the control devices 100, 200, and/or 300, the inlet 412 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, PICC

line, and/or the like). The outlet 416 is configured to be fluidically coupled to fluid collection device, a syringe, a transfer adapter, and/or the like (not shown in FIG. 4). Furthermore, the control device 400 includes and/or defines one or more fluid flow paths 413 between the inlet 412 and at least the sequestration chamber 414 and/or one or more fluid flow paths 454 between the inlet 412 and the outlet 416.

[0115] In some embodiments, the device 400 can include a first portion 424 and a second portion 425. As shown in FIG. 4, in some embodiments, the second portion 425 can be, for example, a bypass and/or diversion portion that is physically coupled to and selectively in fluid communication with the first portion 424. Moreover, the device 400 includes and/or forms a first junction 417 at a position where a first end (e.g., an inlet end) of the second portion 425 is coupled to the first portion 424 and includes and/or forms a second junction 418 at a position where a second end (e.g., an outlet end) of the second portion 425 is coupled to the first portion 424. That is to say, the device 400 can be configured to have and/or form a bifurcation (e.g., the second portion 425) at the first junction 417 which is rejoined at, for example, the second junction 418. In some embodiments, the first portion 424 and/or the second portion 425 of the device 400 can include and/or can be formed by flexible tubing or the like having any suitable shape and/or size and being reconfigurable or movable to be placed in any suitable configuration and/or arrangement.

[0116] The sequestration chamber 414 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 414 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 114. In some embodiments, the sequestration chamber 414 of the device 400 can be substantially similar in form and/or function to one or more of the sequestration chambers 114, 214, and/or 314. Accordingly, portions of the sequestration chamber 414 may not be described in further detail herein.

[0117] As shown in FIG. 4, the sequestration chamber 414 can be formed by and/or included in the second portion 425 of the device 400 and can be selectively placed in fluid communication with (1) the inlet 412 via the fluid flow path 413 and the first junction 417, and (2) the outlet 416 via the fluid flow path 454 and the second junction 418. As such, the sequestration chamber 414 can be configured to (1) selectively receive a flow and/or volume of bodily fluid from the inlet 412 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein.

[0118] The second portion 425 of the device 400 and/or the sequestration chamber 414 specifically, can include, form, and/or define a flow controller 415 disposed on, at, or near a proximal or second end of the sequestration chamber 414. In other words, the flow controller 415 can be positioned at, on, or near an outlet or outlet portion of the sequestration chamber 414. Said another way, the flow controller can be positioned at, on, or near an end portion of the sequestration chamber 414 that is closer to the second junction 418 than it is to the first junction 417. In some embodiments, the flow controller 415 can be, for example, a membrane, a porous material, an absorbent material, a hydrophilic or hydrophobic material, a selectively permeable barrier, etc. The flow controller 415 can be any suitable shape, size, and/or configuration. In some embodiments, the flow controller 415 can be substantially similar to the flow controller 215 and/or the flow controller 315 and thus, is not described in further detail herein.

[0119] As described in detail above, the flow controller 415 is positioned within the second portion 425 of the device to selectively establish fluid communication between the second portion 425 and/or the sequestration chamber 414 and the outlet 416 via the junction 418. Thus, with the flow controller 415 configured to selectively control fluid flow therethrough (e.g., configured as a semi-permeable member), the flow controller 415 can be configured to at least temporarily allow a gas or air to transfer from the second portion 425 of the device 400 and/or the sequestration chamber 414, through the flow controller 415 and the junction 418, and into the fluid flow path 454 and can be configured to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) between the second portion 425 and/or the sequestration chamber and the fluid flow path 454 (e.g., via the junction 418), as described in further detail herein.

[0120] As described above with reference to the devices 100, 200, and/or 300, the device 400 can include one or more flow controllers that is/are configured to selectively control a flow of gas or liquid (e.g., air or bodily fluid, respectively) through the device 400. For example, in the embodiment illustrated in FIG. 4, the device 400 includes a first flow restrictor 431 and a second flow restrictor 432. The flow restrictors 431 and 432 (and/or any other suitable flow controllers that may be included but not illustrated in FIG. 4) can be included at predetermined and/or desired positions along the first portion 424 and/or the second portion 425 of the device 400 to control, manipulate, divert, and/or direct the flow of air, liquid (e.g., bodily fluid), and/or negative pressure. The flow restrictors 431 and 432 can be configured with varying flow permitting or flow obstructing properties. For example, in some embodiments, the flow restrictor 431 and/or the flow restrictor 432 can have and/or can define any suitable inner cross-

sectional shape, size, and/or configuration to selectively allow fluid flow therethrough, as described in further detail herein.

[0121] In the embodiment shown in FIG. 4, the flow restrictors 431 and 432 each can be a flow restrictor configured to define a flow path therethrough having one or more specific, desired, and/or predetermined characteristics. Moreover, in some embodiments, the second flow restrictor 432 (e.g., the flow restrictor positioned between the second junction 418 and the sequestration chamber 414) can have a flow path that is less restrictive than the flow path of the first flow restrictor 431 (e.g., the flow restrictor positioned between the outlet 416 and the first junction 417). In other words, a pressure differential sufficient to allow fluid (e.g., a gas or liquid) to pass through the second flow restrictor 432 can be less than a pressure differential sufficient to allow fluid (e.g., gas or liquid) to pass through the first flow restrictor 431. Accordingly, the first flow restrictor 431 and the second flow restrictor 431 can be similar to the first valve 221 and second valve 222 described above with reference to FIG. 2.

[0122] As described in further detail herein, the arrangement of the flow restrictors 431 and 432 can be such that when a source of negative pressure (e.g., a fluid collection device and/or the like) is coupled to the outlet 416, the negative pressure differential can result in a flow through the second flow restrictor 432 prior to a flow through the first flow restrictor 431. In some instances, this sequential opening of the flow restrictors (e.g., the flow restrictor 432 before the flow restrictor 431), can be operable to direct a flow of fluid (e.g., a first flow) towards the sequestration chamber 414 and then direct the flow of fluid (e.g., a second flow) towards the fluid collection device and/or negative pressure source coupled to the outlet 416. Said another way, in some embodiments, the device 400 can be configured to transition between a first state in which (1) the inlet 412 is placed in fluid communication with the second portion 425 of the device 400 (e.g., the sequestration chamber 414) and (2) the second flow restrictor 432 establishes selective fluid communication between the sequestration chamber 414 and the outlet 416, and a second state in which (1) the second flow restrictor 432 isolates the sequestration chamber 414 from the outlet 416 and (2) the first flow restrictor 431 establishes selective fluid communication between the inlet 412 and the first portion 424 of the device 400 and/or the outlet 416.

[0123] As described above, with respect to devices 100, 200, and 300, the device 400 can be used to procure a bodily fluid sample having reduced contamination. In some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 400 to establish fluid communication between the inlet 412 and the bodily fluid source (e.g., a

vein of a patient). For example, in some embodiments, the user can couple the inlet 412 to an inlet device, a needle, an indwelling catheter or IV, and/or any other suitable lumen-containing device. Once the inlet 412 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 416 can be fluidically coupled to the fluid collection device. As described herein, the fluid collection device can be any suitable reservoir, syringe, pump, and/or device configured to define and/or produce a negative pressure. In other embodiments, the outlet 416 can be coupled to the fluid collection device, which in turn, is coupled to a downstream source of negative pressure.

[0124] The control device 400 can be in a first or initial state prior to coupling the outlet 416 to the fluid collection device. Coupling the outlet 416 to the fluid collection device selectively exposes at least a portion of the fluid flow path 454 to the negative pressure within the fluid collection device. For example, with the device 400 in its initial or first state, the flow controller 415 can be in its first state or configuration such that the flow controller 415 is permeable to a flow of air or gas but impermeable to a flow of liquid (e.g., bodily fluid). Moreover, the arrangement of the flow restrictors 431 and 432 is such that the first flow restrictor 431 is more restrictive toward a flow of liquid or air therethrough than is the second flow restrictor 432.

[0125] The negative pressure differential defined and/or produced by the fluid collection device results in a suction or drawing of fluid (e.g., air or gas) from the fluid flow path 454. In other words, the negative pressure within and/or produced by the fluid collection device results in a negative pressure differential within the fluid flow path 454. The arrangement of the flow restrictors 431 and 432, and the flow controller 415 can be such that the negative pressure differential within the fluid flow path 454, results in a negative pressure differential through and/or across the outlet 416, the second junction 418, the second flow restrictor 432, the flow controller 415, and the sequestration chamber 414. Moreover, with the first flow restrictor 431 configured to be more restrictive than the second flow restrictor 432, the flow through the second flow restrictor 432 can at least partially maintain a magnitude of the negative pressure within the fluid flow path 454 below a threshold magnitude of negative pressure otherwise operable to induce a flow of fluid through the first flow restrictor 431. That is to say, when the device 400 is in the first state, the negative pressure within the fluid flow path 454 is sufficient to result in a flow through the second flow restrictor 432 but is insufficient to result in a flow through the first flow restrictor 431. Accordingly, the negative pressure within and/or produced by the fluid collection device (coupled to the outlet 416) can draw air and/or gas through the

flow controller 415 and the second flow restrictor 432 and into the fluid flow path 454. Although not shown in FIG. 4, in some embodiments, the device 400 can include a vent or one-way valve configured to allow the air or gas withdrawn from the sequestration chamber 414 to be vented to the atmosphere. In other embodiments, the air and/or gas can be transferred to the fluid collection device, which in turn, can directly or indirectly allow the air or gas to be vented. Thus, the negative pressure within and/or produced by the fluid collection device can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 414.

[0126] The negative pressure within the sequestration chamber 414 can be operable in drawing an initial flow of bodily fluid from the inlet 412, through the fluid flow path 413 and the first junction 417, and into the sequestration chamber 414 when the control device 400 is in the first or initial state. In some instances, it may be desirable to modulate and/or control a magnitude of the negative pressure differential by any suitable means such as those described herein, including manipulating the permissibility and/or permeability of flow restrictors 431 and/or 432 and/or the flow controller 415. In some embodiments, the flow restrictors 431 and/or 432 can be configured to have one or more external actuators, controllers, and/or adjusters configured to control the amount of flow through the flow restrictors 431 and/or 432 (e.g., by altering or adjusting an inner diameter of the flow restrictors 431 and/or 432). In some other embodiments, the flow restrictors 431 and/or 432 can be configured to adjust and/or alter their properties of permitting fluid flow therethrough based on time, interaction with one or more fluids, and/or any other suitable parameter. In some embodiments, the structure of the flow restrictors 431 and/or 432 can be manipulated (e.g., squeezed, squished, pinched, compressed, etc.) to modulate the degree of negative pressure.

[0127] In some embodiments, modulating and/or controlling a magnitude of the pressure to which the sequestration chamber 414 is exposed can, in turn, modulate a magnitude of pressure (i.e., negative pressure) exerted on the bodily fluid and/or within a vein of a patient. In some instances, such pressure modulation can reduce, for example, hemolysis of a blood sample and/or a likelihood of collapsing a vein. In some instances, the ability to modulate and/or control an amount or magnitude of negative pressure can allow the control device 400 to be used across a large spectrum of patients that may have physiological challenges whereby negative pressure is often needed to facilitate collection of bodily fluid such as, for example, blood but not so much pressure that a rapid force flattens, collapses, caves-in, and/or otherwise inhibits patency and ability to collect blood, as described above.

[0128] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control devices 100, 200, and/or 300. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 415. In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition the flow controller 415 to a second state (e.g., a saturated or fully wetted state or a sealed state), in which the flow controller 415 is placed in a sealed state and/or configuration. In some embodiments, transitioning the flow controller 415 to the second state sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents a flow of air, gas, and/or liquid (e.g., bodily fluid) through the flow controller 415.

[0129] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 414, the control device 400 can be in and/or can be placed in its second state or operating mode to sequester, segregate, retain, contain, isolate, etc. the initial volume in the sequestration chamber 414. As described above, the flow controller 415 in its second state or sealed state substantially prevents a flow of fluid including air and liquid therethrough (e.g., and into the second flow restrictor 432 and/or fluid flow path 454). Therefore, the sequestration chamber 414 is fluidically isolated from the fluid collection device and/or source of negative pressure, which in turn, can allow a pressure differential between the sequestration chamber 414 and, for example, the inlet 412 to equalize such that the flow of bodily fluid to the sequestration chamber 414 is limited and/or substantially stops.

[0130] As described previously, an amount of negative pressure sufficient to induce and/or allow a flow of fluid through the first flow restrictor 431 can be greater than an amount of negative pressure sufficient to induce and/or allow a flow of fluid through the second flow restrictor 432. In this embodiment, the arrangement of the control device 400 is such that when the flow controller 415 is placed in the second or sealed configuration, at least a portion of the negative pressure otherwise being exerted through the flow controller 415 builds and/or increases within the fluid flow path 454 to an extent sufficient to induce and/or allow a flow of fluid through the first flow restrictor 431. Thus, with the device 400 in its second state, the negative pressure exerted by the fluid collection device and/or negative pressure source can result in negative pressure within the fluid flow path 454 sufficient to allow bodily fluid to flow from the inlet 412, through the first flow restrictor 431, the fluid flow path 454, and the outlet 416, and into the fluid collection device. As described above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture

event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 414. Moreover, as described for devices 100, 200, 300, in some embodiments, the arrangement of the fluid control device 400 can be such that the device cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 414.

[0131] While the flow restrictors 431 and 432 are particularly described above with reference to FIG. 4, in other embodiments, a fluid control device can include other forms of flow controllers and/or restrictors in addition to and/or instead of those described in association with device 400. In some embodiments, a fluid control device can include any other suitable means or combination of means for controlling fluid flow therethrough. For example, FIGS. 5-7 illustrate three different embodiments of flow controllers and/or flow restrictors, each according to a different embodiment. FIG. 5 shows a flow restrictor 433 defining an orifice or channel for the passage of air and/or fluid. In this embodiment, the fluid restrictor 433 can have a relatively large inner diameter and a relatively long length. FIG. 6, on the other hand, shows a flow restrictor 434 defining an orifice or channel having a relatively small inner diameter (e.g., smaller than the inner diameter of the flow restrictor 433) and a relatively short length (e.g., shorter than the length of the flow restrictor 433).

[0132] As will be understood, adjusting a length and/or diameter of an orifice or channel of a flow restrictor can allow for an adjusting of a magnitude of a pressure differential sufficient to induce and/or result in a flow of fluid (e.g., bodily fluid) through the orifice or channel. For example, in some embodiments, a flow restriction and/or a restricted flow path can have a diameter of about 1.0 micrometers (μm), about 10.0 μm, about 100.0 μm, about 1000.0 μm, about 10,000.0 μm, about 100,000.0 μm, and/or any suitable diameter therebetween. In other embodiments, the restricted flow path can have a diameter smaller than 1.0 μm or larger than 100,000.0 μm. In such embodiments, a restricted flow path having a smaller diameter may be designed such that a magnitude of a pressure (e.g., negative pressure) sufficient to induce or draw a flow of fluid through the restricted flow path is greater than a magnitude of a pressure sufficient to induce or draw a flow of fluid through a restricted flow path having a larger diameter. Similarly, a longer restricted flow path may be designed such that a magnitude of a pressure (e.g., negative pressure) sufficient to induce or draw a flow of fluid through the restricted flow path is greater than a magnitude of a pressure sufficient to induce or draw a flow of fluid through a restricted flow path having a shorter length.

[0133] FIG. 7 shows a flow controller 435 including a porous material 436 disposed within the flow controller 435. In such embodiments, a porosity and/or permeability of the porous material 436 can be adjusted to adjust a magnitude of a pressure differential sufficient to induce and/or result in a flow of fluid (e.g., bodily fluid) through the orifice or channel. Other examples of flow restrictors and/or flow controllers can include but are not limited to, flow controllers where the restricted or restrictive regions include regions with varying diameter of the cross-section permitting fluid flow or include structures (e.g., porous material) designed to selectively allow or deter fluid flow or air flow as desired. Other embodiments can include, for example, valves, actuators, selectively permeable membranes and/or materials, and/or the like.

[0134] FIGS. 8-10 illustrate a fluid control device 500 according to an embodiment. FIG. 8 shows, for example, a top view of the device 500 and FIGS. 9 and 10 each show a cross-sectional view of the device 500, in a first state and a second state, respectively. The fluid control device 500 can be similar in at least form and/or function to any of the fluid control devices 100, 200, 300, and/or 400. Accordingly, portions of the fluid control device 500 that can be similar to portions of the fluid control devices 100, 200, 300, and/or 400 are not described in further detail herein.

[0135] As shown in FIGS. 8-10, the fluid control device 500 (also referred to herein as "control device" or "device") includes an inlet 512 and an outlet 516, and a sequestration chamber 514. As described above with reference to the control devices 100, 200, 300, and/or 400, the inlet 512 is configured to be placed in fluid communication with a bodily fluid source to receive a fluid of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like). The outlet 516 is configured to be fluidically coupled to a fluid collection device (not illustrated). The inlet 512, the outlet 516, and the fluid collection device can be substantially similar to those described above and thus, are not described in further detail herein.

[0136] As described above, the control device 500 is configured to (1) receive an initial flow and/or volume of bodily fluid via the inlet 512 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within the sequestration chamber 514. The device 500 can be any suitable shape, size, and/or configuration. In some embodiments, the device 500 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 514. For example, in the embodiment shown in FIGS. 8-10, the device 500 can be arranged in and/or

can have a substantially "inline" configuration in which portions of the device 500 are at least partially aligned.

[0137] The device 500 includes and/or defines one or more fluid flow paths 513 between the inlet 512 and at least the sequestration chamber 514 and/or one or more fluid flow paths 554 between the inlet 512 and the outlet 516. In some embodiments, the device 500 can include a first portion 524 and a second portion 525. As shown in FIGS. 9 and 10, in some embodiments, the second portion 525 can be, for example, a bypass and/or diversion portion that is physically coupled to and selectively in fluid communication with the first portion 524. Moreover, the device 500 includes and/or forms a junction 517 at a position where each of a first end (e.g., an inlet end) of the first portion 524 and a first end (e.g., an inlet end) of the second portion 525 couple to the inlet 512. In some embodiments, the first portion 524 and the second portion 525 can be collectively disposed in a housing or otherwise at least partially enclosed by a common structure. In other embodiments, the first portion 524 and/or the second portion 525 of the device 500 can include and/or can be formed by flexible tubing or the like having any suitable shape and/or size and being reconfigurable or movable to be placed in any suitable configuration and/or arrangement.

[0138] The sequestration chamber 514 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 514 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 114. The sequestration chamber 514 can be formed by and/or included in the second portion 525 of the device 500 and can be selectively placed in fluid communication with (1) the inlet 512 via the fluid flow path 513 and the first junction 517, and (2) the outlet 516 via the fluid flow path 554 and a flow controller 515 (described in further detail herein). In some embodiments, the sequestration chamber 514 of the device 500 can be substantially similar in form and/or function to one or more of the sequestration chambers 114, 214, 314, and/or 414. Accordingly, portions of the sequestration chamber 514 may not be described in further detail herein.

[0139] As shown in FIGS. 9 and 10, the second portion 525 of the device 500 and/or the sequestration chamber 514 specifically, can include, form, and/or define the flow controller 515 disposed on, at, or near a proximal or second end of the sequestration chamber 514. In other words, the flow controller 515 can be positioned at, on, or near an outlet or outlet portion of the sequestration chamber 514 to establish selective fluid communication between the sequestration chamber 514 and the fluid flow path 554. The flow controller 515 can be any

suitable shape, size, and/or configuration. In some embodiments, the flow controller 515 can be, for example, a membrane, a porous material, an absorbent material, a hydrophilic or hydrophobic material, a selectively permeable barrier, etc. In some embodiments, the flow controller 515 can be configured to at least temporarily allow a gas or air to transfer from the second portion 525 of the device 500 and/or the sequestration chamber 514, through the flow controller 515, and into the fluid flow path 554 and can be configured to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) between the second portion 525 and/or the sequestration chamber 514 and the fluid flow path 554. In some embodiments, the flow controller 515 can be substantially similar in at least form and/or function to the flow controllers 215, 315, and/or 415 and thus, aspects of the flow controller 515 are not described in further detail herein.

[0140] In some embodiments, the device 500 can include one or more flow controllers in addition to the flow controller 515 configured to selectively control, direct, divert, and/or manipulate fluid flow through at least a portion of the flow paths 513 and/or 554. In some embodiments, such flow controllers can be configured to selectively control a flow of fluid through the device 500 in response to, for example, an external force or actuation (e.g., manual intervention by the user), or automatically (e.g., after a period of time and/or in response to a predetermined force, pressure, flow rate, volume of fluid, saturation level, etc. For example, in this embodiment, the device 500 includes a diaphragm 576 movably disposed within the body of the device 500 and configured to at least partially define the sequestration chamber 514. In some embodiments, the diaphragm 576 can be configured to transition, flip, move, switch, deform, etc., from a first configuration or state (FIG. 9) to a second configuration or state (FIG. 10) in response to a negative pressure differential within and/or across at least a portion of the device 500 (e.g., a negative pressure differential associated with and/or resulting from the coupling of the fluid collection device to the outlet 516).

[0141] In some embodiments, the diaphragm 576 can be coupled to a piercing member 578 and configured to move through at least a portion of the device 500 in response to movement of the diaphragm 576. As shown in FIGS. 9 and 10, the device 500 includes a film, barrier, and/or frangible member 574 (referred to herein as "barrier") configured to at least temporarily isolate, separate, and/or sequester the fluid flow path 513 (e.g., an inlet fluid flow path) from the fluid flow path 554 (e.g., an outlet fluid flow path). In some embodiments, the arrangement of the diaphragm 576 and/or the piercing member 578 can be such that as the diaphragm 576 is transitioned from its first state, configuration, and/or position to its second state,

configuration, and/or position, the piercing member 578 is transitioned and/or moved through a portion of the device 500 to pierce, puncture, rupture, break, and/or otherwise reconfigure the barrier 574.

[0142] More specifically, as shown in FIG. 9, the diaphragm 576 can have, for example, a concave shape relative to the barrier 574 when in its first or initial state and the piercing member 578 coupled to the diaphragm 576 is disengaged with and/or separated from the barrier 574. As such, the barrier 574 can be in a first or initial state in which the barrier 574 is sealed, unbroken, not punctured, and/or otherwise acting to fluidically isolate the fluid flow path 513 from the fluid flow path 554. As shown in FIG. 10, the diaphragm 576 can have, for example, a convex shape relative to the barrier 574 when in its second or subsequent state and the piercing member 578 coupled to the diaphragm 576 is engaged with, in contact with, and/or otherwise reconfiguring the barrier 574, thereby piercing through and/or defining an opening through the barrier 574. In other words, as illustrated in FIGS. 9 and 10 respectively, the device 500 and/or the diaphragm 576 is configured to move between a first or initial state in which the fluid flow path 513 is fluidically isolated and/or sequestered from the fluid flow path 554 such that a flow of fluid (e.g., bodily fluid) can flow from the inlet 512, through at least a portion of the fluid flow path 513, and into the sequestration chamber 514, and a second or subsequent state in which the fluid flow path 513 is in fluid communication with the fluid flow path 554 such that a flow of fluid (e.g., bodily fluid) can flow from the inlet 512, through the barrier 574 and the fluid flow path 554, and to the outlet 516. In some embodiments, the transitioning of the device 500 and/or diaphragm 576 from the first state to the second state can be such that a volume of the device 500 defined between the diaphragm 576, the flow controller 515, and the one or more walls of the sequestration chamber 514 is increased (i.e., a volume of the sequestration chamber 514 is increased), which in turn, results in a negative pressure therein that can be operable in drawing at least a portion of the initial volume of bodily fluid through the inlet 512 and into the sequestration chamber 514, as described further below.

[0143] As described above, with respect to devices 100, 200, 300, and/or 400, the device 500 can be used to procure a bodily fluid sample having reduced contamination. For example, in some instances, the control device 500 can be in the first or initial state and a user can manipulate the device 500 to establish fluid communication between the inlet 512 and the bodily fluid source (e.g., a vein of a patient) and to establish fluid communication between the outlet 516 and the fluid collection device (e.g., a sample vessel, syringe, reservoir, etc.). With the device 500 in its initial or first state, coupling the outlet 516 to the fluid collection device

selectively exposes at least a portion of the fluid flow path 554 to the negative pressure within the fluid collection device. Moreover, when the device 500 is in its initial or first state, the flow controller 515 can be in its first state or configuration such that the flow controller 515 is permeable to a flow of air or gas but impermeable to a flow of liquid (e.g., bodily fluid). The barrier 574 is also in its first or initial state such that the barrier 574 fluidically isolates the fluid flow path 513 from the fluid flow path 554. As such, the negative pressure differential defined and/or produced by the fluid collection device results in a suction force within the fluid flow path 554, which in turn, is exerted on or through the flow controller 515. Thus, coupling the outlet 516 to the fluid collection device exposes the sequestration chamber 514 to the negative pressure defined and/or produced by the fluid collection device, thereby resulting in a negative pressure differential operable in drawing the initial volume and/or amount of bodily fluid from the bodily fluid source (e.g., the patient's vasculature), through the inlet 512, at least a portion of the fluid flow path 513, and the junction 517, and into the sequestration chamber 514. Although not shown in FIGS. 8-10, in some embodiments, the device 500 can include any suitable device and/or mechanism configured to modulate the negative pressure to which the sequestration chamber 514 is exposed, as described in detail above.

[0144] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control devices 100, 200, 300, and/or 400. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 515 (e.g., transition the flow controller 515 from its first or selectively open state to its second or sealed state). With the flow controller 515 in its second state or sealed state, the flow controller 515 substantially prevents a flow of fluid including air and liquid therethrough, thereby sequestering and/or fluidically isolating the sequestration chamber 514 from the fluid flow path 554. As a result, in some instances, a pressure differential between, for example, the sequestration chamber 514 and the inlet 512 can equalize such that the flow of bodily fluid to the sequestration chamber 514 is limited and/or substantially stops.

[0145] In this embodiment, the arrangement of the control device 500 is such that when the flow controller 515 is placed in the second or sealed configuration, at least a portion of the negative pressure otherwise being exerted through the flow controller 515 builds and/or increases within the fluid flow path 554 to an extent sufficient to transition the diaphragm 576 from its first state or configuration (FIG. 9) to its second state or configuration (FIG. 10). In some embodiments, for example, the diaphragm 576 can flip and/or can be moved from a

concave configuration relative to the barrier 574 to a convex configuration relative to the barrier 574. Moreover, as described above, the transitioning of the diaphragm 576, in turn, moves the piercing member 578 such that the piercing member 578 engages, pierces, punctures, opens, breaks, and/or otherwise reconfigures the barrier 574, thereby placing the fluid flow path 513 in fluid communication with the fluid flow path 554. Thus, with the device 500 in its second state, the negative pressure exerted by the fluid collection device and/or negative pressure source can result in negative pressure within the fluid flow path 554 sufficient to allow bodily fluid to flow from the inlet 512, through the fluid flow path 513, barrier 574, fluid flow path 554, and outlet 516, and into the fluid collection device.

[0146] As described above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 514. Moreover, as described for devices 100, 200, 300, and/or 400, in some embodiments, the arrangement of the fluid control device 500 can be such that the device cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 514.

[0147] While the flow controller 515 is shown in FIGS. 8-10 as being in fluid communication with the fluid flow path 554 without a feature, device, mechanism, and/or means to modulate an amount of negative pressure disposed therebetween, in other embodiments, a fluid control device can include any suitable feature, device, mechanism, and/or means configured to modulate an amount or magnitude of negative pressure to which a flow controller is exposed. For example, FIGS. 11 and 12 are schematic illustrations of a fluid control device 600 in a first state and a second state, respectively, according to another embodiment. The fluid control device 600 (also referred to herein as "control device" or "device") can be any suitable shape, size, and/or configuration. For example, in some embodiments, the device 600 can be substantially similar in at least form and/or function to any of the devices 100, 200, 300, 400, and/or 500 described herein. More particularly, the device 600 can be substantially similar in at least form and/or function to the device 500 described above with reference to FIGS. 8-10. Accordingly, portions and/or aspects of the fluid control device 600 are not described in further detail herein.

[0148] As shown in FIGS. 11 and 12, the device 600 includes an inlet 612, an outlet 616, and a sequestration chamber 614. In addition, the device 600 includes and/or defines one or more fluid flow paths 613 between the inlet 612 and at least the sequestration chamber 614

and/or one or more fluid flow paths 654 between the inlet 612 and the outlet 616. The inlet 612 is configured to be placed in fluid communication with a bodily fluid source to receive a fluid of bodily fluid therefrom. The outlet 616 is configured to be fluidically coupled to a fluid collection device substantially similar to those described above. The sequestration chamber 614 can be included in and/or formed by a portion of the device 600 and can be selectively placed in fluid communication with (1) the inlet 612 via the fluid flow path 613, and (2) the outlet 616 via the fluid flow path 654 and a flow controller 615. The flow controller 615 can be any suitable shape, size, and/or configuration and can be configured to selectively control, permit, allow, and/or transfer a flow of fluid therethrough. For example, as described above, the flow controller 615 can be a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid (e.g., bodily fluid). In some embodiments, the inlet 612, the outlet 616, the sequestration chamber 614, and the flow controller 615 can be substantially similar to the inlet 512, the outlet 516, the sequestration chamber 514, and the flow controller 515, respectively, described above with reference to the device 500 shown in FIGS. 8-10. Accordingly, portions and/or aspects of the inlet 612, the outlet 616, the sequestration chamber 614, and/or the flow controller 615 are not described in further detail herein.

[0149] In some embodiments, the device 600 can include a first portion 624 and a second portion 625. As shown in FIGS. 11 and 12, in some embodiments, the second portion 625 can be, for example, a bypass and/or diversion portion that (1) is physically coupled to and selectively in fluid communication with the first portion 624 and (2) includes and/or forms the sequestration chamber 614. Moreover, the device 600 includes and/or forms a junction 617 at a position where each of a first end (e.g., an inlet end) of the first portion 624 and a first end (e.g., an inlet end) of the second portion 625 couple to the inlet 612. In some embodiments, the first portion 624 and the second portion 625 can be collectively disposed in a housing or otherwise at least partially enclosed by a common structure. In other embodiments, the first portion 624 and/or the second portion 625 of the device 600 can include and/or can be formed by flexible tubing or the like having any suitable shape and/or size and being reconfigurable or movable to be placed in any suitable configuration and/or arrangement.

[0150] As described above with reference to the device 500, the device 600 includes a diaphragm 676 movably disposed within at least a portion of the device 600 and a piercing member 678 coupled to the diaphragm 676. In some embodiments, the diaphragm 676 can define at least a portion of the sequestration chamber 614. In some embodiments, the

diaphragm 676 and the piercing member 678 can be substantially similar in at least form and/or function to the diaphragm 576 and piercing member 578, respectively, of the device 500. For example, as described above with reference to the diaphragm 576 of the device 500, the diaphragm 676 is configured to transition between a first state, in which the fluid flow path 613 is fluidically isolated from the fluid flow path 654, and a second state, in which the fluid flow path 613 is in fluid communication with the fluid flow path 654, as described in further detail herein.

[0151] While the device 500 is shown and described above as including a single barrier 574 configured to selectively isolate and/or otherwise selectively prevent fluid communication between the fluid flow paths 513 and 554, in the embodiment shown in FIGS. 11 and 12, the device 600 includes a set of barriers configured to selectively prevent or selectively allow fluid flow through the device 600. For example, in some embodiments, the device 600 can include two barriers 674 and 675. Each of the barriers 674 and 675 can be substantially similar in at least form and/or function to the barrier 574 of the device 500 described above with reference to FIGS. 9 and 10. Accordingly, the arrangement of the device 600 can be such that when the diaphragm 676 is in its first state, the piercing member 678 can be disengaged and/or separated from the barriers 674 and 675, which in turn, remain in a sealed, closed, and/or substantially undeformed state (FIG. 11). As the diaphragm 676 is transitioned to its state, however, the piercing member 678 can be moved within the device 600 such that the piercing member 678 engages, contacts, pierces, punctures, and/or otherwise reconfigures each of the barriers 674 and 675, thereby transitioning the barriers 674 and 675 to an unsealed, opened, pierced, and/or deformed state (FIG. 12), as described in further detail herein.

[0152] As described above, the device 600 can include one or more features, mechanisms, devices, and/or means of modulating a negative pressure exerted through one or more portions of the device 600. For example, as shown in FIGS. 11 and 12, the device 600 includes and/or defines a restricted flow path 631 (also referred to herein as a "flow restrictor") configured to establish fluid communication between, for example, the flow controller 615 and the fluid flow path 654. As described above with reference to the flow restrictors 431 and 432 of the device 400 shown in FIG. 4, the flow restrictor 631 can be configured to define a restricted and/or limited flow path therethrough having one or more specific, desired, and/or predetermined characteristics. As described in further detail herein, the arrangement of the flow restrictor 631 can be such that when a source of negative pressure (e.g., a fluid collection device and/or the like) is coupled to the outlet 616, a negative pressure differential can result in a restricted and/or

modulated flow or suction force through the flow restrictor 631, which in turn, results in a restricted and/or modulated negative pressure being exerted on the flow controller 615. Accordingly, the flow restrictor 631 can be substantially similar in at least form and/or function to the flow restrictor 432 described above with reference to FIG. 4.

[0153] As described above with respect to devices 100, 200, 300, 400, and/or 500, the device 600 can be used to procure a bodily fluid sample having reduced contamination. For example, in some instances, the control device 600 can be in the first or initial state (see e.g., FIG. 11) and a user can manipulate the device 600 to establish fluid communication between the inlet 612 and the bodily fluid source (e.g., a vein of a patient) and to establish fluid communication between the outlet 616 and the fluid collection device (e.g., a sample vessel, syringe, reservoir, etc.). With the control device 600 in its first or initial state, coupling the outlet 616 to the fluid collection device selectively exposes at least a portion of the fluid flow path 654 to the negative pressure within the fluid collection device. When the control device 600 is in the first state, the diaphragm 676, the flow controller 615, and the barriers 674 and 675 each can be in their respective first states. Accordingly, the diaphragm 676 can be disposed in a position and/or state such that the piercing member 678 is separated and/or disengaged from the barriers 674 and 675. As such, the barriers 674 and 675 are in their first or sealed state such that the barrier 674 (e.g., a first barrier) fluidically isolates and/or sequesters the fluid flow path 613 from the flow restrictor 631 (e.g., restricted flow path) and such that the barrier 675 (e.g., a second barrier) fluidically isolates and/or sequesters the fluid flow path 613 (e.g., an inlet flow path) from the fluid flow path 654 (e.g., an outlet flow path), as shown in FIG. 11.

[0154] With the fluid collection device coupled to the outlet 616, the negative pressure within the fluid collection device can result in a negative pressure (or negative pressure differential) within at least a portion of the fluid flow path 654. As shown in FIG. 11, however, the barrier 675 fluidically isolates at least a portion of the fluid flow path 654 from other portions of the device 600 and thus, the negative pressure within the fluid flow path 654 is transferred and/or exerted through the flow restrictor 631. Accordingly, a modulated and/or desired portion of the negative pressure within and/or produced by the fluid collection device (coupled to the outlet 616) is transferred through the flow restrictor 631 and in turn, exerted on the flow controller 615. Moreover, with the flow controller 615 in its first state (e.g., a selectively permeable state), the modulated and/or desired portion of the negative pressure within and/or produced by the fluid collection device can result in a negative pressure (or

negative pressure differential) within at least a portion of the sequestration chamber 614 that is operable in drawing an initial flow of bodily fluid from the inlet 612, through at least a portion of the fluid flow path 613, and into the sequestration chamber 614, as described above with reference to, for example, the devices 100, 200, 300, 400, and/or 500.

[0155] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control devices 100, 200, 300, 400, and/or 500. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 615 (e.g., transition the flow controller 615 from its first or selectively open state to its second or sealed state). With the flow controller 615 in its second or sealed state, the flow controller 615 substantially sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents a flow of fluid (e.g., gas and liquid) through the flow controller 615, thereby sequestering and/or fluidically isolating the sequestration chamber 614 from the fluid flow path 654. As a result, in some instances, a pressure differential between, for example, the sequestration chamber 614 and the inlet 612 can equalize such that the flow of bodily fluid to the sequestration chamber 614 is limited and/or substantially stops.

[0156] As described above with reference to the device 500, the arrangement of the control device 600 is such that when the flow controller 615 is placed in its second or sealed state, at least a portion of the negative pressure otherwise being exerted through the flow controller 615 is instead exerted on a concave side or surface of the diaphragm 676. The increased negative pressure on the concave side and/or surface of the diaphragm 676 can be operable to flip, switch, and/or transition the diaphragm 676 from its first state (e.g., a concave state relative to the barrier 674) to its second state (e.g., a convex state relative to the barrier 674). In some embodiments, the flow restrictor 631 can be configured to modulate and/or regulate a magnitude or change in magnitude of the negative pressure being exerted on the diaphragm 676 in substantially the same manner as the modulation and/or regulation of the negative pressure being exerted on or through the flow controller 615. In some instances, modulating the negative pressure exerted on the diaphragm 676 can in turn, modulate, reduce, and/or control a rate at which the diaphragm 676 is transitioned from its first state to its second state.

[0157] As described above, the transitioning of the diaphragm 676, in turn, moves the piercing member 678 coupled thereto such that the piercing member 678 engages, pierces, punctures, opens, breaks, and/or otherwise reconfigures each of the barriers 674 and 675 such that each barrier 674 and 675 is placed in an open state and/or otherwise defines an opening

through which fluid can flow. In other embodiments, the barrier 674 can be configured to form a substantially fluid tight seal with an outer surface of the piercing member 678 as the piercing member 678 extends therethrough. Moreover, as described above with reference to the device 500, the opening of the barrier 675 places the fluid flow path 613 in fluid communication with the fluid flow path 654. As such, the device 600 can be in and/or can be placed in its second state, and the negative pressure exerted by the fluid collection device and/or negative pressure source can result in negative pressure within the fluid flow path 654 sufficient to allow bodily fluid to flow from the inlet 612, through the fluid flow path 613, barrier 675, fluid flow path 654, and outlet 616, and into the fluid collection device (not shown). As described above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 614. Moreover, as described for devices 100, 200, 300, 400, and/or 500, in some embodiments, the arrangement of the fluid control device 600 can be such that the device cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 614.

[0158] While the device 600 is described above as including the piercing member 678 that pierces the barrier 675 to place the device 600 in the second state, in other embodiments, a device can include any suitable member configured to transition any suitable barrier. For example, FIGS. 13 and 14 illustrate a device 700 according to an embodiment. The device 700 can be substantially similar to the device 600 and thus, similar portions are not described in further detail herein. The device 700 (FIGS. 13 and 14) can differ from the device 600 (FIGS. 11 and 12), however, by including a diaphragm 776 that includes and/or that is coupled to a rod, a pusher, a plunger, an actuator, and/or the like (referred to herein for simplicity as an "actuator"). Moreover, rather than including the barriers 674 and 675 that are configured to be pierced, as described above with reference to the device 600), the device 700 includes barriers 774 and 775 that can have any suitable shape, size, and/or configuration and that can be transitioned, in some instances, in any suitable manner. For example, the barrier 774 can be configured and/or otherwise disposed to form a substantially fluid tight seal with one or more inner surfaces of the device 700 and with one or more outer surfaces of the actuator 778. In this manner, the barrier 774 can limit and/or substantially prevent bodily fluid from undesirably flowing out of a fluid flow path 754 and into other portions of the device 700 (e.g., in a manner similar to that described above with reference to the barrier 674).

[0159] As shown in FIG. 13, when the device 700 is in a first state, the diaphragm 776 can be in a first state (e.g., a non-flipped, unactuated, and/or initial state). Similarly, the actuator 778 coupled to the diaphragm 776 and the barrier 775 can be in a first or initial state. As described in detail above with reference to the device 600, when the barrier 775 is in the first state, a flow path 713 of the device 700 (e.g., an inlet flow path or the like) can be sequestered from the flow path 754 (e.g., an outlet flow path or the like). In other words, the barrier 775 (e.g., a flow controller) can be configured to sequester the flow path 713 from the flow path 754. Thus, when a negative pressure is generated within a portion of the device 700 (e.g., in response to coupling a fluid collection device to an outlet of the device 700), an initial volume of bodily fluid can flow into a sequestration chamber of the device 700 (e.g., a sequestration portion of the device 700, a sequestration flow path, a sequestration reservoir or container, etc.), as described in detail above with reference to the device 600.

[0160] After the initial volume of bodily fluid is received in the sequestration chamber, the arrangement of the device 700 can be such that the diaphragm 776 flips, actuates, moves, and/or otherwise transitions from the first state (FIG. 13) to a second state (FIG. 14). As described in detail above, the movement of the diaphragm can result in a similar movement of the actuator 778 such that the actuator 778 is placed in contact with and moves and/or otherwise transitions the barrier 775 within the device 700. For example, as shown in FIG. 14, the actuator 778 can move the barrier 775 in a substantially linear motion from a first position to a second position, which in turn, can be a position in which the barrier 775 no longer sequesters the flow path 713 from the flow path 754. Thus, a subsequent volume of bodily fluid that is substantially free of contaminants can flow through the device 700 and into the fluid collection device coupled thereto. In this manner, the device 700 can be substantially similar in at least form and/or function to the device 600 and thus, is not described in further detail herein.

[0161] Referring now to FIG. 15, a flowchart is shown illustrating a method 10 of using a fluid control device, such as those described herein, to divert an initial volume of bodily fluid to procure bodily fluid samples with reduced contamination, according to an embodiment. The fluid control device (also referred to herein as "control device") can be similar to and/or substantially the same as any of the control devices 100, 200, 300, 400, 500, 600, and/or 700 described herein.

[0162] The method 10 includes establishing fluid communication between a bodily fluid source and an inlet of the control device, at 11. In some instances, for example, the bodily fluid source can be a fluid source within a patient's body. More specifically, in some instances, the

bodily fluid source can be a vein and/or vascular structure in the patient's body. As described above, the control device can be configured to couple to and/or include an inlet device such as, for example, an intravenous catheter, a butterfly needle, and/or the like. In other embodiments, the inlet device can be any suitable coupler, port, etc. configured to fluidically couple to the bodily fluid source. As such, the inlet device can be manipulated to establish fluid communication between the bodily fluid source and the fluid control device, as described in detail above.

[0163] Having established fluid communication with the bodily fluid source, an initial volume of bodily fluid is transferred from the bodily fluid source to a sequestration chamber included in and/or defined by the control device when the control device is in a first state, at 12. In some embodiments, the control device or a portion thereof (e.g., the sequestration chamber, a junction, an actuator, a flow controller, etc.) is in a first state and/or configuration prior to use. As such, establishing fluid communication with the bodily fluid source automatically establishes fluid communication with the sequestration chamber. More particularly, in some embodiments, a flow controller such as, for example, a valve, a flow restrictor, a selectively permeable member, and/or the like can be in a first state and/or configuration such a flow of at least a gas can pass and/or can be conveyed therethrough.

[0164] As described in detail herein, the initial volume can be any suitable volume of bodily fluid. For example, in some instances, the initial volume can be as small as one drop of bodily fluid (or a relatively few drops of bodily fluid). In other instances, the initial volume can be, for example, up to about 30 mL, 40 mL, 50 mL, or more. Moreover, as described in detail above with reference to specific embodiments, the initial volume can be at least partially based on and/or can be associated with an amount of bodily fluid that can be contained and/or sequestered in the sequestration chamber. In some instances, the initial volume can be at least partially based on and/or associated with a desired amount of fluid sufficient to transition the control device from an initial or first state to a subsequent or second state, using a negative pressure differential defined and/or produced by a negative pressure source coupled to the outlet of the fluid control device. In some instances, the initial volume can be at least partially based on and/or associated with a desired amount of fluid sufficient to transition one or more flow controllers included in the fluid control device from its/their first state to its/their second state. For example, in some instances one or more flow controllers can be driven and/or transitioned by a pressure differential, a predetermined and/or desired fluid volume, a fluid contact, the passage of predetermined and/or desired time, and/or the like, as described herein.

In some instances, the initial volume can be a volume that is sufficient to entrain and/or contain substantially all the undesired microbes that may have been dislodged and/or the like as the fluid communication was being established between the bodily fluid source and the inlet device.

[0165] In response to the initial volume of bodily fluid being disposed in the sequestration chamber, the control device is transitioned (e.g., automatically, passively, or in response to an actuation) from the first state to the second state to sequester the initial volume of bodily fluid in the sequestration chamber, at 13. In some embodiments, for example, the initial volume of bodily fluid can fill the sequestration chamber such that any additional volume of bodily fluid is substantially prevented from entering and/or being contained in the sequestration chamber. In such embodiments, the filled sequestration chamber can form, for example, a fluid lock or the like that substantially prevents additional amounts of bodily fluid from entering the sequestration chamber and/or that substantially prevents bodily fluid from exiting the sequestration chamber. In some embodiments, the sequestration chamber can include a membrane or material interacting with the bodily fluid (e.g., a semi-permeable membrane or the like such as described above with reference to the control devices 100, 200, 300, 400, 500, 600, and/or 700). In some embodiments, the sequestration chamber and/or device can include one or more flow controllers that can be activated (e.g., diaphragms as described with reference to control device 500, 600, and/or 700, and/or any other suitable flow controller) that are activated using any suitable mechanism to draw, divert, and/or sequester bodily fluid. For example, such flow controllers can use a change in a pressure differential (e.g., a pressure differential that can occur when portions of the flow path are sealed and/or closed off from interacting with bodily fluid), as described with reference to control device 500, 600, and/or 700, or can be user activated or activated on the basis of other variables like time, gravity, or the like.

[0166] In some instances, two or more of these mechanisms can be used in combination. For example, in some embodiments, the diversion and/or sequestration of bodily fluid can be carried out using passive mechanisms (e.g., based on one or more pressure differentials and/or filling of the sequestration chamber). In other embodiments, the diversion and sequestration or fluid can also result from one or more active methods such as, for example, one or more actuators operated with or without user intervention. In some embodiments, one or more user mediated mechanisms, actuators, controllers, etc. can be included to provide additional control functions such as, for example, a supervisory or safety override function that may be used in

certain settings such as, for example, during training of personnel on the use of the control devices. In other embodiments, the sequestration chamber can retain and/or sequester the initial volume of bodily fluid in any suitable manner such as those described herein and/or any suitable combination(s) thereof.

[0167] With the control device being transitioned to the second state (e.g., passively or through user intervention), a subsequent volume of bodily fluid is transferred from the bodily fluid source to a fluid collection device (e.g., any of those described herein) in fluid communication with the control device, at 14. As described in detail above, the sequestering of the initial volume of bodily fluid in the sequestration chamber can be operable to sequester any contaminants contained in the initial volume of bodily fluid in the sequestration chamber. Accordingly, the subsequent volume of bodily fluid transferred to the fluid collection device is substantially free of contaminants.

[0168] Referring now to FIG. 16, a flowchart is shown illustrating a method 20 of using a fluid control device, such as those described herein, to divert an initial volume of bodily fluid to procure bodily fluid samples with reduced contamination, according to an embodiment. The fluid control device (also referred to herein as "control device") can be similar to and/or substantially the same as any of the control devices 100, 200, 300, 400, 500, 600, and/or 700 described herein. In some embodiments, for example, the fluid control device can include an inlet configured to be placed in fluid communication with a bodily fluid source and an outlet configured to be coupled to a fluid collection device. Moreover, the fluid control device can include a sequestration portion that is in fluid communication with the inlet and a sampling portion that is in fluid communication with the outlet.

[0169] The method 20 includes coupling a fluid collection device to the outlet of the fluid control device, at 21. The fluid collection device can be any of those described herein. For example, in some embodiments, the fluid collection device can be an evacuated container, sample bottle, syringe, and/or the like. Moreover, the coupling of the fluid collection device to the outlet can be such that a negative pressure differential is produced and/or generated within at least a portion of the fluid control device, as described in detail above.

[0170] A first flow controller of the fluid control device is transitioned from a first state to a second state when the negative pressure differential within the fluid control device has a first magnitude, at 22. As described above, the first flow controller can be a valve, selectively permeable material, restricted flow path, and/or the like configured to sequester the

sequestration portion of the fluid control device from the outlet when in the first state and to establish fluid communication between the sequestration portion and the outlet when in the second state, as described in detail above.

[0171] An initial volume of bodily fluid is received from the inlet of the fluid control device and into the sequestration portion of the fluid control device in response to the negative pressure differential when the first flow controller is in the second state, at 23. In some instances, for example, the inlet can be in fluid communication with a bodily fluid source such as a bodily fluid source within a patient's body (e.g., a vein and/or vascular structure in the patient's body). In some embodiments, for example, the inlet can be coupled to an inlet device such as, for example, an intravenous catheter, a butterfly needle, and/or the like, which in turn, is inserted into a portion of the patient. Thus, bodily fluid can flow from the bodily fluid source, through the inlet of the fluid control device, and into the sequestration portion.

[0172] The first flow controller is transitioned from the second state to a third state in response to the sequestration portion receiving the initial volume of bodily fluid, at 24. As described in detail herein, the initial volume can be any suitable volume such as, for example, a volume as small as one drop of bodily fluid (or a relatively few drops of bodily fluid) up to, for example, 50.0 mL or more. In some instances, the initial volume can be at least partially based on and/or associated with a desired amount of fluid sufficient to transition the first flow controller from the second state to the third state. In some instances, the initial volume can be a volume of bodily fluid that is transferred into the sequestration portion until a negative pressure differential (e.g., between the first flow controller and the inlet) is in substantial equilibrium or the like. In such instances, the first flow controller can automatically transitioned from the second state to the third state when the negative pressure differential operable to draw the initial volume of bodily fluid is in substantial equilibrium. In some embodiments, the first flow controller can include, for example, a selectively permeable material that can be saturated by at least a portion of the initial volume of bodily fluid to transition the first flow controller from the second state to the third state, as described in detail above. As such, the first flow controller can sequester the sequestration portion from the outlet when in the third state.

[0173] With the first flow controller in the third state, the negative pressure differential within a portion of the fluid control device can increase from the first magnitude to a second magnitude. When the negative pressure differential has the second magnitude, a second flow controller is transitioned from a first state to a second state, at 25. The second flow controller

can be configured to, for example, sequester the sampling portion of the fluid control device from the inlet when in the first state and is configured to establish fluid communication between the sampling portion and the inlet when in the second state. As described above with reference to specific embodiments, the second flow controller can be any suitable control device or mechanism such as, for example, a valve, a selectively permeable material, a restricted flow path, a dissolvable material, a frangible barrier, a movable barrier, and/or the like.

[0174] As described above, a pressure differential sufficient to transition the second flow controller from the first state (e.g., a non-flow state) to the second state (e.g., a flow state) is greater than a pressure differential sufficient to transition the first flow controller from the first state (e.g., a non-flow state) to the second state (e.g., a flow state). As such, the second flow controller can be configured to transition to the second state after the first flow controller has transitioned between its first, second, and third states. Thus, a subsequent volume of bodily fluid is transferred from the inlet to the fluid collection device via the sampling portion and the outlet, at 26. As described in detail above, receiving the initial volume of bodily fluid in the sequestration portion and sequestering the sequestration portion from the outlet can be operable to sequester any contaminants contained in the initial volume of bodily fluid in the sequestration portion of the fluid control device. Accordingly, the subsequent volume of bodily fluid transferred to the fluid collection device can have reduced contamination and/or can be substantially free of contaminants.

[0175] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Where schematics and/or embodiments described above indicate certain components arranged in certain orientations or positions, the arrangement of components may be modified. While the embodiments have been particularly shown and described, it will be understood that various changes in form and details may be made. For example, while the control devices 100, 200, 300, 400, 500, 600, and/or 700, are described as transferring a bodily fluid into the device as a result of a negative pressure within a fluid collection device, in other embodiments, the devices described herein can be used with any suitable device configured to establish a pressure differential (e.g., a negative pressure differential). For example, in some embodiments, an outlet of a control device can be coupled to a syringe or pump. In other embodiments, a control device can include a pre-charged sequestration chamber, a vented sequestration chamber, a manually activated device configured to produce a negative pressure, an energy source, and/or

any other suitable means of defining and/or forming a pressure differential within a portion of the control device.

[0176] In some other embodiments, the source of negative pressure can be associated with but independent of the fluid collection device. For example, a source of negative pressure such as a syringe, a pump, a passive source like a gravity aided or structurally aided container, etc., can be placed downstream of the outlet of the fluid control device such that the negative pressure imparted is communicated to the fluid collection device and the outlet. For example the source of negative pressure may be in fluid communication with the outlet via the fluid collection device. In other embodiments, under some circumstances, the source of negative pressure may be placed in fluid communication with the outlet to impart the pressure differential and the outlet may then be placed in fluid communication with the collection device to collect the fluid drawn by the pressure differential imparted, as described in further detail herein.

[0177] In some embodiments, any of the fluid control devices described herein can be formed from any suitable components that can be manufactured, sterilized, and packaged as individual parts or components. In such embodiments, a user can, for example, open one or more packages containing one or more components, can assemble the components to form the fluid control device, and can use the fluid control device as described above. In other embodiments, any of the fluid control devices described herein can be formed from any suitable components that can be manufactured, sterilized, assembled, and packaged as an assembly or integrated device. In such embodiments, a user can, for example, open a packaging containing such an assembly or integrated device and can use the device as described above without further assembly of components. In some embodiments, any of the control devices can be monolithically formed in whole or at least in part.

[0178] In some embodiments, any of the control devices can be physically and/or fluidically coupled to a collection device (e.g., a sample reservoir, a syringe, a blood culture bottle, a collection vial, a fluid transfer container, and/or any other suitable reservoir, collection device, and/or transfer device) by a user prior to or during use, as described in detail above. In other embodiments, any of the control devices can be physically coupled, attached, formed, and/or otherwise mated to a fluid collection device during a manufacturing process. This can be done prior to sterilization so the collection pathway(s) and connection interface(s) (e.g., where the control device couples to the fluid collection device) maintain a closed-system,

mechanical diversion device within a sterile environment that is not subject to touch-point contamination from external sources.

[0179] In some embodiments, the pre-assembly of the control device and the collection device can be such that the user is forced first to sequester, segregate, and/or isolate at least a portion of the initial bodily fluid volume or flow prior to transferring a sample volume to the pre-assembled fluid collection device. For example, the control device can include an actuator that is configured to isolate an outlet from other portions of the control device, thereby isolating the collection device from such portions of the control device. Moreover, after transferring the initial volume of bodily fluid, the actuation of the actuator can result in sequestration of the initial volume of bodily fluid and the fluidic coupling of the outlet to additional portions of the control device (e.g., an inlet). In some embodiments, pre-assembling the control device and the collection device (e.g., during manufacturing) can, for example, force compliance with a sample procurement protocol that calls for the sequestration of an initial amount of bodily fluid prior to collecting a sample volume of bodily fluid.

[0180] In some embodiments, the coupling, mating, and/or attachment of the fluid control device to the fluid collection device (e.g., during manufacturing) can be executed such that the control device can be removed (physically decoupled, removed with a specific "key," and/or any other approach used to separate the control device from the fluid collection device) after use to allow access to the fluid collection device. After decoupling, the collection device can be placed in an incubator and/or any other type of analytical machine, and accessed for analysis and/or otherwise further processed. In some embodiments, such decoupling may be blocked, limited, and/or substantially prevented prior to use and unblocked or allowed after use. In other embodiments, the fluid control device and the fluid collection device can be permanently coupled and/or monolithically formed (at least in part) to prevent such decoupling.

[0181] Any of the embodiments described herein can be used in conjunction with any suitable fluid transfer, fluid collection, and/or fluid storage device such as, for example, the fluid reservoirs described in the '420 patent, the transfer devices described in the '510 publication, and/or the transfer adapters described in the '352 publication. In some embodiments, any of the embodiments described herein can be used in conjunction with fluid transfer, fluid collection, and/or fluid storage devices such as, for example, the devices described in U.S. Patent No. 8,535,241 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed October 12, 2012; U.S. Patent No. 9,060,724 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed May 29, 2013; U.S. Patent No. 9,155,495

entitled, "Syringe-Based Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed December 2, 2013; U.S. Patent Publication No. 2016/0361006 entitled, "Devices and Methods for Syringe Based Fluid Transfer for Bodily-Fluid Sampling," filed June 13, 2016; U.S. Patent Publication No. 2018/0140240 entitled, "Systems and Methods for Sample Collection with Reduced Hemolysis," filed November 20, 2017; and/or U.S. Patent Publication No. 2017/0065733 entitled, "Apparatus and Methods for Maintaining Sterility of a Specimen Container," filed September 6, 2016, the disclosures of each of which are incorporated herein by reference in their entireties.

[0182] While some of the embodiments described above include a flow controller that selectively establishes fluid communication between a sequestration chamber and a fluid collection device (or other source of negative pressure) in other embodiments, a control device can be arranged to transfer a flow of bodily fluid in response to negative pressure differentials resulting from any suitable portion(s) of the device. For example, while the control device 200 is described above as including the flow controllers (e.g., the membrane 215, and/or the like) that place the sequestration chamber 214 in selective fluid communication with the fluid collection device (e.g., a sample reservoir or syringe) until the membrane 215 is transitioned to a sealed or closed state (e.g., until the membrane 215 is sufficiently wetted), in other embodiments, a control device can include a sequestration chamber that is a pre-sealed, evacuated, and/or pre-charged chamber such that establishing fluid communication between an inlet and the sequestration chamber results in a negative pressure differential that is sufficient to draw an initial volume of bodily fluid into the sequestration chamber. In such embodiments, the control device can be configured to transfer bodily fluid to the sequestration chamber until the pressure differential is sufficiently reduced and/or until pressures otherwise substantially equalize. Moreover, in some such embodiments, the sequestration chamber and/or the inlet can include a coupler, an actuator, a needle, a septum, a port, and/or any other suitable member that can establish fluid communication therebetween (e.g., that can transition the sequestration chamber from a sealed to an unsealed configuration).

[0183] While the embodiments have been described above as including particular means for modulating and/or controlling a magnitude of negative pressure applied on or through at least a portion of the device(s), in other embodiments, a control device can include any suitable feature, mechanism, and/or device configured to modulate, create, and/or otherwise control one or more pressure differentials through at least a portion of the control device. For example, in some embodiments, a user can transition and/or move an actuator to change (e.g., reduce or

increase) the size of one or more portions of a fluid flow path or fluid flow interface within a portion of the control device to manually modulate and/or otherwise control an amount or magnitude of negative pressure within one or more portions of a control device.

[0184] By way of another example, any of the embodiments described herein can include any suitable actuator and/or flow controller configured to selectively control fluid flow through at least a portion of the device. Specifically, a flow controller or the like can be one or more of a selectively permeable material or membrane, a valve, a diaphragm, and/or any other suitable flow controller. While some of the embodiments have been described as including an actuator rod configured to be transitioned from a first configuration or position to a second configuration or position, in other embodiments, any actuator described herein can include an actuator rod configured to transition from between a first position and second position to at least temporarily isolate an outlet from of the device from one or more other portions of the device. In some embodiments, such an actuator can be configured for use with a given and/or predetermined collection device such as, for example, a syringe. In other embodiments, such an actuator can be used with any suitable collection device.

[0185] While the embodiments have been described above as including or coupling to an inlet device such as a needle or the like that is configured to puncture the skin of a patient to place the lumen of the needle in fluid communication with a vein in the patient, in other embodiments, a fluid control device can include and/or can couple to any suitable inlet device. For example, in some embodiments, an inlet device can include a trocar or the like and a catheter. The trocar is configured to puncture the skin of a patient and then configured to be withdrawn from the patient, leaving the catheter of the inlet device placed within the patient. In other embodiments, the inlet device need not puncture the skin of a patient. For example, in some embodiments, the inlet device can include a needle or catheter that can be placed in a dish, well, sample volume, container, reservoir, etc. In still other embodiments, the inlet device can be and/or can include a coupler or port configured to couple to an indwelling needle or intravenous catheter. In other embodiments, such a coupler or port can be configured to couple to any suitable bodily fluid source (or port thereof) such as, for example, a syringe, a reservoir, a container, etc.

[0186] Accordingly, while the embodiments are described above as withdrawing and sequestering an initial volume of bodily fluid to sequester contaminants such as, for example, dermally-residing microbes, in other embodiments, the inlet device can be coupled to any suitable bodily fluid source and the control device can be configured to sequester an initial

volume of bodily fluid withdrawn from that bodily fluid source to sequester contaminants that may be present within the source and/or any an interface of the container or reservoir containing the bodily fluid. For example, in some embodiments, a needle of an inlet device can be configured to puncture a port or surface of a reservoir to place the needle in fluid communication with an interior volume of the container or device. In such embodiments, the devices described herein can be used to sequester an initial volume of bodily fluid from the bodily fluid source, which in turn, can sequester contaminants or the like that may have been present on the interface, port, or surface that was punctured. Thus, the devices and methods described herein can be used to procure bodily fluid samples having reduced contamination from any suitable bodily fluid source. Moreover, while some such contaminants are described herein as being dermally residing microbes, it should be understood that the contaminants can be any contaminant that is, for example, exterior to the bodily fluid source and/or otherwise that is or that includes any constituent component (e.g., microbe, virus, molecule, particle, element, etc.) that is otherwise foreign to the bodily fluid.

[0187] Although various embodiments have been described as having particular features, concepts, and/or combinations of components, other embodiments are possible having any combination or sub-combination of any features, concepts, and/or components from any of the embodiments described herein. For example, as described above, the device 700 includes concepts, features, and/or elements of the device 600, the device 600 includes concepts, features, and/or elements of the device 500, and the device 400 includes concepts, features, and/or elements of the devices 200 and 300. The specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. More specifically, the size and shape of the various components can be specifically selected for a desired rate and/or volume of bodily fluid flow into a fluid reservoir. Likewise, the size and/or shape of the various components can be specifically selected for a desired or intended usage. Thus, it should be understood that the size, shape, and/or arrangement of the embodiments and/or components thereof can be adapter for a given use unless the context explicitly states otherwise.

[0188] In some embodiments, the specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. More specifically, the size and shape of the various components can be specifically selected

for a desired rate and/or volume of bodily fluid flow into a fluid reservoir. Likewise, the size and/or shape of the various components can be specifically selected for a desired or intended usage. For example, in some embodiments, a device such as those described herein can be configured for use with or on seemingly healthy adult patients. In such embodiments, the device can include a sequestration chamber that has a first volume (e.g., about 0.5 ml to about 5.0 ml). In other embodiments, a device such as those described herein can be configured for use with or on, for example, very sick patients and/or pediatric patients. In such embodiments, the device can include a sequestration chamber that has a second volume that is less than the first volume (e.g., less than about 0.5 ml). Thus, it should be understood that the size, shape, and/or arrangement of the embodiments and/or components thereof can be adapted for a given use unless the context explicitly states otherwise.

[0189] Although not shown, any of the devices described herein can include an opening, port, coupler, septum, Luer-Lok, gasket, valve, threaded connecter, standard fluidic interface, etc. (referred to for simplicity as a "port") in fluid communication with the sequestration chamber. In some such embodiments, the port can be configured to couple to any suitable device, reservoir, pressure source, etc. For example, in some embodiments, the port can be configured to couple to a reservoir, which in turn, can allow a greater volume of bodily fluid to be diverted and/or transferred into the sequestration chamber. In other embodiments, the port can be coupled to a negative pressure source such as an evacuated container, a pump, a syringe, and/or the like to collect a portion of or the full volume of bodily fluid in the sequestration chamber, channel, reservoir, etc. and use that volume of bodily fluid (e.g., the pre-sample volume) for additional clinical and/or in vitro diagnostic testing purposes. In other embodiments, the port can be coupled to any suitable pressure source or infusion device configured to infuse the initial volume of bodily fluid sequestered in the sequestration chamber back into the patient and/or bodily fluid source (e.g., in the case of pediatric patients, very sick patients, patients having a low blood volume, and/or the like).

[0190] In some embodiments, the port can be configured to receive a probe, sampling tool, testing device, and/or the like that can be used to perform one or more tests (e.g., tests not sensitive to potential contamination) on the initial volume while the initial volume is disposed or sequestered in the sequestration chamber. In other embodiments, the sequestration channel, chamber, and/or reservoir can be configured with the addition of other diagnostic testing components integrated into the chamber (e.g., a paper test) such that the initial bodily fluid is used for that test. In still other embodiments, the sequestration chamber, channel, and/or

reservoir can be designed, sized and configured to be removable and compatible with testing equipment and/or specifically accessible for other types of bodily fluid tests commonly performed on patients with suspected conditions. By way of example, a patient with suspected sepsis commonly has blood samples collected for lactate testing, procalcitonin testing, and blood culture testing. All of the fluid control devices described herein can be configured such that the sequestration chamber, channel, reservoir, etc. can be removed (e.g., after receiving the initial volume of bodily fluid) and the bodily fluid contained therein can be used for these additional testing purposes before or after the subsequent sample is collected for microbial testing.

[0191] Although not shown, in some embodiments, a fluid control device can include one or more lumen, channels, flow paths, etc. configured to selectively allow for a "bypass" flow of bodily fluid, where an initial amount or volume of bodily fluid can flow from the inlet, through the lumen, cannel, flow path, etc. to bypass the sequestration chamber, and into the collection device. In some embodiments, the fluid control device can include an actuator having, for example, at least three states – a first in which bodily fluid can flow from the inlet to the sequestration chamber, a second in which bodily fluid can flow from the inlet to the outlet after the initial volume is sequestered in the sequestration chamber, and a third in which bodily fluid can flow from the inlet, through the bypass flow path, and to the outlet. In other embodiments, the control device can include a first actuator configured to transition the device between a first and second state, as described in detail above with reference to specific embodiments, and can include a second actuator configured to transition the device to a bypass configuration or the like. In still other embodiments, the control device can include any suitable device, feature, component, mechanism, actuator, controller, etc. configured to selectively place the fluid control device in a bypass configuration or state.

[0192] In some embodiments, a method of using a fluid control device employing an external negative pressure source can include the ordered steps of establishing fluid communication between a bodily fluid source (e.g., a vein of a patient or the like) and an inlet of the fluid control device. An outlet of the fluid control device is then placed in fluid communication with and/or otherwise engages a negative pressure source. Such a negative pressure source can be a sample reservoir, a syringe, an evacuated container, an intermediate transfer device, and/or the like. The fluid control device can be in a first state or operating mode when the outlet is coupled to the negative pressure source and, as such, a negative pressure differential is applied through at least a portion of the fluid control device that can be

operable to draw an initial volume of bodily fluid into a sequestration chamber of the fluid control device. Once the initial volume of bodily fluid is disposed in the sequestration chamber, the fluid control device is transitioned, either automatically or via user intervention, from the first state or operating mode to a second state or operating mode such that (1) the initial volume is sequestered in the sequestration chamber and (2) fluid communication is established between the inlet and the outlet. The sequestration of the initial volume can be such that contaminants entrained in the flow of the initial volume are likewise sequestered within the sequestration chamber. With the initial volume of bodily fluid sequestered in the sequestration chamber and with fluid communication established between the inlet and the outlet, subsequent volumes of bodily fluid that are substantially free of contamination can be collected in one or more sample reservoirs.

[0193] While the method of using the fluid control device is explicitly described as including the recited ordered steps, in other embodiments, the ordering of certain events and/or procedures in any of the methods or processes described herein may be modified and such modifications are in accordance with the variations of the invention. Additionally, certain events and/or procedures may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above. Certain steps may be partially completed or may be omitted before proceeding to subsequent steps.

[0194] For example, while the devices are described herein as transitioning from a first state to a second state in a discrete operation or the like, it should be understood that the devices described herein can be configured to automatically and/or passively transition from the first state to the second state and that such a transitioning may occur over a period of time. In other words, the transitioning from the first state to the second state may, in some instances, be relatively gradual such that as a last portion of the initial volume of bodily fluid is being transferred into the sequestration chamber, the housing begins to transition from the first state to the second state. In some instances, the rate of change when transitioning from the first state to the second state can be selectively controlled to achieve one or more desired characteristics associated with the transition. Moreover, in some such instances, the inflow of the last portion of the initial volume can limit and/or substantially prevent bodily fluid already disposed in the sequestration chamber from escaping therefrom. Accordingly, while the transitioning from the first state to the second state may occur over a given amount of time, the sequestration chamber can nonetheless sequester the volume of bodily fluid disposed therein.

What is claimed:

1. A fluid control device, comprising:

an inlet configured to be placed in fluid communication with a bodily fluid source;

an outlet configured to be placed in fluid communication with a fluid collection device, a negative pressure differential being produced between the outlet and the inlet when the outlet is placed in fluid communication with the fluid collection device;

a sequestration portion in fluid communication with the inlet, the sequestration portion including a first flow controller configured to transition from a first state in which the sequestration portion is sequestered from the outlet to a second state in which the sequestration portion is in fluid communication with the outlet when the negative pressure differential has a first magnitude; and

a sampling portion in fluid communication with the outlet, the sampling portion including a second flow controller configured to transition from a first state in which the sampling portion is sequestered from the inlet to a second state in which the sampling portion is in fluid communication with the inlet when the negative pressure differential has a second magnitude greater than the first magnitude.

2. The system of claim 1, wherein the fluid collection device is a sample bottle, the sample bottle being at least partially evacuated such that coupling the outlet to the sample bottle generates the negative pressure differential.

3. The system of claim 1, wherein the fluid collection device is a syringe that is configured to be manipulated after the outlet is coupled to the syringe to generate the negative pressure differential.

4. The system of claim 1, wherein the first flow controller is configured to transition from the first state to the second state automatically.

5. The system of claim 1, wherein the second flow controller is configured to transition from the first state to the second state automatically.

6. The system of claim 1, wherein the sequestration portion is configured to receive an initial volume of bodily fluid withdrawn from the bodily fluid source in response to the first flow controller transitioning to the second state.

7. The system of claim 6, wherein the first flow controller has a third state in which the sequestration portion is sequestered from the outlet, the first flow controller configured to transition from the second state to the third state as a result of the sequestration portion receiving the initial volume of bodily fluid.

8. The system of claim 7, wherein the first flow controller being placed in the third state results in an increase in a magnitude of the negative pressure differential within the sampling portion from the first magnitude to the second magnitude.

9. The system of claim 7, wherein the first flow controller includes a selectively permeable material, the selectively permeable material configured to (1) allow a flow of a gas and prevent a flow of bodily fluid through the selectively permeable material when in a first state and (2) prevent a flow of gas and bodily fluid through the selectively permeable material when in a second state.

10. The system of claim 9, wherein the selectively permeable material is configured to transition from the first state to the second state as a result the initial volume of bodily fluid being received in the sequestration portion, thereby placing the first flow controller in the third state.

11. A fluid control device, comprising:

a housing having an inlet configured to establish fluid communication with a bodily fluid source and an outlet configured to be coupled to a fluid collection device, the coupling of the outlet to the fluid collection device resulting in a negative pressure differential within at least a portion of the housing, the housing defining a sequestration flow path in fluid communication with the inlet and a sampling flow path in fluid communication with the outlet;

a first flow controller having a flow state in which fluid communication is established between the sequestration flow path and the outlet and a non-flow state in which the sequestration flow path is sequestered from the outlet; and

a second flow controller having a flow state in which fluid communication is established between the sampling flow path and the inlet and a non-flow state in which the sampling flow path is sequestered from the inlet,

the first flow controller configured to be in the flow state when the negative pressure differential generated by coupling the outlet to the fluid collection device has a first magnitude

such that an initial volume of bodily fluid flows through the sequestration flow path toward the first flow controller, and

the first flow controller configured to transition to the non-flow state when the initial volume of bodily fluid is received in the sequestration flow path such that (1) the sequestration flow path is sequestered from the outlet and (2) the negative pressure differential is increased to a second magnitude operable to transition the second flow controller from the non-flow state to the flow state.

12. The system of claim 11, wherein the fluid collection device is a sample bottle, the sample bottle being at least partially evacuated such that coupling the outlet to the sample bottle generates the negative pressure differential.

13. The system of claim 11, wherein the fluid collection device is a syringe that is configured to be manipulated after the outlet is coupled to the syringe to generate the negative pressure differential.

14. The system of claim 11, wherein the first flow controller is configured to transition from the first state to the second state automatically.

15. The system of claim 11, wherein the second flow controller is configured to transition from the first state to the second state automatically.

16. The system of claim 11, wherein the first flow controller is at least one of a valve, a selectively permeable material, or a restricted flow path.

17. The system of claim 16, wherein the second flow controller is at least one of a valve, a selectively permeable material, a dissolvable material, a frangible barrier, a movable barrier, or a restricted flow path.

18. The system of claim 11, wherein the first flow controller includes a selectively permeable material configured to (1) allow a flow of a gas and prevent a flow of bodily fluid through the selectively permeable material when in a first state and (2) prevent a flow of gas and bodily fluid through the selectively permeable material when in a second state.

19. The system of claim 18, wherein the selectively permeable material is configured to transition from the first state to the second state as a result of the sequestration flow path receiving the initial volume of bodily fluid, the transitioning of the selectively permeable material from the first state to the second state places the first flow controller in the non-flow state.

20. The system of claim 19, wherein the first state of the selectively permeable material is an unsaturated state and the second state of the selectively permeable material is a saturated state.

21. A method of using a fluid control device to obtain a bodily fluid sample with reduced contamination, the method comprising:

coupling a fluid collection device to an outlet of the fluid control device, the coupling of the fluid collection device to the outlet configured to produce a negative pressure differential within at least a portion of the fluid control device;

transitioning a first flow controller from a first state to a second state when the negative pressure differential has a first magnitude, the first flow controller sequestering a sequestration portion of the fluid control device from the outlet when in the first state and establishing fluid communication between the sequestration portion and the outlet when in the second state;

receiving an initial volume of bodily fluid from an inlet of the fluid control device and into the sequestration portion in response to the negative pressure differential when the first flow controller is in the second state;

transitioning the first flow controller from the second state to a third state in response to the receiving, the first flow controller sequestering the sequestration portion from the outlet when in the third state, the negative pressure differential being increased from the first magnitude to a second magnitude when the first flow controller is in the third state;

transitioning a second flow controller from a first state to a second state when the negative pressure differential has the second magnitude, the second flow controller sequestering a sampling portion of the fluid control device from the inlet when in the first state and establishing fluid communication between the sampling portion and the inlet when in the second state; and

transferring a subsequent volume of bodily fluid from the inlet to the fluid collection device via the sampling portion and the outlet.

22. The method of claim 21, wherein the transitioning of the first flow controller from the first state to the second state includes automatically transitioning the first flow controller from the first state to the second state without manual intervention.

23. The method of claim 22, wherein the transitioning of the first flow controller from the second state to the third state includes automatically transitioning the first flow controller from the first state to the second state without manual intervention.

24. The method of claim 21, wherein the transitioning of the second flow controller from the first state to the second state includes automatically transitioning the second flow controller from the first state to the second state without manual intervention.

25. The method of claim 21, wherein the first flow controller includes a selectively permeable material configured to (1) allow a flow of a gas and prevent a flow of bodily fluid through the selectively permeable material when in a first state and (2) prevent a flow of gas and bodily fluid through the selectively permeable material when in a second state,

the transitioning of the first flow controller from the second state to the third state includes the selectively permeable material being placed in its second state.

26. The method of claim 21, further comprising:

establishing fluid communication between the inlet and a bodily fluid source, wherein the initial volume of bodily fluid contains contaminants associated with the establishing of fluid communication between the inlet and the bodily fluid source.

27. The method of claim 26, wherein the initial volume of bodily fluid and the contaminants are sequestered within the sequestration portion when the first flow controller is in the third state such that the subsequent volume of bodily fluid is substantially free of contaminants.

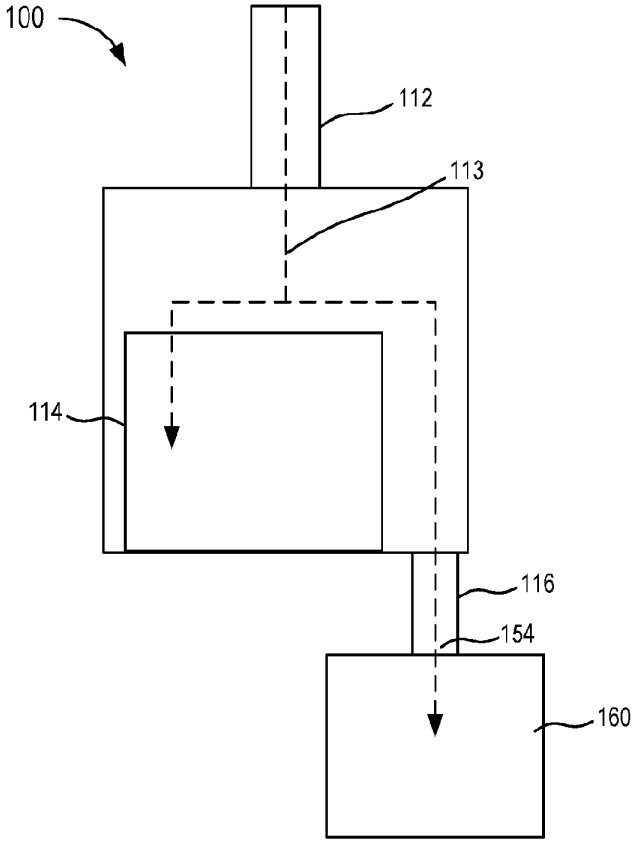


FIG. 1

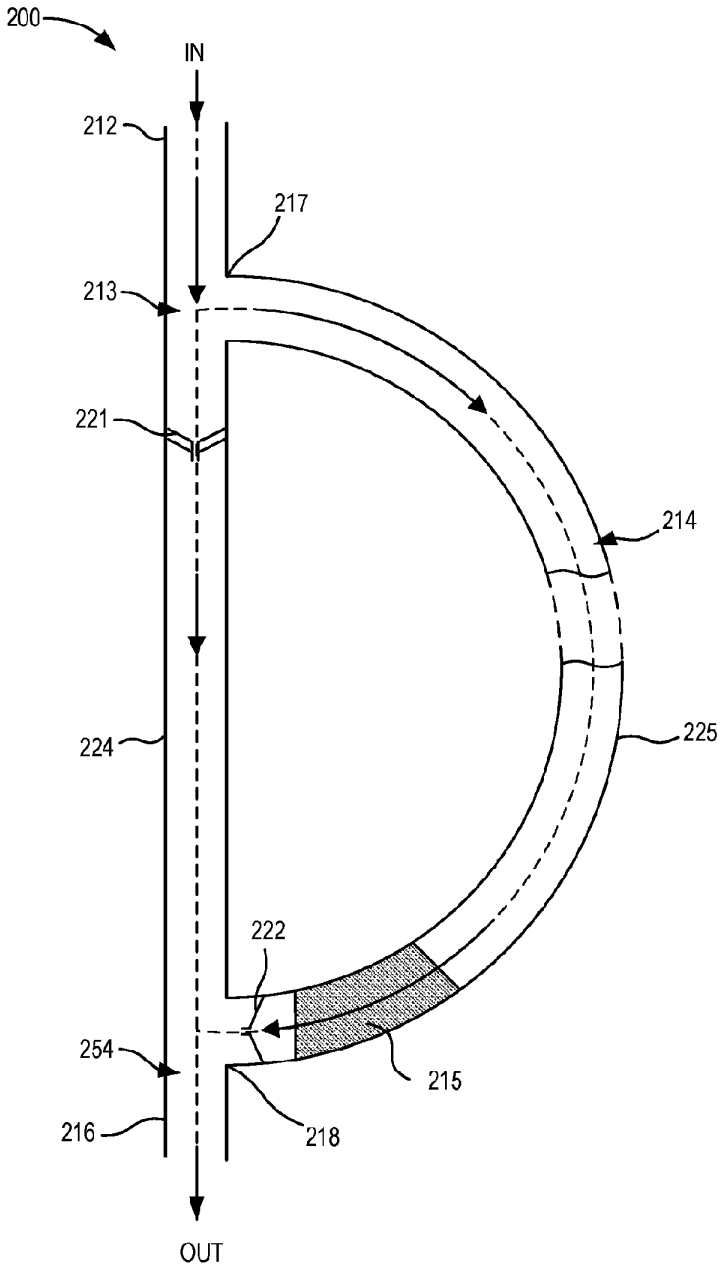


FIG. 2

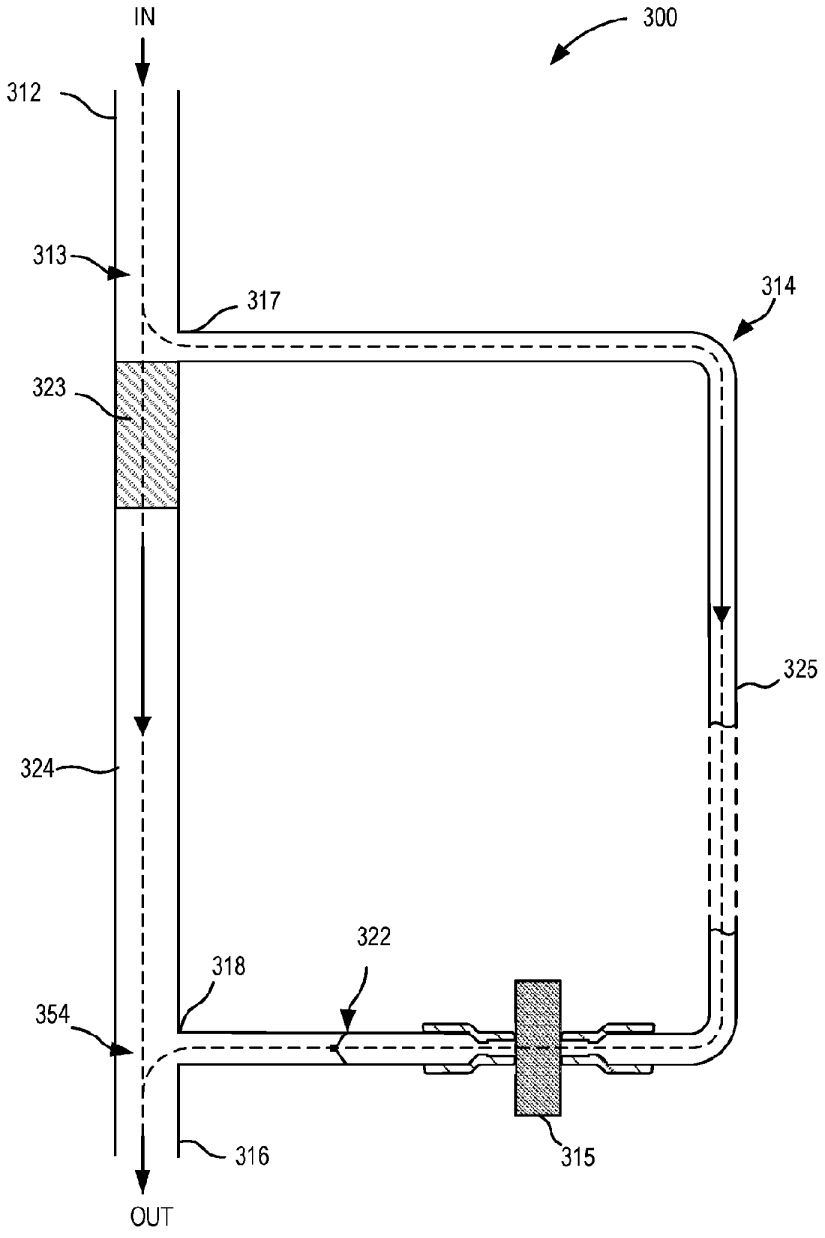


FIG. 3

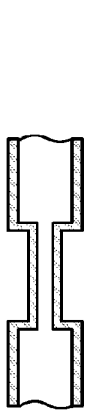


FIG. 5

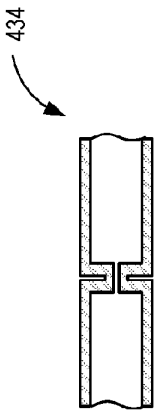


FIG. 6

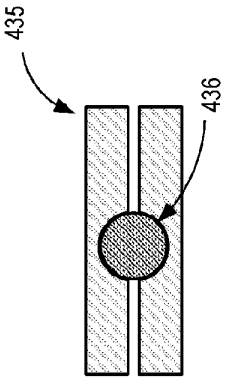


FIG. 7

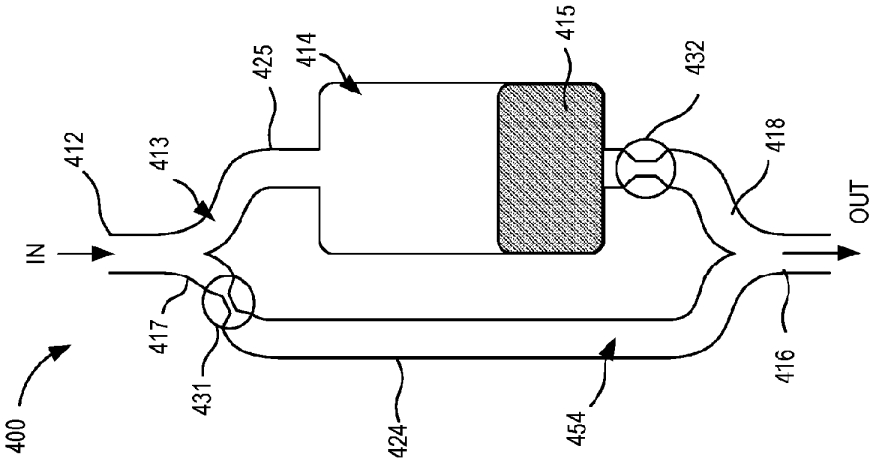


FIG. 4

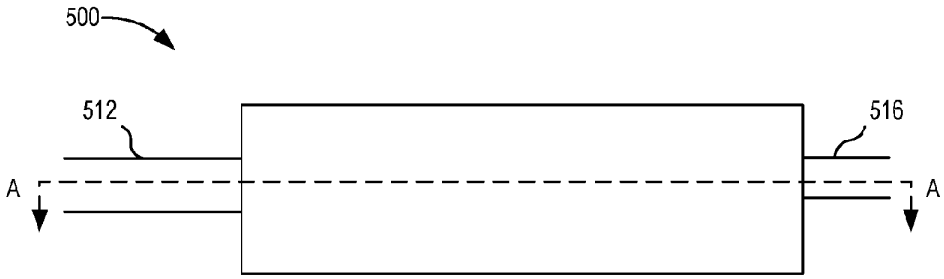


FIG. 8

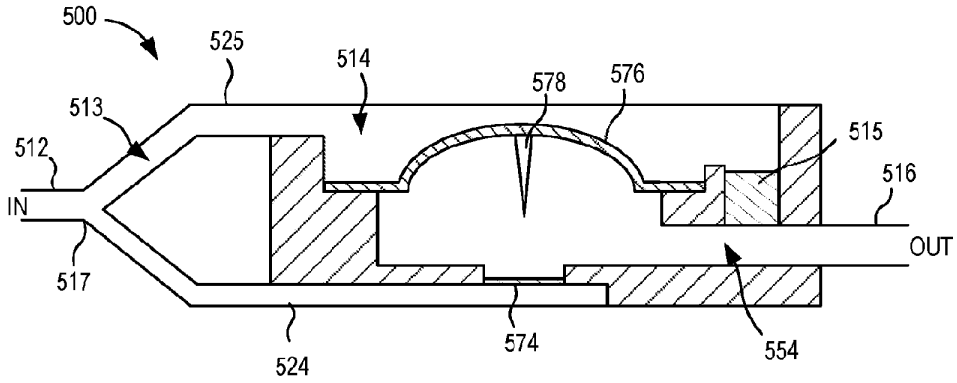


FIG. 9

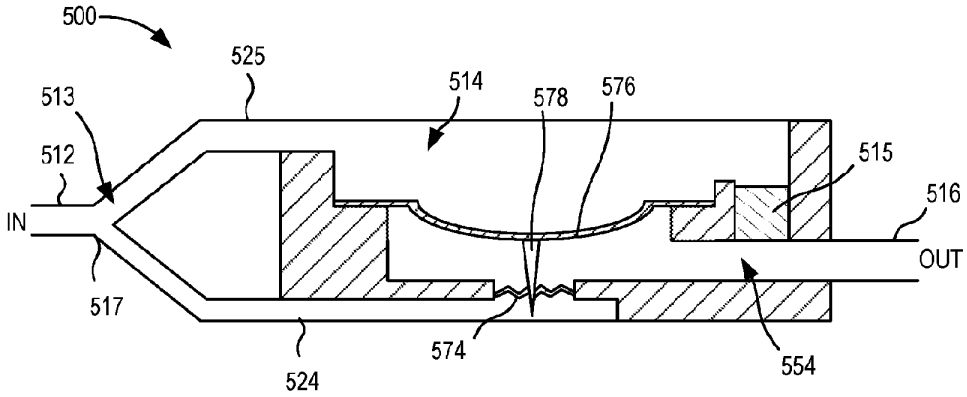


FIG. 10

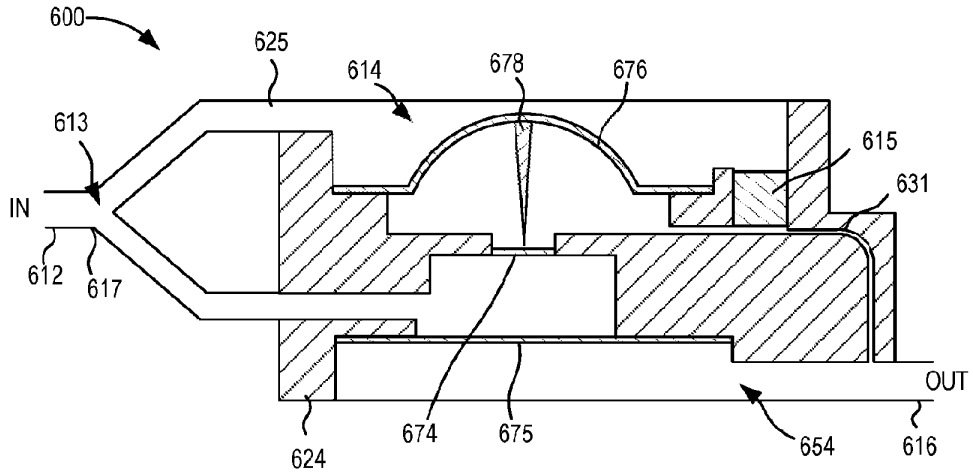

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FIG. 11

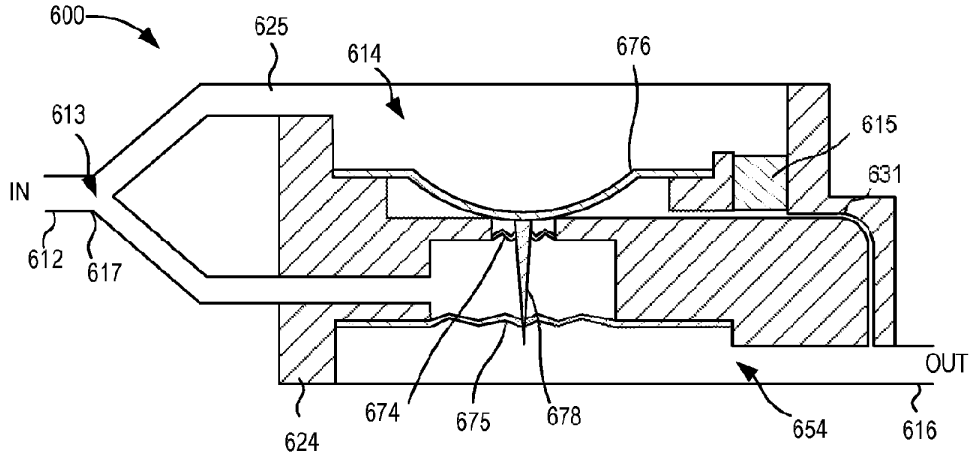

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FIG. 12

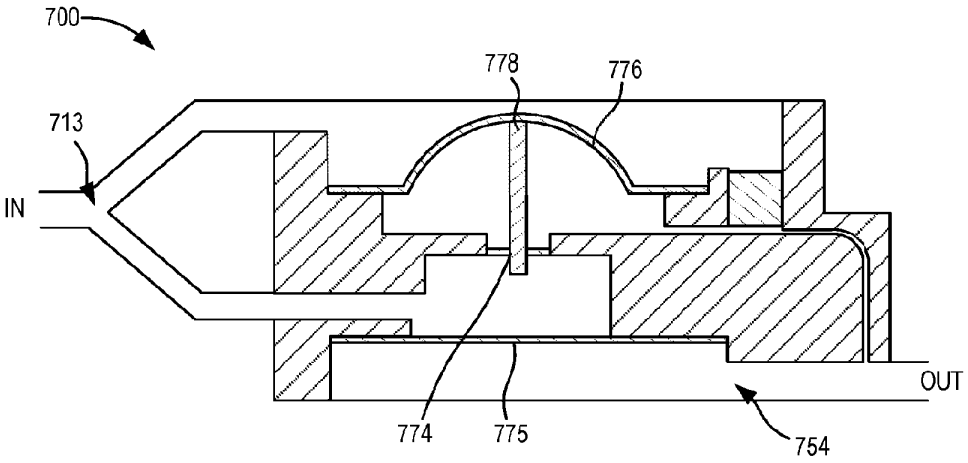

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FIG. 13

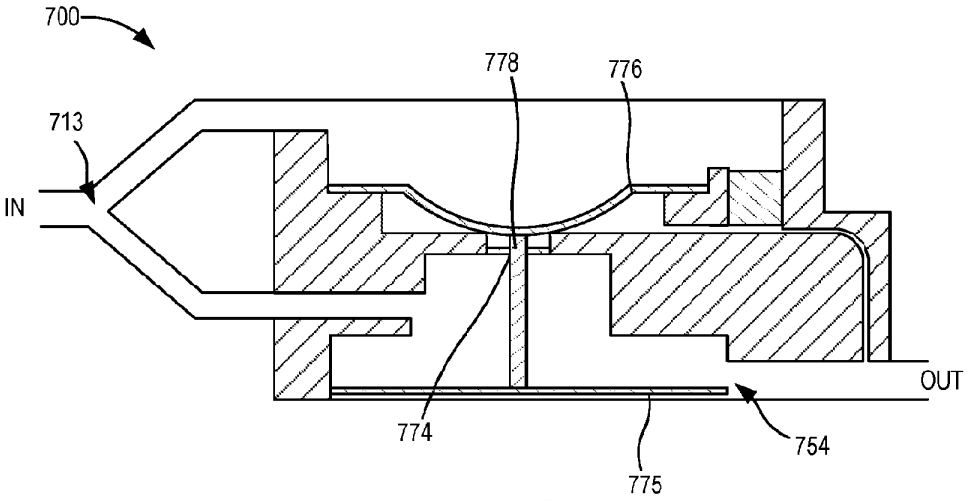

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FIG. 14

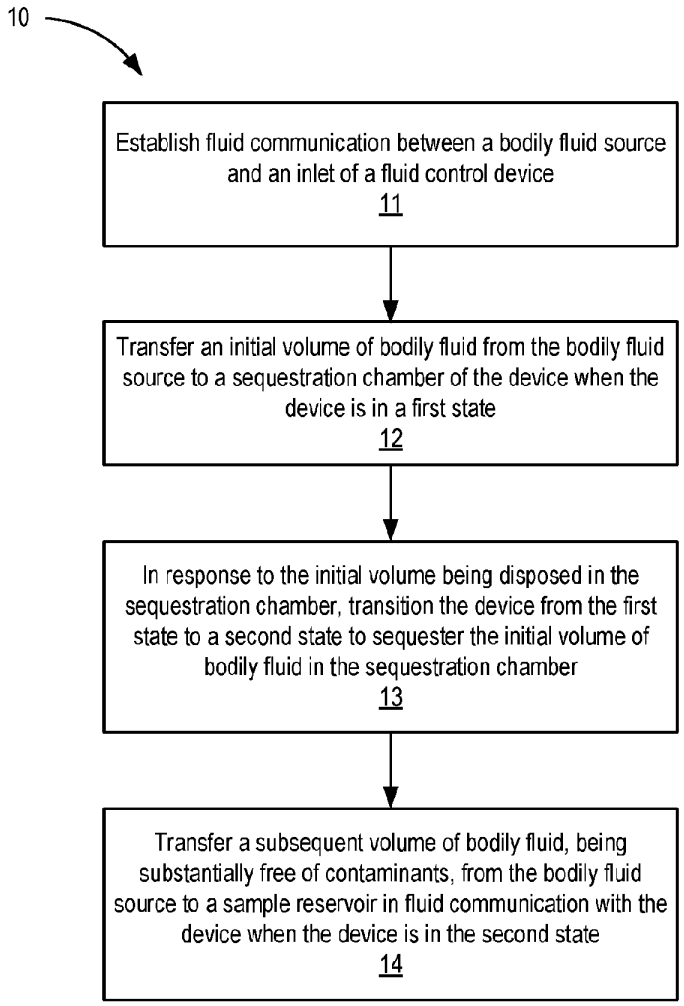

10
Establish fluid communication between a bodily fluid source and an inlet of a fluid control device
11
Transfer an initial volume of bodily fluid from the bodily fluid source to a sequestration chamber of the device when the device is in a first state
12
In response to the initial volume being disposed in the sequestration chamber, transition the device from the first state to a second state to sequester the initial volume of bodily fluid in the sequestration chamber
13
Transfer a subsequent volume of bodily fluid, being substantially free of contaminants, from the bodily fluid source to a sample reservoir in fluid communication with the device when the device is in the second state
14

FIG. 15

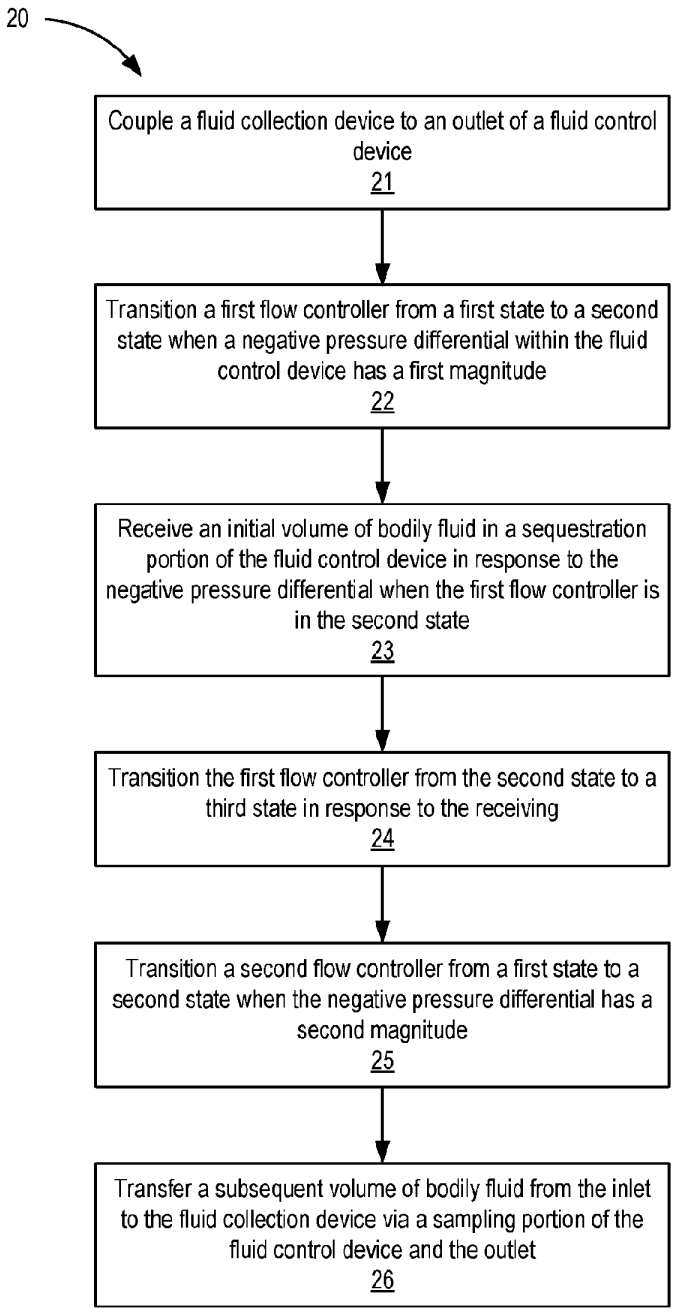

20
Couple a fluid collection device to an outlet of a fluid control device
21
Transition a first flow controller from a first state to a second state when a negative pressure differential within the fluid control device has a first magnitude
22
Receive an initial volume of bodily fluid in a sequestration portion of the fluid control device in response to the negative pressure differential when the first flow controller is in the second state
23
Transition the first flow controller from the second state to a third state in response to the receiving
24
Transition a second flow controller from a first state to a second state when the negative pressure differential has a second magnitude
25
Transfer a subsequent volume of bodily fluid from the inlet to the fluid collection device via a sampling portion of the fluid control device and the outlet
26

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/034626

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/020427 A1 (ROGERS BOBBY E [US] ET AL) 26 January 2017 (2017-01-26) paragraphs [0125], [0126] figures 23A, 23B	1-27
A	US 2016/361006 A1 (BULLINGTON GREGORY J [US] ET AL) 15 December 2016 (2016-12-15) cited in the application paragraphs [0040] - [0073] figures 1-7	1-27
A	US 2015/011910 A1 (BULLINGTON GREGORY [US] ET AL) 8 January 2015 (2015-01-08) paragraphs [0078] - [0104] figures 2-12	1-27

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2019	22/08/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schultz, Ottmar

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/034626

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/163419 A1 (BULLINGTON GREGORY J [US] ET AL) 12 June 2014 (2014-06-12) the whole document	1-27
A	US 8 535 241 B2 (BULLINGTON GREGORY [US]; PATTON RICHARD G [US] ET AL.) 17 September 2013 (2013-09-17) cited in the application the whole document	1-27

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/034626

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(54) IMPROVEMENTS IN NEEDLE ASSEMBLIES FOR USE WITH APPARATUS FOR COLLECTING SAMPLES OF BLO OD

(71) We, BECTON, DICKINSON & COMPANY, a Corporation organised and existing under a laws of the State of New Jersey, United States of America, and having a principle place of business at East Rutherford, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

In the blood sampling field, there are several well known systems. One of the commonly used systems collects blood from a vein through a needle assembly into an evacuated container. The evacuated container provides the pressure differential necessary to transfer the blood from the vein through the needle assembly into the container. The basic system and apparatus for collecting bleed in this manner is disclosed in U.S. Patent Specification No. 2,689,564 to Kleiner.

Improvements have been made in recent years to the basic evacuated container system for blood sampling such as by the provision of a valve on the assembly to automatically open and close the flow path through the assembly as the evacuated containers are coupled in succession with the assembly. In this manner, a multiplicity of samples can be collected in a multiplicity of containers with only one venapuncture being required. Needle assemblies with automatic valves are shown and described in British Patent Specification No. 1,132,197 to Nehring and U.S. Patent No. 3,494,352 to Russo et al.

Frequently the evacuated containers contain chemical materials, useful in the clinical laboratory tests to be conducted after mixing with the patient's blood. However, these chemical materials may be harmful to a patient if any were to flow from the evacuated container into the patient's blood system. This problem has been successfully eliminated by the use of a one-way valve as shown and described in our co-pending Application No. 20921/73 (Serial No. 1,378,603) filed on 2 May 1973.

In systems such as those referred to above, it has often been found that it is desirable to provide an indication means on the needle assembly to inform an operator that a venapuncture has been successfully accomplished. Consequently, it is desirable to provide a single device which includes a one-way valve for use in collecting multiple samples of blood from a single venapuncture into a multiplicity of collection containers whilst eliminating the danger of back flow of fluid into the patient and which includes a blood flow indication means which indicates that a venapuncture has successfully been accomplished so that the evacuated collection container can be coupled to the needle assembly to withdraw a blood sample from the patient.

According to our invention a needle assembly for use with apparatus for collecting blood samples from a patient has means for indicating when a venapuncture has been accomplished and then for transferring blood from the patient into an evacuated container, whilst preventing any back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing backflow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passage-way for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in com-

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munication with the evacuated container, a valve assembly mounted in the chamber and normally in an unarmed position in which passages therein permit blood to flow from the vein into the chamber upon venapuncture and being movable to an armed position in which the valve assembly forms a non-return valve and in which the passageway from the vein to the chamber is closed by means of a resilient elastomeric valve member in the chamber, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from the blood vessel to the rearward end and into the container, the valve member thereafter being responsive to an increase in pressure at the rearward end to automatically return to the closed position and thereby prevent the backflow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly.

Preferably the needle assembly also includes a second cannula which is slidably mounted in a bore in the rearward end of the housing, the second cannula having its forward end in the chamber and its rear end extending from the rear end of the housing for connection to the container.

The needle assembly may have the rear end of the first cannula extending into the chamber and have an elastomeric sleeve, having an open end and a closed end, slidably mounted on the rear end of the first cannula in sealing engagement therewith, the sleeve being movable between the unarmed position and the armed position on the first cannula, a transverse hole in the wall of the sleeve which permits communication between the rear end of the first cannula and the exterior of the sleeve when the sleeve is in the unarmed position and the hole being obscured when the sleeve is moved to the armed position, a slit in the wall of the sleeve, the slit normally being closed when the sleeve is in the armed and unarmed position but which opens automatically when there is a reduction in pressure at the rearward end as the container is coupled with the assembly and the slit thereafter automatically closing when there is an increase in pressure at the rearward end and when a predetermined pressure differential exists between the forward and reward end of the assembly, and an annular flange extending around the forward open end of the sleeve.

The invention also includes a method of transferring blood from a patient into an evacuated container whilst indicating that a venapuncture has been accomplished and preventing the back flow of fluid from the container into the patient during and after the collection of a blood sample with the use of a needle assembly having a forward end for penetration into the blood vessel of a patient, a rearward end adapted to be coupled in fluid communication with the evacuated container, a continuous passageway through the assembly, and a valve assembly including means for visually indicating a venapuncture and including a resilient elastomeric valve member on the assembly adapted to deform and open when subjected to pressure in one direction and adapted to close when the pressure in the one direction is relieved, the method comprising, inserting the forward penetrating end of the assembly into the blood vessel of a patient until the visual indicating means denotes a successful venapuncture, coupling the evacuated container to the rearward end of the needle assembly and initially shifting the resilient elastomeric valve member to an armed position in which the valve member prevents flow between the ends of the assembly and subsequently coupling the evacuated interior of the container to the passageway through the needle assembly so that the elastomeric valve is subjected to a pressure differential in one direction and automatically responds to the pressure differential to deform and open and permit blood to flow from the patient to the container, and removing the container from coupling engagement with the needle assembly after the pressure differential has been relieved so that the valve has automatically returned to the normally closed position thereby preventing flow between the ends of the needle assembly.

An example of a needle assembly in accordance with our invention will now be described with reference to the accompanying drawings in which:—

Figure 1 is a side elevation of a needle assembly attached to a holder and with an evacuated container in a position ready for coupling with the needle assembly;

Figure 2 is an enlarged fragmentary section of the apparatus shown in Figure 1 after it has been used to achieve a venapuncture prior to the initial closure of a valve member;

Figure 3 is an enlarged section of the needle assembly shown in Figure 2;

Figure 4 is a similar view to Figure 2 but showing the valve member in an armed position;

Figure 5 is an enlarged section of the needle assembly shown in Figure 4;

Figure 6 is a similar view to Figure 2 and Figure 4 but showing the evacuated container coupled to the needle assembly and the valve member in the opened position to

permit blood to flow from a vein to the container;

Figure 7 is an enlarged section of the needle assembly shown in Figure 6;

Figure 8 is a similar view to Figure 6 but showing the assembly after the container has been removed and showing a second valve member in a closed position preventing the flow of blood between the ends of the needle assembly;

Figure 9 is an enlarged section of the needle assembly shown in Figure 8; and

Figure 10 is an exploded fragmentary perspective view of the needle assembly.

The separate components of a needle assembly 20 are shown in Figure 10. The assembly includes a housing 21 which is in two parts, a forward part 22 and a rear part 23. Mounted in the forward part 22 is a cannula 24 and mounted in the rear part 23 is a second cannula 25. When the forward part 22 is engaged with the rear part 23 a chamber 26 is formed as shown in Figures 1 to 9. Housed within chamber 26 is an elastomeric sleeve 27, a rigid cage 28, a retaining disc 29, and an elastomeric sealing disc 30.

The forward part 22 has a frusto-conical surface 31 which fits into and engages with an inner cylindrical surface 32 of a tubular portion of the rear part 23. The engagement between parts 22 and 23 is tight enough to keep the parts of housing 21 together during operation of the assembly. If required, to ensure this engagement of the parts of housing 21, an epoxy resin adhesive may be employed between surfaces 31 and 32 to achieve a positive locking engagement.

A bore 33 in the forward part 22 provides communication between the space in front of the forward part 22 and the chamber 26. The cannula 24 is mounted in the bore 33 with a rear blunt end 34 extending into the chamber 26 and a forward end terminating in a tip 35 extending forward from the part 22 and fixed in the bore by an epoxy resin adhesive 51. The tip 35 is pointed to enable it to penetrate a patient's vein.

The rear part 23 of the housing 21 has a sleeve 36 for engagement with the forward part 22 and to provide the sidewalls of the chamber 26. The remainder of the part 23 is a reduced diameter cylinder having a screw thread 37 formed on its outer surface to connect the needle assembly 20 to a holder 38. The holder 38 forms a guide for an evacuated container 39. The container 39 is formed by a tube 40 which is evacuated and is closed at its open end by a self-sealing punctureable stopper 41.

The rear part 23 has an axial bore 42 providing communication between the rear end of the part 23 and chamber 26. The cannula 25 is slidably mounted in the bore 42.

The rear end of the cannula 25 extends rearwardly from the housing 21 and has a pointed tip 43 for penetration through the stopper 41 of the evacuated container 39. The cannula 25 is slidably mounted in the bore 42 and has a forward blunt end 44 extending into the chamber 26. Adjacent the forward end of the cannula 25 is a side opening 45 which is movable into and out of the chamber 26 as the cannula 25 slides through the bore 42. The elastomeric sealing disc 30 rests against a rear wall of the chamber 26 and has a central hole, the diameter of which is smaller than the external diameter of the cannula 25, so that the elastomeric sealing disc 30 maintains a seal with the external surface of the cannula 25 as it slides through the disc 30. Thus the chamber is liquid-tight so that liquid flow into and out of the chamber 26 only occurs through the cannulae 24 and 25. The sealing disc 30 is held in place by the rigid disc 29 which is a 'push fit' in the rear of the housing 21. The sealing disc 30 is sandwiched between the disc 29 and the rear wall of the housing 21. An annular bead 46 projecting from the rear wall of the housing engages with the under surface of the disc 30 to ensure a seal between the disc 30 and the rear wall of the chamber and prevent leakage from the chamber 26 through the bore 42 in the rear part 23.

The cage 28 is stuck on the end 44 of the cannula 25 with an epoxy resin adhesive 47. The cage 28 is constructed from a plastics material and it seals the open end of the end 44 of cannula 25. This means that the access from the chamber 26 into the bore of cannula 25 is solely by the side opening 45. The cage 28 is a hollow cylinder and has a closed end mounted on cannula 25 and an opposite open end. Adjacent to the closed end are four transverse side ports 48. The side ports are equi-spaced about the circumference of the cage 28. The external diameter of the cage 28 is less than the internal diameter of the housing 21 so the cage 28 is free to slide axially with the cannula 25. The hollow cage 28 receives the major portion of the sleeve 27 and there is a clearance between the cage 28 and the elastomeric sleeve 27 to enable the cage 28 to slide with respect to sleeve 27. A cylindrical rim at the open end of the cage 28 engages with a flange 50 formed at the open end of sleeve 27. The open end portion of sleeve 27 is slidably mounted on the rear, blunt end 34 of cannula 24. To achieve this the sleeve 27 has its open end expanded so that it surrounds and frictionally engages with the end 34 of the cannula 24 and seals with it. The sleeve 27 is movable to an armed position as shown in Figures 4 to 9 in contrast to its initial unarmed position as shown in Figures 2 and 3. The operational sequence of the needle assembly will be discussed in detail

below. The sleeve 27 is formed as a hollow cylinder having a closed end and an open end. As described above a flange 50 is formed about its open end and the bore 52 of the cylindrical sleeve receives the rear end 34 of the cannula 24.

Initially, in the unarmed position only the forward open end of the sleeve 27 is mounted on the cannula 24 and, rearwardly of blunt end 53 of the cannula 24, the sleeve 27 has one or more transverse holes 54 which pass from the interior to the exterior of the sleeve 27. Additionally, adjacent the rear, closed, end of the sleeve 27 is a slit 55 which is normally in the closed position due to the self-sealing elastomeric properties of the sleeve 27. Any well known elastomeric self-sealing material such as natural or synthetic rubber can be utilized for the sleeve 27.

The housing 21 and the cage 28 are made from a transparent plastics material so that the presence of blood within the chamber 26 is readily visible through them for indication purposes. The housing may not be wholly transparent, but may merely include a transparent portion and the presence of blood within the chamber 26 be observed through the transparent portion. Additionally, sleeve 27 may be constructed of a transparent elastomeric material, however, this is not generally utilized, since the blood will flow into the surrounding spaces provided and will be visible through the transparent portions of the housing during the indication procedures and this will be discussed in detail below. All of the components of the assembly with the exception of the cannula and the sleeve may be constructed of a standard low cost, transparent, plastics material or any readily available substitute.

The cannula 25 is slidable into and out of the housing 21 a predetermined distance, its travel being limited in the downward direction by the cage 28 engaging the disc 29 and in the opposite direction by the rim 49 engaging the flange 50 and pressing this against the face 57 of the part 22. The cannula 25 is moved as the evacuated tube 39 is reciprocated within holder 38 during the blood collection procedure since the cannula 25 when inserted through the stopper 41 is gripped tightly by the stopper 41 and thus caused to move by movement of the evacuated tube 39 and stopper 41.

Although slidable, the cannula 25 is continuously hermetically sealed relative to the bore 42 by the elastomeric sealing disc 30 which has been penetrated by the cannula 25.

Figure 1 shows the needle assembly ready for use having been screwed into the holder 38, the holder having the evacuated container 39 in a position ready for engagement with the assembly. The needle assembly 20 is in the initial position as shown in Figures 1 to 3, with the transverse holes 54 behind the end 34 of the cannula 24. In this manner, an open air way exists from the tip 35 of the cannula 24 through the assembly to the side opening 45 in the sliding cannula 25.

When sleeve 27 is pushed forward to encompass all of the rear portion 34 of cannula 24 so that the forward edge of flange 50 of the sleeve rests against inner wall of the housing, the cannula will be positioned so as to occlude transverse openings 54 and cannula 24 will be sealed by the sleeve 27.

Sliding cannula 25 supports valve cage 28. The tip of forward end 44 of cannula 25 is inserted into a recess in the rear end of the valve cage 28 and is sealed therein by epoxy 47 or any other common sealing means. The inner diameter of cylindrical cage 28 is substantially greater than the outer diameter of sleeve 27 so that blood or air can readily flow out of the valve sleeve 27 around the spaces between sleeve 27 and cage 28, and out through one or more of the ports 48 of cage 28.

As shown in Figure 10, portion 22 of housing 21 has a tapered exterior surface 31 which mechanically fits and supports and seals portion 32 of the cylindrical rear portion 23 of housing 21. Rear portion 23 supports sliding needle 25 which is mounted in a close sliding fit within passageway 42 through rear end portion 23. Rear end portion 23 also supports elastomeric sealing disc 30 and the retaining disc 29. Retaining disc 29 is a plastic moulded part. It may be constructed of any other common material for the purpose required. It has an outside diameter which has a push fit in a narrowed region of the inside of rear housing portion 23. In assembly of this seal, rear portion 23 is positioned vertically. Then the elastomeric sealing disc 30 is dropped inside. It is positioned to lie flat across the end of passageway 42. Then the sealing disc 29 is dropped in and stops at the narrowed portion 56 of rear end 23, then a small press or similar device is used to push disc 29 down as far as it will go. The annular bead 46 projecting from the inner surface of portion 23 bites into the elastomeric disc 30 under this pressure thereby assuring a continuous seal.

Then the cage 28 is joined to the tip of needle 25 by epoxy or any other common affixing means. Thereafter, the pointed end 43 of needle 25 is passed through the central hole of retainer disc 29 and pierces the elastomeric disc 30 and is then pushed into the position shown in Figures 1 to 3. The cylindrical member forming end portion 22 including cannula 24 is inserted into rear end portion 23 until the respective walls meet and seal. This action also inserts a partial amount of end portion 34 of cannula 24 into the open end of sleeve 27. The assembly is

then positioned for use as depicted in Figure 3.

In operation, threaded outer surface 37 of rear end 23 is screwed into the threaded receiving surface of holder 38 in a conventional manner. The evacuated container 39 is then positioned in the rear part of holder 38 in position for use. This arrangement is depicted in Figure 1 of the drawings. The operator should not couple any portion of the stopper 41 with the rear end of cannula 25 before inserting cannula 24 into the vein of a patient. In this manner, effectiveness of the blood flow indication portion of the needle assembly will be assured.

Then, as shown in Figures 2 and 3, the tip 35 of the cannula 24 is inserted into a patient's vein. Blood will start to flow from the patient's vein through the airway from the tip 35 to the side opening 45 as follows. The blood will pass through the cannula 24 and out through the transverse holes 54 in the sleeve 27. It will then flow through the space between the outside of the sleeve 27 and the inside of the cage 28 until it passes out through the ports 48 in the wall of the cage 28. The blood will then begin to fill the annular space between the outside of the cage 28 and the inside of the chamber 26. If the blood is allowed to continue to flow from the vein, it will pass through the side opening 45 in the sliding cannula 25 and out through the tip 43 of the cannula 25. The pressure in the patient's blood vessels causes the blood to flow through this series of open passageways. When blood is present in the chamber 26, it will be visible to an operator, who will be watching for this indication. The operator will then push the evacuated container 39 further into the holder 38 so that the cannula 25 penetrates through the stopper 41. The action of pushing the tube 39 into holder 38 forces the cannula 25, firstly to slide forward so that the sleeve 27 is forced further onto the end 34 of the cannula 24 until the flange 50 abuts the interior surface 57 of the housing 21 which acts as a positive stop. In this position the transverse openings 54 will be occluded by the wall of the cannula 24. The only restriction to the sliding of the cannula 25 is the friction acting between the sealing disc 30 and the external surface of the cannula 25. This friction is considerably less than the friction between the cannula 25 and the stopper 41 when the cannula 25 penetrates the stopper 41. Thus the sleeve 27 will be moved forward to its position in which it operates as a valve member before the cannula 25 enters the evacuated space in the container 29. The sleeve 27 stays in its forward position and operates as a valve member thereafter. Figures 4 and 5 show the assembly after the sleeve 27 has been transferred to its forward position just prior to the penetration of the stopper 41 by the cannula 25.

As the evacuated container 39 is pushed further into the holder 38 the cannula 25 pierces the stopper 41 and the cannula 25 enters the evacuated space within the container 39. Figures 6 and 7 show the evacuated container after the forward movement has been completed and with the cannula 25 in the interior of the tube 40. The slit 55 opens because of the large pressure differential that exists between the vacuum within the container 39 and the blood pressure within the patient's vein, thus blood flows into the tube 40 via the path shown by the arrows in Figure 7. As blood flows into the tube 40 the pressure differential across the slit 55 is reduced and eventually the slit 55 closes when a predetermined pressure differential is reached. After the tube 40 is filled with blood, and it is desired to fill one or more additional tubes, the operator pulls the container 39 out of the holder 38. In doing this, because the friction between the stopper 41 and the cannula 25 is greater than the friction between the cannula 25 and the sealing disc 30, the cannula 25 is moved rearwardly until the rear end of the cage 28 abuts the retaining disc 29 which provides a positive stop. This action is completed before the cannula 25 is pulled out of the stopper 41. In this position, the side opening 45 of the cannula 25 is behind the sealing disc 30 and is no longer in communication with the chamber 26. Therefore, no more blood can flow out of the cannula 25. However when another container is inserted this will once again force the cannula 25 and the cage 28 forward exposing the opening 45 to the chamber 26 and thus permitting blood to flow into the container when the cannula 25 has pierced the stopper on this other container. The closed position at the end of the collection of the first sample of blood and prior to the insertion of a second collection container is shown in Figures 8 and 9 of the drawings. It should be noted that the tip 35 remains in the vein thereby enabling multiple samples to be taken in a succession of collecting containers with only a single venapuncture. After the desired number of samples have been taken, the assembly is discarded.

Thus, the needle assembly 20 performs a combination of functions. It provides a one-way valve which is normally closed and alleviates the danger of the back flow during blood sampling procedures whilst at the same time providing an indication to notify the operator when a proper venapuncture has been accomplished as well as providing a multiple sampling device.

WHAT WE CLAIM IS:—

1. A needle assembly for use with appar-

atus for collecting blood samples from a patient, the needle assembly having means for indicating when a venauncture has been accomplished and then for transferring blood from the patient into an evacuated container, whilst preventing back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing backflow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passageway for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in communication with the evacuated container, a valve assembly mounted in the chamber and normally in an unarmed position in which passages therein permit blood to flow from the vein into the chamber upon venapuncture and being movable to an armed position in which the valve assembly forms a non-return valve and in which the passageway from the vein to the chamber is closed by means of a resilient elastomeric valve member in the chamber, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from the blood vessel to the rearward end and into the container, the valve member thereafter, being responsive to an increase in pressure at the rearward end to automatically return to the closed position and thereby prevent the back flow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly.

2. A needle assembly according to claim 1, in which a second cannula is slidably mounted in a bore in the rearward end of the housing, the cannula having its forward end in the chamber and its rear end extending from the rear end of the housing for connection to the container.

3. A needle assembly according to claim 2, in which an elastomeric sealing member is in sealing engagement with the external surface of the second cannula and the wall of the rear end of the housing to thereby eliminate leakage between the wall of the rear end of the housing and the second, sliding cannula.

4. A needle assembly according to claim 3, in which a retaining disc is frictionally mounted in the chamber so that the elastomeric sealing disc is sandwiched between the retaining disc and the housing, the retaining disc having a bore through which the sliding cannula passes.

5. A needle assembly according to claim 3 or claim 4, in which an annular bead projects from the inner surface of the housing into the chamber and engages with the elastomeric sealing disc to provide the seal at the rear end of the housing.

6. A needle assembly according to any one of the preceding claims, in which the rear end of the first cannula mounted in the forward penetrating end of the housing extends rearwardly into the chamber, an elastomeric sleeve having an open end and a closed end is slidably mounted on the rear end of the first cannula in sealing engagement therewith, the sleeve being movable between the unarmed position and the armed position on the cannula, a transverse hole in the wall of the sleeve which permits the communication between the rear end of the first cannula and the exterior of the sleeve when the sleeve is in the unarmed position and the hole being obscured when the sleeve is moved to the armed position, a slit in the wall of the sleeve, the slit normally being closed when the sleeve is in the armed and unarmed posision but which opens automatically when there is a reduction in pressure at the rearward end as the container is coupled with the assembly and the slit thereafter automatically closing when there is an increase in pressure at the rearward end and when there is a predetermined pressure differential between the forward and rearward end of the assembly, and an annular flange extending around the forward open end of the sleeve.

7. A needle assembly according to claim 6 when dependent on any of claims 2 to claim 5, in which a tubular hollow cage is mounted in the chamber, on the forward end of the sliding cannula and surrounding the elastomeric sleeve, the cage being in engagement with the flange on the sleeve so that moving the sliding cannula will move the cage and the engaged sleeve from the unarmed to the armed position when the cannula is moved towards the sleeve and will disengage the cage from the sleeve when the sliding cannula is moved away from the sleeve.

8. A needle assembly according to claim 7, in which there is a transverse opening in the side wall of the cage so that when the sleeve is in the unarmed position and a venapuncture is accomplished, blood will flow through the penetration cannula, through the

transverse opening in the sleeve and through the transverse opening in the cage into the chamber where its presence can be seen and this provides an indication that the venapuncture has been accomplished.

9. A needle assembly according to claim 7 or claim 8, in which the cage is mounted on the forward end of the sliding cannula to seal the end thereof and the sliding cannula has a side opening therein adjacent its forward end, the side opening being positioned within the chamber when the sliding cannula is in its forward position and outside the chamber and being sealed therefrom by the elastomeric sealing disc when the sliding cannula is in its rearmost position in which a surface on the cage engages with a surface on the housing to provide a stop and limit the further withdrawal of the sliding cannula.

10. A needle assembly according to any one of the preceding claims in which the housing is formed in two separate parts a forward end portion and a rearward end portion, the two portions being held together in frictional engagement.

11. A needle assembly according to any one of the preceding claims having a holder coupled to it, the holder being of a hollow cylindrical configuration so that, in use, it receives the evacuated container within and directs the container to couple with the needle assembly.

12. A needle assembly according to any one of claims 2 to claim 10 or claim 11 when dependent on any one of claims 2 to claim 10, having an evacuated container coupled with it, the container including a punctureable self-sealing stopper pierced by and engaged with the sliding cannula.

13. A method of transferring blood from a patient into an evacuated container whilst indicating that a venapuncture has been accomplished and preventing the back flow of fluid from the container into the patient during and after the collection of a blood sample with the use of a needle assembly having a forward end for penetration into the blood vessel of a patient, a rearward end adapted to be coupled in fluid communication with the evacuated container, a continuous passaway through the assembly, and a valve assembly including means for visually indicating a venapuncture and including a resilient elastomeric valve member in the assembly adapted to deform and open when subjected to pressure in one direction and adapted to close when the pressure in the one direction is relieved, the method comprising, inserting the forward penetrating end of the assembly into the blood vessel of a patient until the visual indicating means denotes a successful venapuncture, coupling the evacuated container to the rearward end of the needle assembly and initially shifting the resilient elastomeric valve member to an armed position in which the valve member prevents flow between the ends of the assembly and subsequently coupling the evacuated interior of the container to the passageway through the needle assembly so that the elastomeric valve is subjected to a pressure differential in the one direction and automatically responds to the pressure differential to deform and open and permit blood to flow from the patient to the container, and removing the container from coupling engagement with the needle assembly after the pressure differential has been delivered so that the valve has automatically returned to the normally closed position thereby preventing flow between the ends of the needle assembly.

14. A method according to claim 13, in which a multiplicity of evacuated containers are coupled successively with the needle assembly to thereby collect a multiplicity of successive blood samples without leakage of blood from the needle assembly and without back flow of fluid from the rear end of the assembly into the patient.

15. A needle assembly for use with apparatus for collecting blood samples from a patient, the needle assembly having means for indicating when a venapuncture has been accomplished and then transferring blood from the patient into an evacuated container, whilst preventing back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing back flow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passageway for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in communication with the evacuated container, a resilient elastomeric valve member in the chamber forming a non-return valve which closes the passageway, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from a blood vessel to the rearward end and into the container, the valve member thereafter being responsive to an increase in pressure at the rearward end to automatically return to the

closed position and thereby prevent the back flow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly, the means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container including a second valve means adapted to permit or prevent the flow of blood through the rearward end and into the evacuated container as successive containers are filled with successive blood samples.

16. A needle assembly according to claim 1 constructed substantially as described with reference to the accompanying drawings.

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1378602 COMPLETE SPECIFICATION
5 SHEETS This drawing is a reproduction of the Original on a reduced scale
Sheet 1

Fig. 1

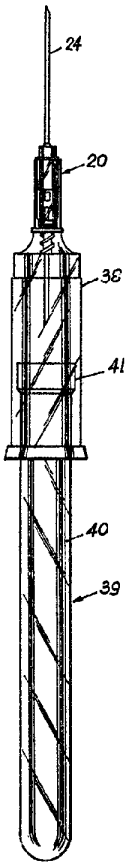


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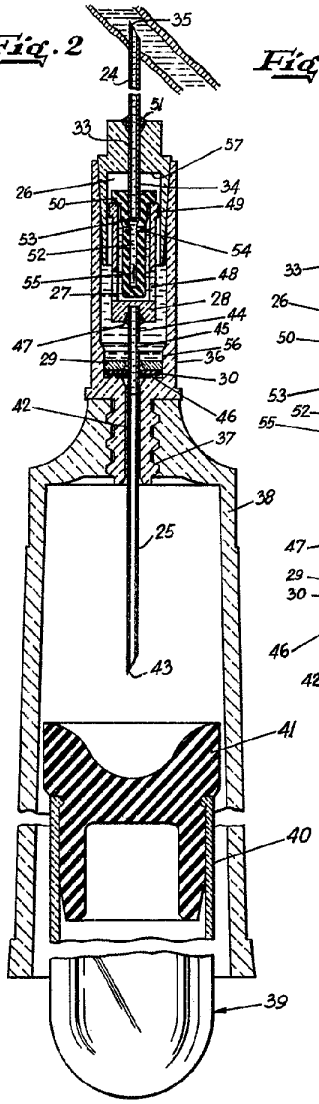


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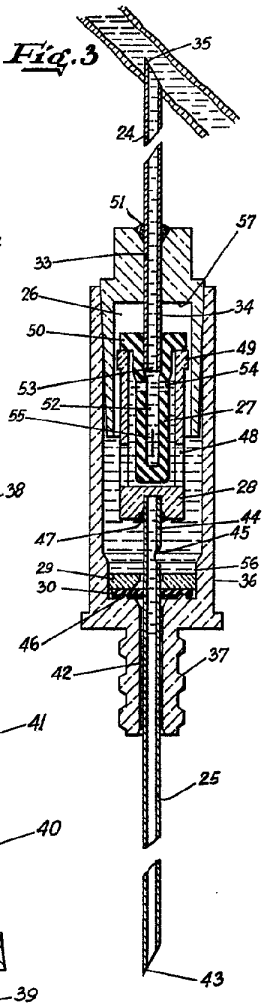


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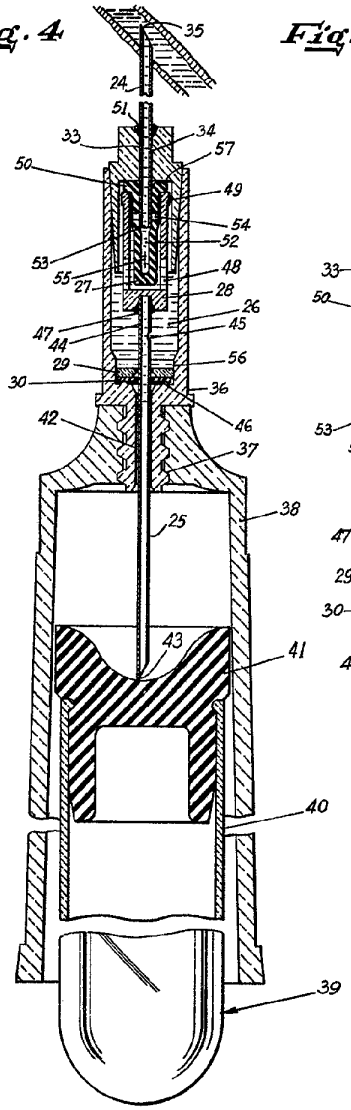

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Fig. 5

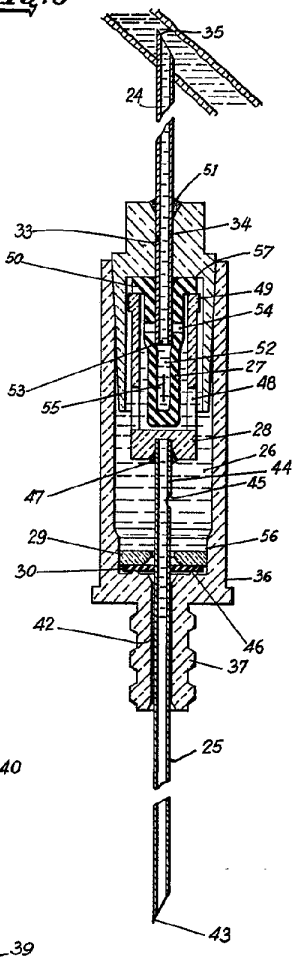

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Fig. 6

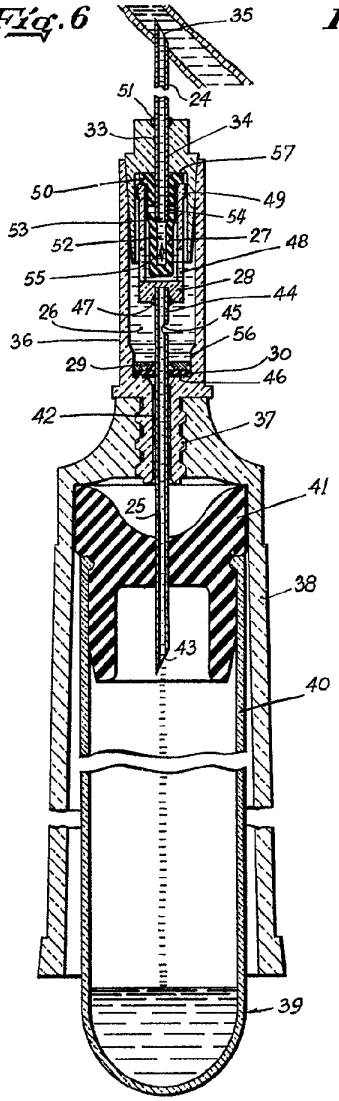

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Fig. 7

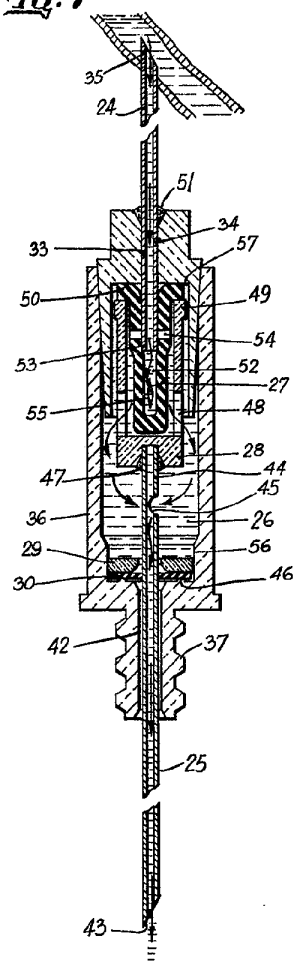

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Fig. 8

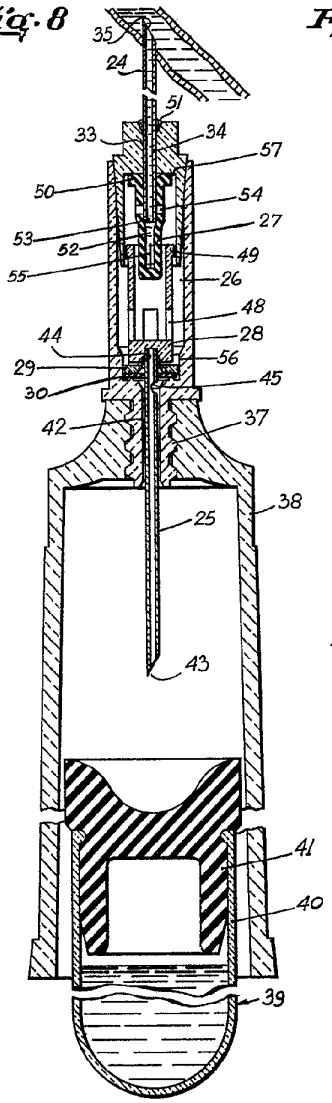
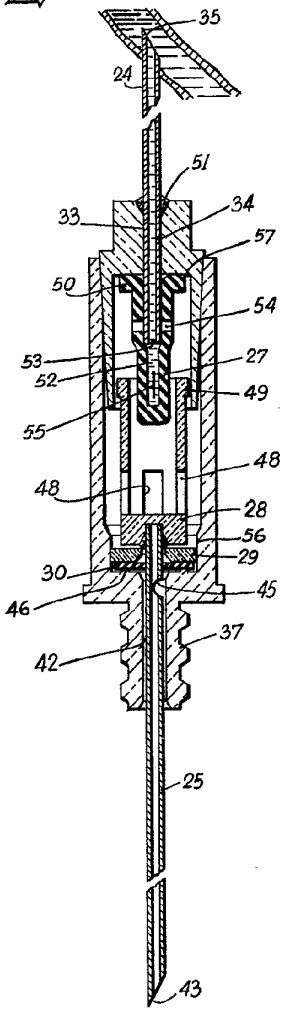

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Fig. 9


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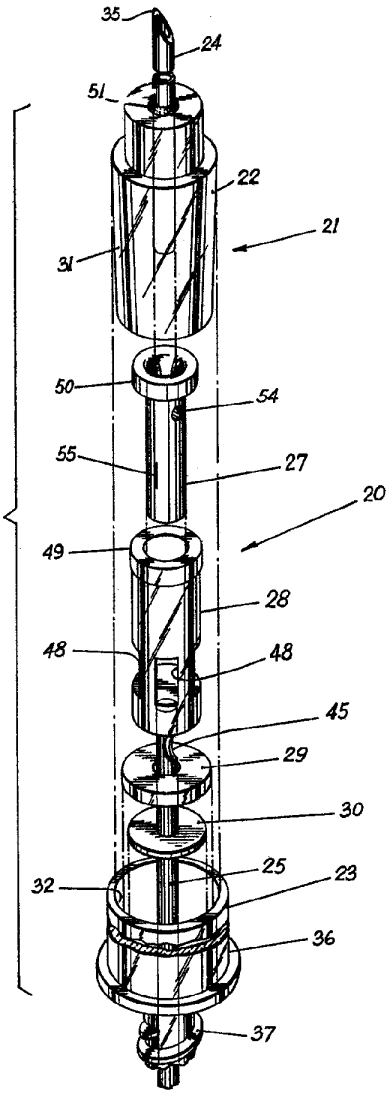


Fig. 10

Bibliographic data: WO2017019552 (A1) — 2017-02-02

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

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Applicant(s): KURIN INC [US] ± (KURIN, INC)

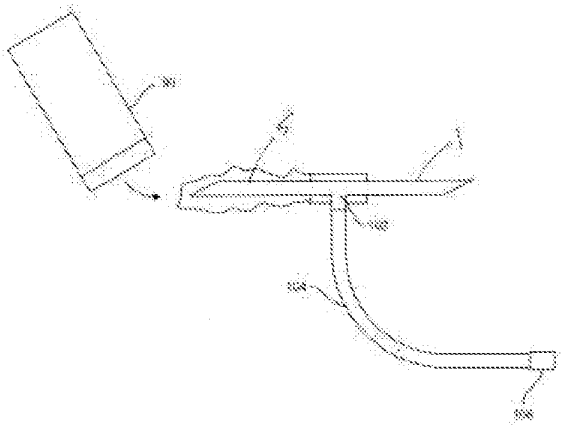
Classification: - **international:** ***A61B5/15; A61B5/153; A61B5/154***
- **cooperative:** **A61B5/15003 (EP, IL, US); A61B5/150213 (EP, IL, US); A61B5/150221 (IL, US); A61B5/150389 (EP, IL, US); A61B5/150473 (EP, IL, US); A61B5/150572 (EP, IL, US); A61B5/150992 (IL, US); A61B5/153 (EP, IL, US); A61B5/154 (EP, IL, US); A61M39/04 (IL, US); A61M39/0693 (IL, US);** A61M2039/0202 (IL, US); A61M2039/0633 (IL, US); A61M2039/068 (IL, US)

Application number: WO2016US43709 20160722 Global Dossier

Priority number(s): US201562196797P 20150724 ; US201562238636P 20151007 ; US201662318194P 20160404 ; US201615140448 20160427 ; US201615140443 20160427

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Abstract of WO2017019552 (A1)



Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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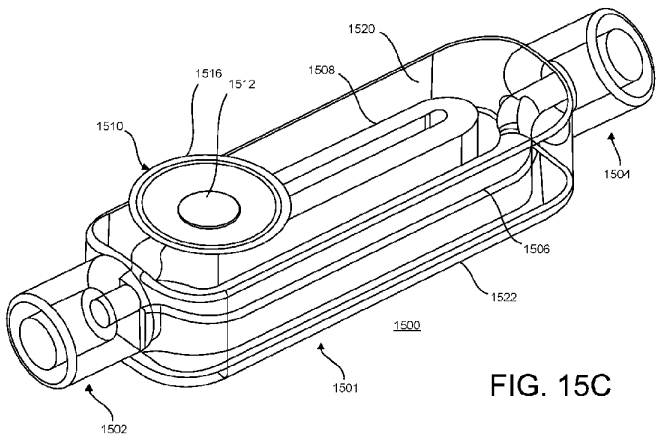


FIG. 15C

(57) Abstract: Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (1500) located between a patient needle and a sample needle. The blood sequestration device can include a sequestration chamber (1508) for sequestering an initial, potentially contaminated aliquot of blood, and may further include a sampling channel (1506) that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

WO 2017/019552 A1

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Non-Provisional Application Serial No. 15/140,443, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD" and U.S. Non-Provisional Application Serial No. 15/140,448, filed on April 27, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD", both of which claim priority to U.S. Provisional Application Serial No. 62/196,797, filed on July 24, 2015 and titled "BLOOD CULTURE IMPROVEMENT SYSTEM AND METHOD"; U.S. Provisional Application Serial No. 62/238,636, filed on October 7, 2015 and titled "BLOOD SEQUESTRATION SYSTEM FOR NON-CONTAMINATED BLOOD SAMPLING"; and U.S. Provisional Application Serial No. 62/318,194, filed on April 4, 2016 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," the disclosures of which are incorporated by reference in their entirety.

BACKGROUND

[0002] Bacteraemia is the presence of microorganisms in the blood. Sepsis, on the other hand, is bacteraemia in the presence of clinical symptoms and signs such as fever, tachycardia, tachypnea and hypotension. Bacteraemia and sepsis are associated with a high mortality and an increased incidence and duration of hospital stay and associated costs. Many bacteraemias, sepsis, fungaemias and other pathogens actually occur within a hospital or other healthcare settings with catheters and venipunctures being a source of contamination as potential carriers of these pathogens.

[0003] Blood cultures are the standard test used to detect microbial pathogens related to bacteraemia and sepsis in a patient's blood. The term blood culture refers to a single venipuncture, either from a peripheral site or central or arterial line, with the blood inoculated into one or more blood culture bottles or containers. One bottle is considered a blood culture where two or more are considered a set. Multiple sets may be obtained from multiple venipunctures and are associated with different sites on the patient.

[0004] These methods allow for microbial identification and susceptibility testing to be performed, which is a critical component to managing sepsis, however the lack of rapid results and decreased sensitivity for fastidious pathogens has led to the development of improved systems and adjunctive molecular or proteomic testing.

[0005] Collection of blood samples for conducting blood cultures is a critical component of modern patient care and can either positively affect the patient outcome by providing an accurate diagnosis, or can adversely affect the outcome by prolonging unnecessary antimicrobial therapy, the length of hospital stays, and increasing costs.

[0006] One outcome of collection of blood cultures is contamination. Blood culture contamination can lead to a false positive culture result and/or significant increase in healthcare related costs. Sources of blood culture contamination include improper skin antisepsis, improper collection tube disinfection, and contamination of the initial blood draw which may then skew results.

[0007] Blood culture collection kits generally consist of a "butterfly" set, infusion set, or other type of venipuncture device as offered by companies like BD, Smiths, B. Braun and others, and aerobic and anaerobic blood culture bottles. Various different bottles are also available depending on the test requirements. These bottles are specifically designed to optimize recovery of both aerobic and anaerobic organisms. In conventional kits, a bottle used is known generally as a "Vacutainer," which is a blood collection tube formed of a sterile glass or plastic tube with a closure that is evacuated to create a vacuum inside the tube to facilitate the draw of a predetermined volume of liquid such as blood.

[0008] False positive blood cultures are typically a result of poor sampling techniques. They cause the use of antibiotics when not needed, increasing hospital costs and patient anxiety. Blood cultures are drawn from a needlestick into the skin, and then a Vacutainer is attached to capture a sample of blood. Contamination may occur from improper or incomplete disinfection of the skin area in and around the puncture site. It may also occur from the coring of the skin by the needle during insertion, with the cored skin cells and any associated contamination being pulled into the sample.

[0009] Blood flow through a hypodermic needle is laminar, and as such, a velocity gradient can be developed over the flow tube as a pressure drop is applied to the hypodermic needle. Either forceful aspiration of blood, or using a very small hypodermic needle, can cause lysis and a release of potassium from the red blood cells, thereby rendering the blood samples abnormal.

[0010] In other instances, some patients have delicate veins that can collapse under a pressure drop or vacuum, particularly as applied by a syringe's plunger that is drawn too quickly for the patient's condition. Since such condition is impossible to know beforehand, such vein collapses are a risk and very difficult to control.

[0011] Various strategies have been implemented to decrease blood culture contamination rates, e.g. training staff with regard to aseptic collection technique, feedback with regard to contamination rates and implementation of blood culture collection kits. Although skin antisepsis can reduce the burden of contamination, 20% or more of skin organisms are located deep within the dermis and are unaffected by antisepsis. Changing needles before bottle inoculation is not advisable as it increases the risk to acquire needle stick injuries without decreasing contamination rates.

[0012] Some conventional systems and techniques for reducing blood culture contamination include discarding the initial aliquot of blood taken from central venous catheters, venipunctures, and other vascular access systems. However, these systems require the user to mechanically manipulate an intravascular device, or require a complex series of steps that are difficult to ensure being followed.

SUMMARY

[0013] This document presents systems and methods for reducing blood culture contamination, lysing of cells, and vein collapse. In some implementations, a system and method can eliminate user variability in disinfection, and also eliminate the risk of skin cells getting into the blood culture sample. The systems and methods disclosed herein do not require a change in existing clinical processes, other than to potentially indicate when a vacutainer or other blood collection device (i.e., syringe) should be attached for drawing contaminant-free blood samples.

[0014] In some implementations of the systems and methods disclosed herein the withdrawal of blood is accomplished passively by use of the patient's own blood pressure, thereby reducing the risk of vein collapse and eliminating any additional user steps over current practice. The systems and methods can be applied to accommodate short-path direct stick or butterfly venipuncture systems. They can also be used with samples drawn through a catheter.

[0015] In one aspect, a blood sequestration device is presented. The blood sequestration device includes an inlet port and an outlet port. The blood sequestration device further includes a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port.

[0016] In another aspect, a blood sequestration device connected with a blood sampling pathway is described. The blood sampling pathway has a patient needle and a sample collection device. The blood sequestration device includes an inlet port connected with the patient needle, and a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, and an outlet port connected with a distal end of the sampling channel and with the sample collection device.

[0017] In yet another aspect, a blood sequestration device connected with a blood sampling system is described. The blood sampling system includes a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed and adapted for receiving an evacuated blood collection tube. The blood sequestration device includes an inlet port connected with the patient needle to receive the blood sample from the patient. The blood sequestration device further includes a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed by the evacuated blood collection tube. The blood sequestration device further includes a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a subsequent portion of the blood sample once the sample needle is unsealed by the evacuated blood collection tube. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel for conveying the subsequent portion of the blood sample to the sample needle.

[0018] In yet another aspect, a blood sample optimization system is disclosed and described. The blood sample optimization system includes a blood sampling system for accessing and acquiring one or more samples of a patient's blood, and a blood sequestration device for receiving and sequestering a first portion of the one or more samples of the patient's blood which might be contaminated by a venipuncture process and which could result in a false positive identification of a pathogen in the patient's blood.

[0019] The blood sampling system includes a patient needle configured for a venipuncture of a patient to access a sample of blood of a patient, a blood sampling pathway connected with the patient needle for conveying the sample of blood, and a sample needle configured for receiving an evacuated blood collection container to collect and contain a subsequent portion of the sample of blood.

[0020] In yet another aspect, a blood sequestration device is disclosed and described. In some implementations, the blood sequestration device can include an inlet port, an outlet port connected with the inlet port, and a sequestration chamber connected with the inlet port. The sequestration chamber can have a vent comprising an air permeable blood barrier.

[0021] The blood sequestration device is connected along the blood sampling pathway between the patient needle and the sample needle, and includes an inlet port for receiving the sample of blood. The blood sequestration device further includes a sequestration chamber connected with the inlet port for receiving a first amount of the sample of blood, the sequestration chamber having a vent comprising an air permeable blood barrier for sequestering at least a first portion of the first amount of the sample of blood. The blood sequestration device may further include a sampling channel having a proximal end connected with the inlet port, the sampling channel conveying a subsequent amount of the sample of blood to the evacuated blood collection container upon the sequestration chamber sequestering at least the first portion of the first amount of the sample of blood. The blood sequestration device further includes an outlet port connected with a distal end of the sampling channel, the outlet port for outputting the subsequent amount of the sample of blood.

[0022] The details of one or more embodiments are set forth in the accompanying drawings and the description below. Other features and advantages will be apparent from the description and drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] These and other aspects will now be described in detail with reference to the following drawings.

[0024] FIG. 1 illustrates a blood sample optimization system.

[0025] FIG. 2 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0026] FIG. 3 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0027] FIG. 4 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0028] FIG. 5 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0029] FIG. 6 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0030] FIG. 7 is a flowchart of a method for optimizing a quality of a blood culture.

[0031] FIGS. 8A – 8E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with some implementations.

[0032] FIG. 9 illustrates a pathway splitter for use in a blood sequestrations system.

[0033] FIGS. 10A – 10D illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with alternative implementations.

[0034] FIGS. 11A – 11E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with other alternative implementations.

[0035] FIGS. 12A-12D illustrate a blood sample optimization system including a blood sequestration device in accordance with yet other alternative implementations.

[0036] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet another alternative implementations.

[0037] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample.

[0038] FIGS. 15A-15G illustrate a blood sequestration device and method of using the same, in accordance with yet another implementation.

[0039] FIGS. 16A-16D illustrate a blood sequestration device in accordance with yet another implementation.

[0040] FIGS. 17A – 17E illustrate a bottom member of a housing for a blood sequestration device.

[0041] FIGS. 18A – 18F illustrate a top member of a housing for a blood sequestration device.

[0042] FIGS. 19A and 19B illustrate a blood sequestration device having a top member mated with a bottom member.

[0043] FIG. 20 shows a blood sample optimization system including a blood sequestration device.

[0044] FIG. 21 illustrates a non-vented blood sequestration device using a wicking material chamber.

[0045] FIGS. 22A and 22B illustrate a material makeup of a filter for sequestering blood in a sequestration chamber of a blood sequestration device.

[0046] FIGS. 23A and 23B illustrate another implementation of a blood sequestration device that uses a vacuum force from a blood collection device.

[0047] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0048] This document describes blood sample optimization systems and methods for reducing or eliminating contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. In some implementations, a blood sample optimization system includes a patient needle for vascular access to a patient's bloodstream, a sample needle for providing a blood sample to a blood collection container, such as an evacuated blood collection container or tube like a Vacutainer™ or the like, or other sampling device, and a blood sequestration device located between the patient needle and the sample needle. The blood sequestration device includes a sequestration chamber for sequestering an initial, potentially contaminated

aliquot of blood, and may further include a sampling channel that bypasses the sequestration chamber to convey likely uncontaminated blood between the patient needle and the sample needle after the initial aliquot of blood is sequestered in the sequestration chamber.

[0049] FIG. 1 illustrates a blood sample optimization system in accordance with some implementations. The system includes a patient needle 1 to puncture the skin of a patient to access the patient's vein and blood therein. The system further includes a sample needle (i.e., a resealably closed needle for use with Vacutainers™ or the like) 5, which may be contained within and initially sealed by a resealable boot 10, a Luer activated valve, or another collection interface or device. The resealable boot 10 can be pushed aside or around the sample needle 5 by application of a Vacutainer™ bottle (not shown) for drawing the patient's blood. The system can further include a low volume chamber 30 that leads to the sample needle 5, but also includes an orifice or one or more channels 45 that lead to a sequestration chamber 55 formed by a housing 50.

[0050] The sequestration chamber 55 is a chamber, channel, pathway, lock, or other structure for receiving and holding a first aliquot of the patient's blood, which may be in a predetermined or measured amount, depending on a volume of the sequestration chamber 55. The first draw of blood typically contains or is more susceptible to containing organisms that cause bacteraemia and sepsis or other pathogens than subsequent blood draws. The sequestration chamber 55 can be a vessel encased in a solid housing, formed in or defined by the housing itself, or can be implemented as tubing or a lumen. The sequestration chamber 55, regardless how formed and implemented, may have a predetermined volume. In some implementations, the predetermined volume may be based on a volume of the patient needle, i.e. ranging from less than the volume of the patient needle to any volume up to or greater than 20 times or more of the volume of the patient needle. The predetermined volume of the sequestration chamber 55 may also be established to economize or minimize an amount of blood to be sequestered and disposed of.

[0051] The sequestration chamber 55 can be formed, contained or housed in a chamber housing 50, and can be made of plastic, rubber, steel, aluminum or other suitable material. For example, the sequestration chamber 55 could be formed of flexible tubing or

other elastomeric materials. The sequestration chamber 55 further includes an air permeable blood barrier 20 that allows air to exit the sequestration chamber 55. As used herein the term "air permeable blood barrier" means an air permeable but substantially blood impermeable substance, material, or structure. Examples may include hydrophobic membranes and coatings, a hydrophilic membrane or coating combined with a hydrophobic membrane or coating, mesh, a filter, a mechanical valve, antimicrobial material, or any other means of allowing air to be displaced from the sequestration chamber 55 as it is filled with blood. In various exemplary embodiments, an air permeable blood barrier may be formed by one or more materials that allow air to pass through until contacted by a liquid, such material then becomes completely or partially sealed to prevent or inhibit the passage of air and/or liquid. In other words, prior to contact with liquid, the material forms a barrier that is air permeable. After contact with a liquid, the material substantially or completely prevents the further passage of air and/or liquid.

[0052] The orifice or channel 45 can be any desired length, cross-sectional shape or size, and/or can be formed to depart from the low volume chamber 30 at any desired angle or orientation. The orifice or channel 45 may also include a one-way flap or valve 60 that maintains an initial aliquot of blood sample within the sequestration chamber 55. In some specific implementations, the orifice or channel 45 can include a "duck bill" or flapper valve 60, or the like, for one-way flow of blood from low volume chamber 30 to the sequestration chamber 55. The air permeable blood barrier 20 can also be constructed of a material that allows air to exit but then seals upon contact with blood, thereby not allowing external air to enter sequestration chamber 55. This sealing would eliminate the need for a valve.

[0053] Valve 60 can be any type of valve or closing mechanism. Chamber 30 is designed to hold virtually no residual blood, and can be designed to be adapted to hold or allow pass-through of a particular volume or rate of blood into sequestration chamber 55. Likewise, sequestration chamber 55 may also include any type of coating, such as an anti-microbial coating, or a coating that aids identification and/or diagnosis of components of the first, sequestered blood draw.

[0054] Housing 50 and 40 can be formed of any suitable material, including plastic, such as acrylonitrile butadiene styrene (ABS) or other thermoplastic or polymeric material, rubber, steel, or aluminum. The air permeable blood barrier 20 can include a color-providing substance, or other signaling mechanism, that is activated upon contact with blood from the initial blood draw, or when air displacement is stopped, or any combination of events with blood in the sequestration chamber 55. The air permeable barrier may also include an outer layer such as a hydrophobic membrane or cover that inhibits or prevents the inadvertent or premature sealing of the filter by an external fluid source, splash etc. Sequestration chamber 55 can also be translucent or clear to enable a user to visually confirm the chamber is filled.

[0055] FIG. 2 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown in FIG. 2, a sequestration chamber 55, or waste chamber, surrounds the patient needle 1, with an open-ended cuff or housing connected with the waste chamber and encircling the sample needle housing base and housing. The patient needle 1 and sample needle 5 are connected together by a boot 56, which forms a continuous blood draw channel therethrough. The boot 56 includes a single orifice or channel leading from the blood draw channel into sequestration chamber 55. The device can include more than one single orifice or channel, in other implementations. Each orifice or channel can include a one-way valve, and can be sized and adapted for predetermined amount of blood flow.

[0056] The sequestration chamber 55 includes an air permeable blood barrier. The filter can further include a sensor or indicator to sense and/or indicate, respectively, when a predetermined volume of blood has been collected in the sequestration chamber 55. That indication will alert a user to attach an evacuated blood collection tube or bottle, such as a Vacutainer™ to the sample needle 5. The housing for the sequestration chamber 55 can be any size or shape, and can include any type of material to define an interior space or volume therein. The interior space is initially filled only with air, but can also be coated with an agent or substance, such as a decontaminate, solidifying agent, or the like. Once evacuated blood collection tube is attached to the sample needle 5, blood will flow automatically into the patient needle 1, through the blood draw channel and sample needle 5, and into the bottle.

The sample needle 5 is covered by a resealable boot, coating or membrane that seals the sample needle when a blood collection bottle is not attached thereon or thereto.

[0057] FIG. 3 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is surrounded by a resealable boot or membrane, and is further connected with a patient needle 1. A blood flow channel is formed through the sample needle and the patient needle. The connection between the sample needle and patient needle includes a "T" or "Y" connector 102, which includes a channel, port or aperture leading out from the main blood flow channel to a sequestration chamber 104.

[0058] The T or Y connector 102 may include a flap or one-way valve, and have an opening that is sized and adapted for a predetermined rate of flow of blood. The sequestration chamber 104 can be formed from tubing, or be formed by a solid housing, and is initially filled with air. The sequestration chamber 104 will receive blood that flows out of a patient automatically, i.e. under pressure from the patient's own blood pressure. The sequestration chamber 104 includes an air permeable blood barrier 106, preferably at the distal end of tubing that forms the sequestration chamber 104, and which is connected at the proximal end to the T or Y connector 102. The T or Y connector 102 can branch off at any desired angle for most efficient blood flow, and can be formed so as to minimize an interface between the aperture and channel and the main blood flow channel, so as to minimize or eliminate mixing of the initial aliquot of blood with main blood draw samples.

[0059] In some alternative implementations, the sample needle may be affixed to a tubing of any length, as shown in FIG. 4, connecting at its opposite end to the T or Y connector 102. The sequestration chamber 104 can be any shape or volume so long as it will contain a predetermined amount of blood sample in the initial aliquot. The T or Y connector 102 may also include an opening or channel that is parallel to the main blood flow channel. The air permeable blood barrier may further include an indicator 107 or other mechanism to indicate when a predetermined amount of blood has been collected in the sequestration chamber, or when air being expelled reaches a certain threshold, i.e. to zero. The tubing can also include a clip 109 that can be used to pinch off and prevent fluid flow therethrough.

[0060] Once the air permeable blood barrier and primary chamber are sealed the initial aliquot of blood is trapped in the sequestration chamber 104, an evacuated blood collection tube, such as a Vacutainer™ bottle may be attached to the sample needle 5 to obtain the sample. The blood collection tube can be removed, and the sample needle 5 will be resealed. Any number of follow-on blood collection tubes can then be attached for further blood draws or samples. Upon completion of all blood draws, the system can be discarded, with the initial aliquot of blood remaining trapped in the sequestration chamber 104.

[0061] FIG. 5 illustrates a blood sample optimization system in accordance with some alternative implementations. In the implementation shown, a sample needle 5 is connected with a patient needle by tubing. A "T" or "Y" connector 120 is added along the tubing at any desired location, and includes an aperture, port or channel leading to a sequestration chamber 204, substantially as described above.

[0062] FIG. 6 illustrates a blood sample optimization system in accordance with some alternative implementations, in which a sequestration chamber 304, formed as a primary collection channel, receives an initial aliquot of blood, and is provided adjacent to the blood sampling channel. The sequestration chamber 304 can encircle the blood sampling channel, the patient needle 1, and/or the sample needle 5. The primary collection channel can include a T or Y connector 120, or other type of aperture or channel. The sequestration chamber 304 includes an air permeable blood barrier, which can also include an indicator of being contacted by a fluid such as blood, as described above.

[0063] In some implementations, either the patient needle 1 or the sample needle 5, or both, can be replaced by a Luer lock male or female connector. However, in various implementations, the connector at a sample needle end of the blood sample optimization system is initially sealed to permit the diversion of the initial aliquot of blood to the sequestration chamber, which is pressured at ambient air pressure and includes the air outlet of the air permeable blood barrier. In this way, the system passively and automatically uses a patient's own blood pressure to overcome the ambient air pressure of the sequestration chamber to push out air through the air permeable blood barrier and displace air in the sequestration chamber with blood.

[0064] FIG. 7 is a flowchart of an exemplary method for optimizing the quality of a blood culture. At 702, a clinician places a needle into a patient's vein. At 704, blood then flows into a sequestration chamber, pushing the air in the sequestration chamber out of the sequestration chamber through an air permeable blood barrier. In some implementations, the volume of the sequestration chamber is less than 0.1 to more than 5 cubic centimeters (cc's), or more. The sequestration chamber is sized and adapted to collect a first portion of a blood sample, which is more prone to contamination than secondary and other subsequent portion of the blood sample or subsequent draws. Since the sequestration chamber has an air-permeable blood barrier through which air can be displaced by blood pushed from the patient's vein, such blood will naturally and automatically flow into the sequestration chamber before it is drawn into or otherwise enters into a Vacutainer or other bottle for receiving and storing a blood sample.

[0065] When the sequestration chamber fills, the blood will gather at or otherwise make contact with the air permeable blood barrier, which will inhibit or prevent blood from passing therethrough. At 706, when the blood comes into contact with the entire internal surface area of the air permeable blood barrier, the air permeable blood barrier is then closed and air no longer flows out or in. At 708, the clinician may be provided an indictor or can see the full chamber, to indicate the evacuated blood collection tube, such as a Vacutainer™ can be attached. The indicator can include visibility into the primary chamber to see whether it is full, the blood barrier changing color, for example, or other indicator. The fill time of the sequestration chamber may be substantially instantaneous, so such indicator, if present, may be only that the sequestration chamber is filled.

[0066] Prior to an evacuated blood collection tube being attached, communication between the needle, sampling channel, and the sequestration chamber is restricted by the sealing of the sequestration chamber blood barrier thereby not permitting air to reenter the system through the sequestration. Sealing the communication path could also be accomplished with a mechanical twist or other movement, a small orifice or tortuous pathway, eliminating the need for a separate valve or mechanical movement or operation by the clinician. At 710, once the evacuated blood collection tube is removed, the self-sealing membrane closes the sample needle, and at 712, additional subsequent evacuated blood

collection tubes may be attached. Once samples have been taken, at 714 the device is removed from the patient and discarded.

[0067] FIGS. 8A – 8E illustrate an exemplary blood sample optimization system 800 for non-contaminated blood sampling, in accordance with some implementations. The blood sample optimization system 800 includes an inlet port 802 that can be connected to tubing, a patient needle (or both), or other vascular or venous access device, and a pathway splitter 804 having a first outlet to a sequestration chamber tubing 806 and a second outlet to sample collection tubing 808. One or both of the sequestration chamber tubing 806 and the sample collection tubing 808 can be formed of tubing. In some implementations, the sequestration chamber tubing 806 is sized so as to contain a particular volume of initial blood sample. The sample collection tubing 808 will receive a blood sample once the sequestration chamber tubing 806 is filled. The sample collection tubing 808 can be connected to a Vacutainer™ base or housing 810, or other blood sample collection device.

[0068] The blood sequestration system 800 further includes a blood sequestration device 812 which, as shown in more detail in FIGS. 8B – 8D, includes a housing 818 that includes a sampling channel 820 defining a pathway for the non-contaminated sample collection tubing 808 or connected at either end to the non-contaminated sample collection tubing 808. The sampling channel 820 can be curved through the housing 818 so as to better affix and stabilize the housing 818 at a location along the non-contaminated sample collection tubing 808.

[0069] The blood sequestration device 812 further includes a sequestration chamber 822 connected with the sequestration chamber tubing 806 or other chamber. The sequestration chamber 822 terminates at an air permeable blood barrier 824. The air permeable blood barrier 824 can also include a coloring agent that turns a different color upon full contact with blood, as an indicator that the regular collection of blood samples (i.e. the non-contaminated blood samples) can be initiated. Other indicators may be used, such as a small light, a sound generation mechanism, or the like. In some implementations, the air permeable blood barrier is positioned at a right angle from the direction of sequestration chamber 822, but can be positioned at any distance or orientation in order to conserve space

and materials used for the housing 818. The housing 818 and its contents can be formed of any rigid or semi-rigid material or set of materials.

[0070] FIG. 9 illustrates a pathway splitter 900 for use in a blood sequestrations system, such as those shown in FIGS. 8A – 8E, for example. The pathway splitter 900 includes an inlet port 902, a main line outlet port 904, and a sequestration channel outlet port 906. The inlet port 902 can be connected to main tubing that is in turn connected to a patient needle system, or directly to a patient needle. The main line outlet port 904 can be connected to main line tubing to a blood sampling system, such as a vacutainer base or housing, or directly to such blood sampling system. The sequestration channel outlet port 906 can be connected to sequestration tubing for receiving and sequestering a first sample of blood, up to a measured amount or predetermined threshold. Alternatively, the sequestration channel outlet port 906 can be connected to a sequestration chamber. The sequestration channel outlet port 906 is preferably 20-70 degrees angled from the main line outlet port 904, which in turn is preferably in-line with the inlet port 902. Once the predetermined amount of initial blood sample is sequestered in the sequestration tubing or chamber, in accordance with mechanisms and techniques described herein, follow-on blood samples will flow into the inlet port 902 and directly out the main line outlet port 904, without impedance.

[0071] FIGS. 10A – 10D illustrate a blood sequestration device 1000 in accordance with alternative implementations. The blood sequestration device 1000 includes an inlet port 1002, a main outlet port 1004, and a sequestration channel port 1006. The inlet port 1002 can be connected to a patient needle or related tubing. The main outlet port 1004 can be connected to a blood sample collection device such as a Vacutainer, associated tubing, or a Luer activated valve, or the like. The sequestration channel port 1006 splits off from the main outlet port 1004 to a sequestration chamber 1008. In some implementations, the sequestration chamber 1008 is formed as a helical channel within a housing or other container 1001.

[0072] The sequestration chamber 1008 is connected at the distal end to an air permeable blood barrier 1010, substantially as described above. Air in the sequestration chamber 1008 is displaced through the air permeable blood barrier 1010 by an initial aliquot

of blood that is guided into the sequestration channel port 1006. Once the sequestration chamber 1008 is filled, further blood draws through the main outlet port 1004 can be accomplished, where these samples will be non-contaminated.

[0073] FIGS. 11A – 11E illustrate a blood sequestration device 1100 in accordance with other alternative implementations. The blood sequestration device 1100 includes an inlet port 1102, similar to the inlet ports described above, a main outlet port 1104, and a sequestration channel port 1106 that splits off from the main outlet port 1104 and inlet port 1102. The sequestration channel port is connected to a sequestration chamber 1108. In the implementation shown in FIGS. 11A – 11E, the blood sequestration device includes a base member 1101 having a channel therein, which functions as the sequestration chamber 1108. The channel can be formed as a tortuous path through the base member 1101, which is in turn shaped and formed to rest on a limb of a patient.

[0074] A portion of the sequestration chamber 1108 can protrude from the base member or near a top surface of the base member, just before exiting to an air permeable blood barrier 1110, to serve as a blood sequestration indicator 1109. The indicator 1109 can be formed of a clear material, or a material that changes color when in contact with blood.

[0075] In some implementations, the blood sequestration device 1100 can include a blood sampling device 1120 such as a normally closed needle, Vacutainer™ shield or other collection device. The blood sampling device 1120 can be manufactured and sold with the blood sequestration device 1100 for efficiency and convenience, so that a first aliquot of blood that may be contaminated by a patient needle insertion process can be sequestered. Thereafter, the blood sampling device 1120 can draw non-contaminated blood samples to reduce the risk of false positive testing and ensure a non-contaminated sample.

[0076] FIGS. 12A-12D illustrate a blood sample optimization system 1200 in accordance with yet other alternative implementations. The system 1200 includes a blood sequestration device 1202 for attaching to a blood sampling device 1204, such as a Vacutainer™ or other collection and sampling device. The blood sequestration device 1202 is configured and arranged to receive, prior to a Vacutainer™ container or vial being attached to a collection needle of the blood sampling device 1204, a first aliquot or amount of blood,

and sequester that first aliquot or amount in a sequestration channel of the blood sequestration device 1202.

[0077] In some implementations, the blood sequestration device 1202 can include an inlet port 1212, a main outlet port, and a sequestration channel port. The inlet port 1212 can be connected to a patient needle or related tubing. The main outlet port 1214 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port splits off from the main outlet port to a sequestration chamber 1218.

[0078] In some implementations, the sequestration chamber 1218 is formed as a channel within the body of a sequestration device 1202. The sequestration chamber 1218 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel. The sequestration device 1202 can include a housing or other containing body, and one or more channels formed therein. As shown in FIGS. 12A and 12B, the sequestration device 1202 includes a main body 1206 and a cap 1208. The main body 1206 is formed with one or more cavities or channels, which are further formed with one or more arms 1210 that extend from the cap 1208, and which abut the cavities or channels in the main body 1206 to form the primary collection port and main outlet port.

[0079] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet other alternative implementations. The system 1300 includes a blood sequestration device 1302 for attaching to a blood sampling device 1304, such as a Vacutainer or other bodily fluid collection and sampling device. The blood sequestration device 1302 is configured and arranged to receive, prior to a Vacutainer container or vial being attached to a collection needle of the blood sampling device 1304, a first aliquot or amount of blood, and to sequester that first aliquot or amount of blood or other bodily fluid in a sequestration channel of the blood sequestration device 1302.

[0080] The blood sequestration device 1302 includes a housing 1301 having an inlet port 1314, a main outlet port 1312, and a sequestration channel port 1316. The inlet port 1314 can be connected to a patient needle or associated tubing. The main outlet port 1312

can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like. The sequestration channel port 1316 splits off from the main inlet port 1314 to a sequestration chamber 1318.

[0081] In the implementation shown in FIGS. 13A-D, the sequestration chamber 1318 is formed as a cavity or chamber within housing 1301 or formed by walls that define housing 1301. The sequestration chamber 1318 can be a winding channel, such as a U-shaped channel, an S-shaped channel, a helical channel, or any other winding channel, that is defined by the cooperation and connection of housing 1301 with cap 1307 which cap 1307 can include a protrusion 1305 that provides one or more walls or directors for the winding channel in the sequestration chamber 1318. The protrusion 1305 from the cap 1307 can be straight or curved, and may have various channels, apertures or grooves embedded therein, and can extend from the cap 1307 any angle or orientation. When the cap 1307 is connected with the housing 1301 to complete the formation of the sequestration chamber 1318, the protrusion 1305 forms at least part of the winding channel to sequester a first aliquot or amount of blood or other bodily fluid in a sequestration channel formed in the sequestration chamber 1318 and by the winding channel.

[0082] The sequestration chamber 1318 includes an air permeable blood barrier 1310, substantially as described above. Air in the sequestration chamber 1318 is displaced through the air permeable blood barrier 1310 by an initial aliquot of blood that is provided into the sequestration chamber 1318 by the blood pressure of the patient. Once the sequestration chamber 1318 is filled and the air in the sequestration chamber 1318 displaced, the blood pressure of the patient will be insufficient to drive or provide further blood into the blood sequestration device 1302, and in particular the outlet port 1312, until a force such as a vacuum or other pressure, such as provided by the blood sample collection device like Vacutainer is provided to draw out a next aliquot or amount of blood or bodily fluid. Further blood draws through the main outlet port 1312 can be accomplished, where these samples will be non-contaminated since any contaminants would be sequestered in the sequestration chamber 1318 with the first aliquot of blood.

[0083] FIGS. 14A-14E illustrate yet another implementation of a blood sampling system 1400 to sequester contaminates of an initial aliquot or sample to reduce false positives in blood cultures or tests performed on a patient's blood sample. The blood sampling system 1400 includes a blood sequestration device 1401 that can be connected between a blood sample collection device 1403 and a patient needle (not shown). The blood sample collection device 1403 can be a Vacutainer or the like. The blood sequestration device 1401 includes an inlet port 1402 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1402 may also be connected with tubing or other conduit that is in turn connected with the patient needle.

[0084] The inlet port 1402 defines an opening into the blood sequestration device 1401, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more. The blood sequestration device 1401 further includes an outlet port 1404, which defines an opening out of the blood sequestration device 1401 and to the blood sample collection device 1403. The outlet port 1404 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device 1403. The outlet port 1404 can further include a connector device such as a threaded cap, a Luer connector (male or female), a non threaded interference or glue joint fitting for attachment of various devices including but not limited to tubing, or the like.

[0085] The blood sequestration device 1401 further includes a sampling channel 1406 between the inlet port 1402 and the outlet port 1404, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1406 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1406 has a substantially similar cross sectional area as the opening of the inlet port 1402. In other implementations, the sampling channel 1406 can gradually widen from the inlet port 1402 to the outlet port 1404.

[0086] The blood sequestration device 1401 further includes a sequestration chamber 1408 that is connected to and split off or diverted from the sampling channel 1406 at any point between the inlet port 1402 and the outlet port 1404, but preferably from a proximal end of the sampling channel 1406 near the inlet port 1402. The sequestration chamber 1408 is at first maintained at atmospheric pressure, and includes an air outlet 1412 at or near a distal end of the sequestration chamber 1408 opposite the diversion point from the sampling channel 1406. The air outlet 1412 includes an air permeable blood barrier 1412. As shown in FIG. 14B, the air permeable blood barrier 1412 can be overlaid with a protective cover 1416. The protective cover 1416 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1412 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1412 as the air is displaced from the sequestration chamber 1408 by blood being forced into the sequestration chamber 1408 by a patient's own blood pressure. In addition the protective cover 1416 can be constructed to inhibit or prevent accidental exposure of the air permeable blood barrier to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0087] As shown in FIGS. 14C and 14D, the sampling channel 1406 can be cylindrical or frusto-conical in shape, going from a smaller diameter to a larger diameter, to minimize a potential to lyse red blood cells. Likewise, the sampling channel 1406 is formed with a minimal amount of or no sharp turns or edges, which can also lyse red blood cells. The sampling channel 1406 splits off to the sequestration chamber 1408 near the inlet port 1402 via a diversion pathway 1409. The diversion pathway 1409 can have any cross-sectional shape or size, but is preferably similar to the cross-sectional shape of at least part of the inlet port 1402.

[0088] In some implementations, the sampling channel 1406 and the sequestration chamber 1408 are formed by grooves, channels, locks or other pathways formed in housing 1414. The housing 1414 can be made of plastic, metal or other rigid or semi-rigid material. The housing 1414 can have a bottom member that sealably mates with a top member. One or both of the bottom member and the top member can include the sampling channel 1406 and the sequestration chamber 1408, as well as the diversion pathway 1409, the inlet port 1402,

and the outlet port 1404. In some other implementations, one or more of the diversion pathway 1409, the inlet port 1402, and/or the outlet port 1404 can be at least partially formed by a cap member that is connected to either end of the housing 1414. In some implementations, the top member and the bottom member, as well as the cap member(s), can be coupled together by laser welding, heat sealing, gluing, snapping, screwing, bolting, or the like. In other implementations, some or all of the interior surface of the diversion pathway 1409 and/or sequestration chamber 1408 can be coated or loaded with an agent or substance, such as a decontaminate, solidifying agent, or the like. For instance, a solidifying agent can be provided at the diversion pathway 1409 such that when the sequestration chamber 1408 is filled and the initial aliquot of blood backs up to the diversion pathway 1409, that last amount of sequestered blood could solidify, creating a barrier between the sequestration chamber 1408 and the sampling channel 1406.

[0089] FIGS. 15A-15G illustrate a blood sequestration device 1500. The blood sequestration device 1500 can be connected to a normally closed needle or device to enable connection with an evacuated blood collection container or other collection device such as a Vacutainer™, associated tubing, luer connectors, syringe, a Luer activated valve, or the like.

[0090] The blood sequestration device 1500 includes an inlet port 1502 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1502 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1502 defines an opening into the blood sequestration device 1500, which opening may be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[0091] The inlet port 1502 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1502, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner,

the blood sequestration device 1500 can be fabricated and sold with the patient needle as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1500 at the time of blood draw or sampling.

[0092] The blood sequestration device 1500 further includes an outlet port 1504, which defines an opening out of the blood sequestration device 1500 and to the blood sample collection device. The outlet port 1504 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1500 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1500 at the time of blood draw or sampling.

[0093] The blood sequestration device 1500 further includes a sampling channel 1506 between the inlet port 1502 and the outlet port 1504, and which functions as a blood sample pathway once a first aliquot of blood has been sequestered. The sampling channel 1506 can be any sized, shaped or configured channel or conduit. In some implementations, the sampling channel 1506 has a substantially similar cross sectional area as the opening of the inlet port 1502. In other implementations, the sampling channel 1506 can gradually widen from the inlet port 1502 to the outlet port 1504.

[0094] The blood sequestration device 1500 further includes a sequestration chamber 1508 that is connected to and split off or diverted from the sampling channel 1506 at any point between the inlet port 1502 and the outlet port 1504, but preferably from a proximal end of the sampling channel 1506 near the inlet port 1502. In some implementations, the diversion includes a Y-shaped junction. The sequestration chamber 1508 is preferably maintained at atmospheric pressure, and includes a vent 1510 at or near a distal end of the sequestration chamber 1508. The vent 1510 includes an air permeable blood barrier 1512. FIG. 15C illustrates the blood sequestration device 1500 with the sequestration chamber 1508 filled with a first aliquot or sample of blood from the patient.

[0095] The air permeable blood barrier 1512 can be covered with a protective cover 1516. The protective cover 1516 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1512 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1512 as the air is displaced from the sequestration chamber 1508 by blood being forced into the sequestration chamber 1508 by a patient's own blood pressure. The protective cover 1516 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[0096] FIG. 15B is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating an initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before a sample collection device is activated. FIG. 15G is a perspective view of the blood sequestration device 1500 from the outlet port 1504 and bottom side of the housing 1501 of the blood sequestration device 1500, and illustrating the initial aliquot of blood filling sequestration chamber 1508 while the sampling channel 1506 is empty, before the sample collection device is activated. FIG. 15C is another perspective view of the blood sequestration device 1500 from the inlet port 1502 and top side of a housing 1501 of the blood sequestration device 1500 that includes the vent 1510, and illustrating blood now being drawn through sampling channel 1506 while the sequestered blood remains substantially in the sequestration chamber 1508.

[0097] FIG. 15D is a cross section of the blood sequestration device 1500 in accordance with some implementations, showing the housing 1501 that defines the sampling channel 1506 and the sequestration chamber 1508. FIGS. 15E and 15F illustrate various form factors of a housing for a blood sequestration device, in accordance with one or more implementations described herein.

[0098] The sequestration chamber 1508 can have a larger cross-sectional area than the sampling channel 1506, and the cross-sectional area and length can be configured for a predetermined or specific volume of blood to be sequestered or locked. The sampling

channel 1506 can be sized to be compatible with tubing for either or both of the patient needle tubing or the blood collection device tubing.

[0099] The housing 1501 can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIG. 15D, the housing 1501 includes a top member 1520 and a bottom member 1522 that are mated together, one or both of which having grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc. The top member 1520 can be connected with the bottom member 1522 by any mating or connection mechanism, such as by laser welding, thermal bonding, ultrasonic welding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like.

[00100] In some implementations, such as shown in FIG. 15D, the top member 1520 can include the grooves, channels, locks, conduits or other pathways, while the bottom member 1522 can include a protrusion 1524 that is sized and adapted to fit into at least one of the grooves, channels, locks or other pathways of the top member 1520. The protrusion 1524 can provide a surface feature, such as a partial groove or channel, for instance, to complete the formation of either the sampling channel 1506 and/or the sequestration chamber 1508. In some implementations, the protrusion 1524 can be formed with one or more angled sides or surfaces for a tighter fit within the corresponding groove, channel, lock or other pathway. In yet other implementations, both the top member 1520 and the bottom member can include grooves, channels, locks or other pathways, as well as one or more protrusions 1524.

[00101] In some implementations, the sampling channel 1506 and the sequestration chamber 1508 are formed by grooves, channels, locks or other pathways formed in housing 1501. The housing 1501 can be made of any suitable material, including rubber, plastic, metal or other material. The housing 1501 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1501 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1506 and/or the sequestration chamber 1508 is clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 1508 is first filled to the

extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1506. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1512 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00102] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will make its way into the input port 1502 blood sequestration device 1500 and flow into the sequestration chamber 1508 by following the path of least resistance, as the patient's own blood pressure overcomes the atmospheric pressure in the sequestration chamber 1508 to displace air therein through the air permeable blood barrier 1512. The patient's blood pressure will not be sufficient to overcome the air pressure that builds up in the sealed sampling channel 1506. Eventually, the sequestration chamber 1508, which has a predetermined volume, is filled with blood that displaces air through the air permeable blood barrier 1512. Once the blood hits the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1512 material to completely or partially seal the vent 1510. A signal or indication may be provided that the practitioner can now utilize the Vacutainer capsule or other blood sample collection device to acquire a next amount of the patient's blood for sampling. The blood in the sequestration chamber 1508 is now effectively sequestered in the sequestration chamber.

[00103] Upon filling the blood sequestration pathway 1508 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1506, possibly resulting in a small amount of blood moving past the diversion point to the sequestration chamber 1508 and into the sampling channel 1506, queuing up the uncontaminated blood to be drawn through the sampling channel 1506.

[00104] FIGS. 16-19 illustrate yet another implementation of a blood sequestration device. FIGS. 16A-16D illustrate a blood sequestration device 1600 that can be connected

between a blood sample collection device, such as an evacuated blood collection container like a Vacutainer™ (not shown), and a patient needle (not shown) and/or associated tubing. FIG. 17 illustrates a bottom member of the blood sequestration device, and FIG. 18 illustrates a top member of the blood sequestration device, which top member and bottom member can be mated together to form an input port, and output port, a sequestration chamber and a sampling channel, as explained more fully below. FIGS. 19A and B show the top member and bottom member mated together. It should be understood that FIGS. 16-19 illustrate one exemplary manner of constructing a blood sequestration device as described herein, and other forms of construction are possible.

[00105] Referring to FIGS. 16A – D, the blood sequestration device 1600 includes an inlet port 1602 that can be connected with a patient needle that is inserted into a patient's vascular system for access to and withdrawing of a blood sample. The inlet port 1602 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 1602 defines an opening into the blood sequestration device 1600, which opening can be the same cross sectional dimensions as tubing or other conduit connected with the patient needle or the patient needle itself. For instance, the opening can be circular with a diameter of approximately 0.045 inches, but can have a diameter of between 0.01 inches or less to 0.2 inches or more.

[00106] The inlet port 1602 can also include a sealing or fluid-tight connector or connection, such as threading or Luer fitting, or the like. In some implementations, tubing or other conduit associated with the patient needle can be integral with the inlet port 1602, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing as a single unit, eliminating the need for connecting the patient needle to the blood sequestration device 1600 at the time of blood draw or sampling.

[00107] The blood sequestration device 1600 further includes an outlet port 1604, which defines an opening out of the blood sequestration device 1600 and to the blood sample collection device. The outlet port 1604 may also be connected with tubing or other conduit that is in turn connected with the blood sequestration device, and may also include a sealing

or fluid-tight connector or connection, such as threading or Luer fitting, or the like. Accordingly, as discussed above, the blood sequestration device 1600 can be fabricated and sold with the patient needle and/or tubing and the blood sample collection device as a single unit, eliminating the need for connecting the patient needle and the blood sample collection device to the blood sequestration device 1600 at the time of blood draw or sampling.

[00108] The blood sequestration device 1600 further includes a sampling channel 1606 between the inlet port 1602 and the outlet port 1604, and a sequestration chamber 1608 that is connected to and split off or diverted from the sampling channel 1606 at any point between the inlet port 1602 and the outlet port 1604. The sampling channel 1606 functions as a blood sampling pathway once a first aliquot of blood has been sequestered in the sequestration chamber 1608. The sampling channel 1606 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 1606 has a substantially similar cross sectional area as the opening of the inlet port 1602. In other implementations, the sampling channel 1606 can gradually widen from the inlet port 1602 to the outlet port 1604. The sequestration chamber 1608 may have a larger cross section to form a big reservoir toward the sequestration channel path so that the blood will want to enter the reservoir first versus entering a smaller diameter on the sampling channel 1606, as is shown more fully in FIGS. 17 and 19.

[00109] In some exemplary implementations, the diversion between the sampling channel 1606 and the sequestration chamber 1608 is by diverter junction 1607. Diverter junction 1607 may be a substantially Y-shaped, T-shaped, or U-shaped. In some preferred exemplary implementations, and as shown in FIG. 17A – 17B, the diverter junction 1607 is configured such that the flow out of the inlet port 1602 is preferentially directed toward the sequestration chamber 1608. The sequestration chamber 1608 may also include or form a curve or ramp to direct the initial blood flow toward and into the sequestration chamber 1608.

[00110] The sequestration chamber 1608 is preferably maintained at atmospheric pressure, and includes a vent 1610 at or near a distal end of the sequestration chamber 1608. The vent 1610 may include an air permeable blood barrier 1612 as described above.

[00111] The blood sequestration device 1600 can include a housing 1601 that can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated in FIGS. 17A – 17D and FIGS. 18A – 18F, the housing 1601 includes a top member 1620 and a bottom member 1622 that are mated together. The blood sequestration device 1600 can also include a gasket or other sealing member (not shown) so that when the top member 1620 is mechanically attached with the bottom member 1622, the interface between the two is sealed by the gasket or sealing member. The FIGS. 17A – 17D illustrate a bottom member 1622 of a housing for a blood sequestration device 1600. The bottom member 1622 can include grooves, channels, locks, conduits or other pathways pre-formed therein, such as by an injection molding process or by etching, cutting, drilling, etc., to form the sampling channel 1606, the sequestration chamber 1608, and diverter junction 1607.

[00112] The sequestration chamber 1608 may have a larger cross section than the sampling channel 1606 so that the blood will preferentially move into the sequestration chamber first versus entering a smaller diameter on the sampling channel 1606.

[00113] FIGS. 18A – 18F illustrate the top member 1620, which can be connected with the bottom member 1622 by any mating or connection mechanism, such as by laser welding, thermal bonding, gluing, using screws, rivets, bolts, or the like, or by other mating mechanisms such as latches, grooves, tongues, pins, flanges, or the like. The top member 1620 can include some or all of the grooves, channels, locks, conduits or other pathways to form the sampling channel 1606, the sequestration chamber 1608, and the diverter junction 1607. In yet other implementations, both the top member 1620 and the bottom member 1622 can include the grooves, channels, locks or other pathways.

[00114] In some implementations, the sampling channel 1606 and the sequestration chamber 1608 are formed by grooves, channels, locks or other pathways formed in housing 1601. The housing 1601 can be made of rubber, plastic, metal or any other suitable material. The housing 1601 can be formed of a clear or translucent material, or of an opaque or non-translucent material. In other implementations, the housing 1601 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 1606 and/or the sequestration chamber 1608 may be clear or translucent, giving a practitioner a

visual cue or sign that the sequestration chamber 1608 is first filled to the extent necessary or desired, and/or then a visual cue or sign that the sequestered blood remains sequestered while a clean sample of blood is drawn through the sampling channel 1606. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 1612 turning a different color upon contact, saturation, or partial saturation with blood; a color-coded tab or indicator at any point along or adjacent to the sequestration chamber; an audible signal; a vibratory signal; or other signal.

[00115] As shown in FIGS. 18A – 18F, the air permeable blood barrier 1612 can be covered with, or surrounded by, a protective member 1616. The protective member 1616 can be sized and configured to inhibit a user from touching the air permeable blood barrier 1612 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 1612 as the air is displaced from the sequestration chamber 1608. In some implementations, the protective member 1616 includes a protrusion that extends up from a top surface of the top member 1620 and around the air permeable blood barrier 1612. The protective cover 1616 can be constructed to inhibit or prevent accidental exposure of the filter to environmental fluids or splashes. This can be accomplished in a variety of mechanical ways including but not limited to the addition of a hydrophobic membrane to the protective cover.

[00116] In use, the blood sequestration device 1600 includes a sampling channel 1606 and a sequestration chamber 1608. Both pathways are initially air-filled at atmospheric pressure, but the sampling channel 1606 is directed to an output port 1604 that will be initially sealed by a Vacutainer or other such sealed blood sampling device, and the sequestration chamber 1608 terminates at a vent 1610 to atmosphere that includes an air permeable blood barrier 1612.

[00117] After a venipuncture by a patient needle of a patient (not shown), which could gather a number of pathogens from the patient's skin, a first amount of the patient's blood with those pathogens will pass through input port 1602 of blood sequestration device 1600. This initial volume of potentially contaminated blood will preferentially flow into the sequestration chamber 1608 by finding the path of least resistance. The patient's own blood

pressure overcomes the atmospheric pressure in the vented sequestration chamber 1608 to displace air therein through the air permeable blood barrier 1612, but is not sufficient to overcome the air pressure that builds up in the sealed sampling channel 1606. In various exemplary embodiments, the sequestration chamber 1608 and sampling channel 1606 can be configured such that the force generated by the patient's blood pressure is sufficient to overcome any effect of gravity, regardless of the blood sequestration device's orientation.

[00118] Eventually, the sequestration chamber 1608 fills with blood that displaces air through the air permeable blood barrier 1612. Once the blood contacts the air permeable blood barrier, the blood interacts with the air permeable blood barrier 1612 material to completely or partially seal the vent 1610. A signal or indication may be provided that the practitioner can now utilize the Vacutainer or other blood sampling device.

[00119] Upon filling the blood sequestration pathway 1608 but prior to use of the Vacutainer or other blood sample collection device, the patient's blood pressure may drive compression of the air in the sampling channel 1606, possibly resulting in a small amount of blood moving past the diversion point into the sampling channel 1606, queuing up the uncontaminated blood to be drawn through the sampling channel 1606.

[00120] FIG. 19A is a side view, and FIG. 19B is a cross-sectional view, of the blood sequestration device 1600, illustrating the top member 1620 mated with the bottom member 1622.

[00121] FIG. 20 shows a blood sample optimization system 2000 that includes a patient needle 2002 for vascular access to a patient's bloodstream, a blood sample collection device 2004 to facilitate the collecting of one or more blood samples, and a conduit 2006 providing a fluid connection between the patient needle 2002 and the blood sample collection device 2004. In some implementations, the blood sample collection device 2004 includes a protective shield that includes a sealed collection needle on which a sealed vacuum-loaded container is placed, which, once pierced by the collection needle, draws in a blood sample under vacuum pressure or force through the conduit 2006 from the patient needle 2002.

[00122] The blood sample optimization system 2000 further includes a blood sequestration device 2008, located at any point on the conduit 2006 between the patient needle 2002 and the blood sample collection device 2004 as described herein.

[00123] FIG. 21 illustrates a non-vented blood sequestration device 2100 using a wicking material chamber. The blood sequestration device 2100 includes a housing 2101 that has a sampling channel 2104 that is at least partially surrounded or abutted by a sequestration chamber 2102 that is filled with a wicking material. An initial aliquot of blood is drawn in from the patient needle into the sampling channel 2104 where it is immediately wicked into the wicking material of the sequestration chamber 2102. The wicking material and/or sequestration chamber 2102 is sized and adapted to receive and hold a predetermined amount of blood, such that follow-on or later blood draws pass by the wicking material and flow straight through the sampling channel 2104 to a sampling device such as a Vacutainer. The wicking material can include a substance such as a solidifier, a decontaminate, or other additive.

[00124] As described herein, an air permeable blood barrier may be created using a wide variety of different structures and materials. As shown in FIGS. 22A and B, an air permeable blood barrier 2202 of a blood sequestration device 2200 can include a polymer bead matrix 2204, in which at least some beads are treated to make them hydrophilic. The air permeable blood barrier 2202 further includes a self-sealing material 2206, such as carboxymethyl cellulose (CMC) or cellulose gum, or other sealing material. The air permeable blood barrier 2202 can further include voids 2208 that permit air flow before contact or during partial contact with a fluid such as blood. As shown in FIG. 22B, contact with a fluid causes the self-sealing material 2206 to swell and close off the voids 2208, occluding air flow through the voids 2208 and creating a complete or partial seal.

[00125] FIGS. 23A and B illustrate yet another implementation of a blood sequestration device 2300, having an inlet port 2302 to connect with a patient needle, an outlet port 2304 to connect with a blood sample collection device, a sequestration chamber 2306, and a sampling channel 2308 that bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be

sequestered. The sequestration chamber 2306 includes a hydrophobic plug 2312 at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302. A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. A small amount of blood may make its way into the sampling channel 2308, which is initially closed off by valve 2308. Upon release of the valve 2308, and under further force of the vacuum or other force, follow-on amounts of blood will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 toward the outlet port 2304 and to the collection device.

[00126] The sampling channel 2308 can have any suitable geometry and can be formed of plastic tubing or any other suitable material. Valve 2308 can be a clip or other enclosing device to pinch, shunt, bend or otherwise close off the sampling channel before the initial aliquot of blood is sequestered in the sequestration chamber 2306.

[00127] Although a variety of embodiments have been described in detail above, other modifications are possible. Other embodiments may be within the scope of the following claims.

CLAIMS

1. A blood sequestration device comprising;

an inlet port;

an outlet port;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port and a distal end connected with the outlet port; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

2. The blood sequestration device in accordance with claim 1, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

3. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber includes a sequestration channel defined in the housing.

4. The blood sequestration device in accordance with claim 3, further comprising a blood sampling pathway connected with the inlet port, and wherein the inlet port defined by the housing has a cross-sectional geometry consistent with the blood sampling pathway.

5. The blood sequestration device in accordance with claim 3, wherein the sampling channel defined by the housing has a cross-sectional geometry consistent with the inlet port.

6. The blood sequestration device in accordance with claim 1, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

7. The blood sequestration device in accordance with claim 3, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

8. A blood sequestration device connected with a blood sampling pathway having a patient needle and a sample collection device, the blood sequestration device comprising;

an inlet port connected with the patient needle;

a sequestration chamber connected with the inlet port, the sequestration chamber having a vent comprising an air permeable blood barrier;

a sampling channel having a proximal end connected with the inlet port; and

an outlet port connected with a distal end of the sampling channel and with the sample collection device; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

9. The blood sequestration device in accordance with claim 8, wherein the inlet port is connected with the patient needle via a first portion of the blood sampling pathway.

10. The blood sequestration device in accordance with claim 8, wherein the outlet port is connected with the sample collection device via a second portion of the blood sampling pathway.

11. The blood sequestration device in accordance with claim 8, wherein the air permeable blood barrier includes an air permeable material that seals at least partially upon contact with blood.

12. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber includes a sequestration channel defined in the housing.

13. The blood sequestration device in accordance with claim 12, wherein the sequestration channel has a proximal end connected with the inlet port, and a distal end having the vent comprising an air permeable blood barrier.

14. The blood sequestration device in accordance with claim 8, wherein the sequestration chamber and the sampling channel are connected with the inlet port by a junction that is configured to direct a first portion of blood to the sequestration chamber.

15. The blood sequestration device in accordance with claim 8, wherein the sampling channel has a substantially uniform cross-sectional geometry that is consistent with the blood sampling pathway.

16. The blood sequestration device in accordance with claim 15, wherein the sequestration chamber includes a sequestration chamber that has a cross-sectional area that is larger than the cross-sectional geometry of the sampling channel.

17. A blood sequestration device connected with a blood sampling system comprising a patient needle for accessing a blood sample from a patient, and a sample needle that is sealed, the blood sequestration device comprising;

an inlet port connected with the patient needle to receive the blood sample from the patient;

a sequestration chamber connected with the inlet port and having a vent comprising an air permeable blood barrier, the sequestration chamber for receiving and sequestering a first portion of the blood sample prior to the sample needle being unsealed; and

a sampling channel having a proximal end connected with the inlet port, the sampling channel for conveying a second portion of the blood sample once the sample needle is unsealed;

an outlet port connected with a distal end of the sampling channel for conveying the second portion of the blood sample to the sample needle; and

a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

18. The blood sequestration device in accordance with claim 17, wherein the sequestration chamber is at ambient air pressure, and wherein the sequestration chamber receives the first portion of the blood sample by blood pressure of the patient overcoming the ambient air pressure in the sequestration chamber.

19. The blood sequestration device in accordance with claim 17, wherein the sampling channel causes the second portion of the blood sample to bypass the sequestered first portion of blood, and exit the outlet port for conveyance to a blood collection device.

20. The blood sequestration device in accordance with claim 17, wherein the air permeable blood barrier includes an air permeable material that seals upon contact with blood.

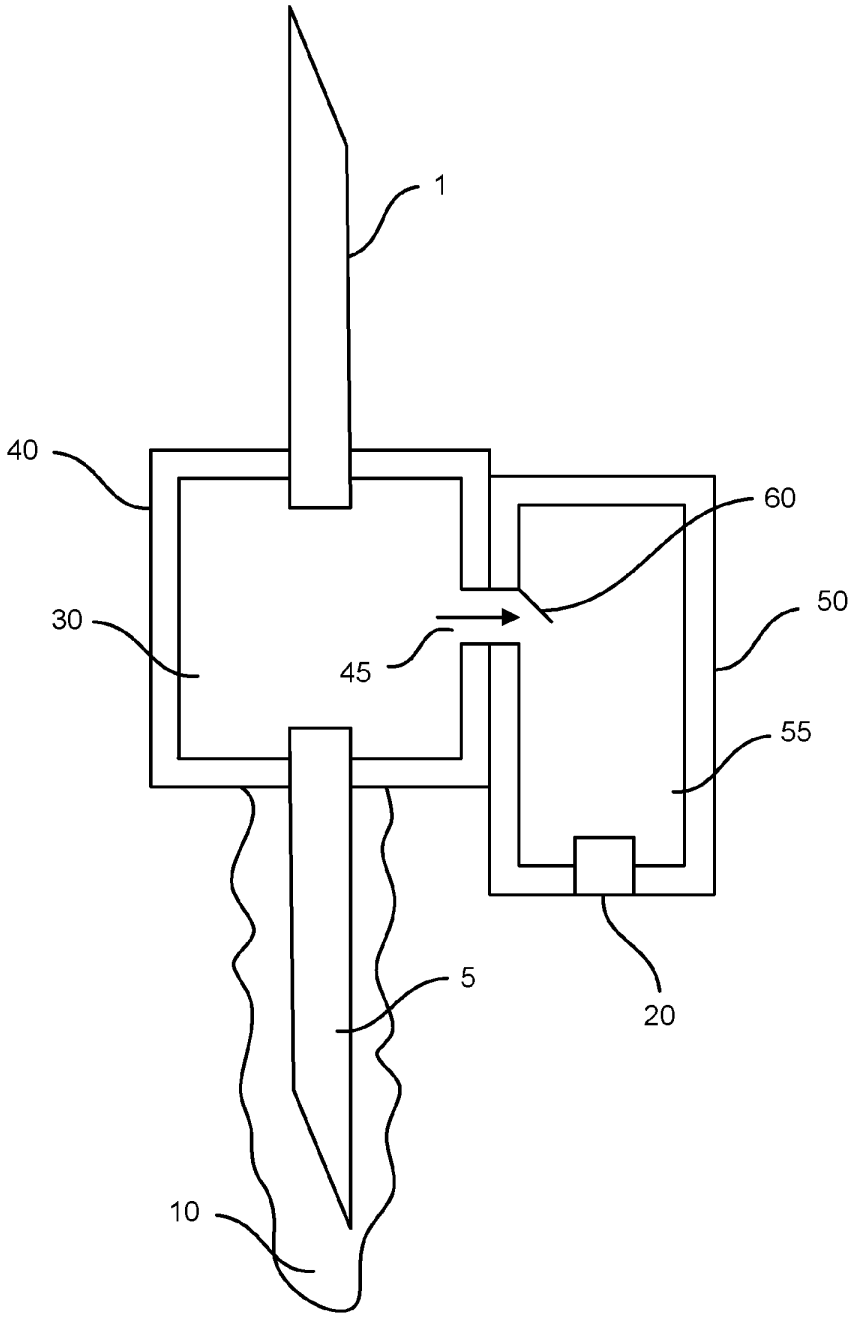


FIG. 1

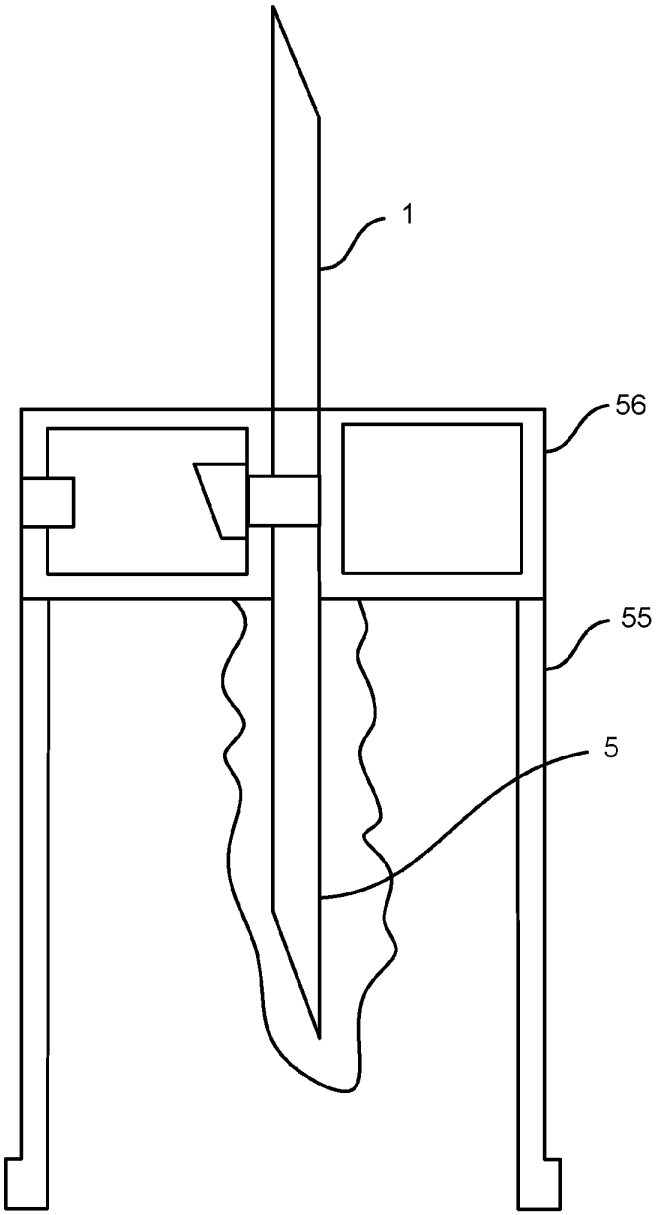


FIG. 2

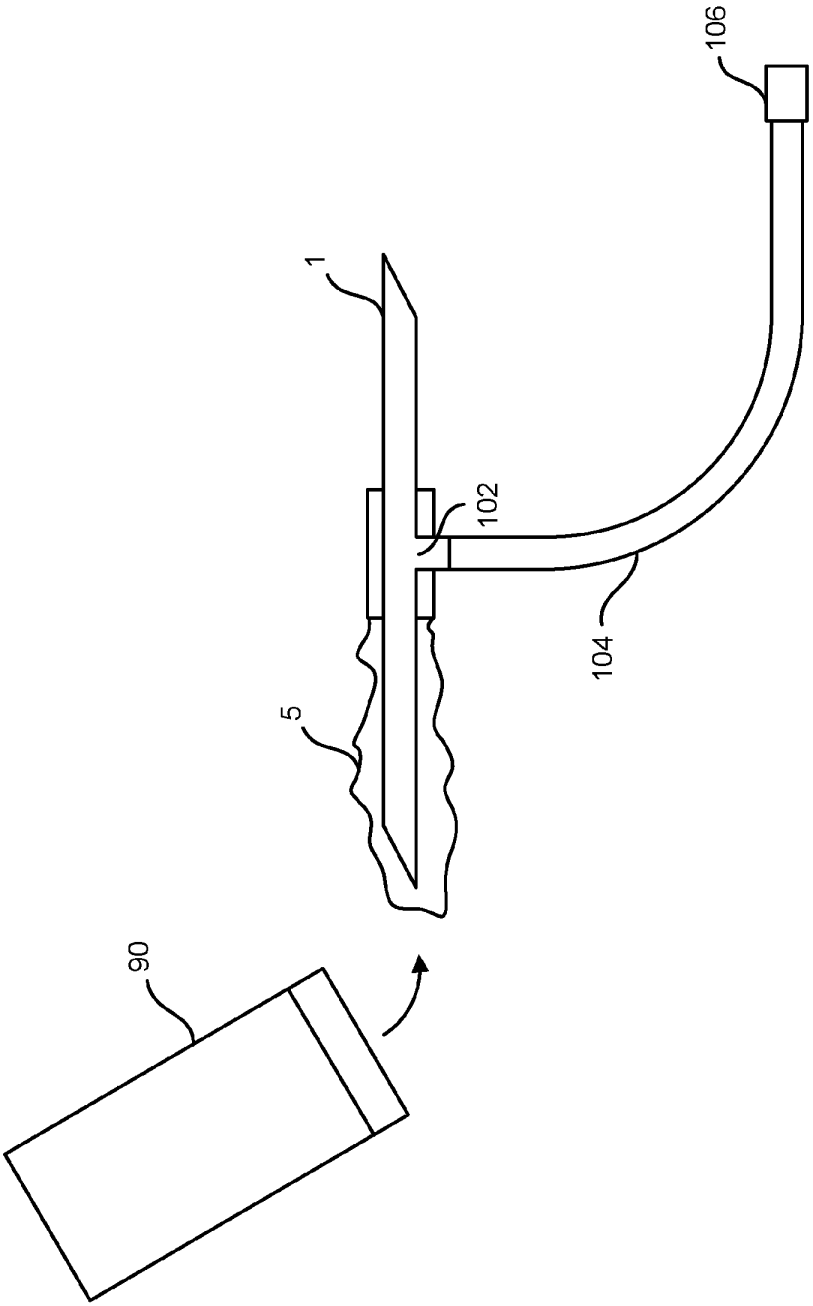


FIG. 3

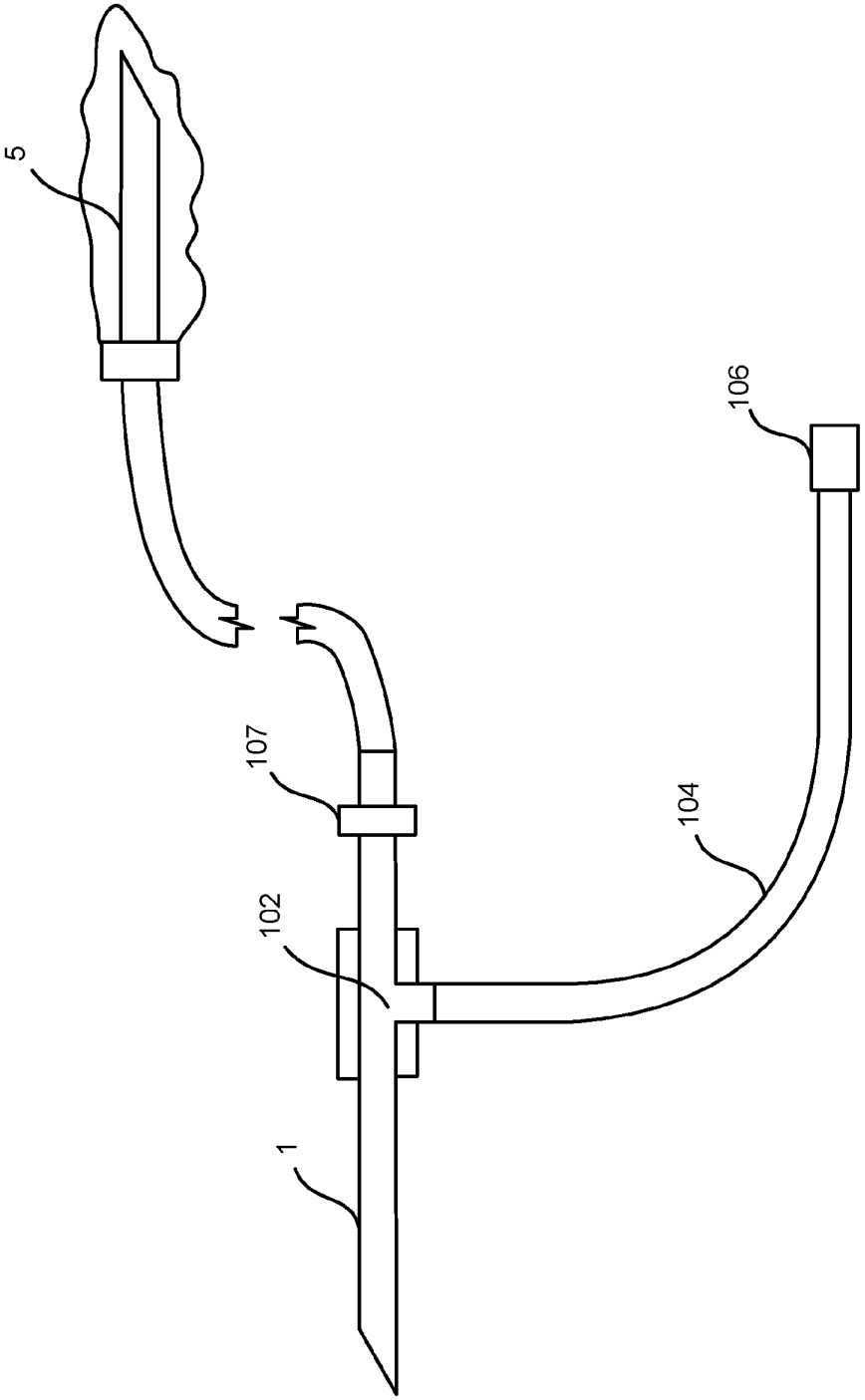


FIG. 4

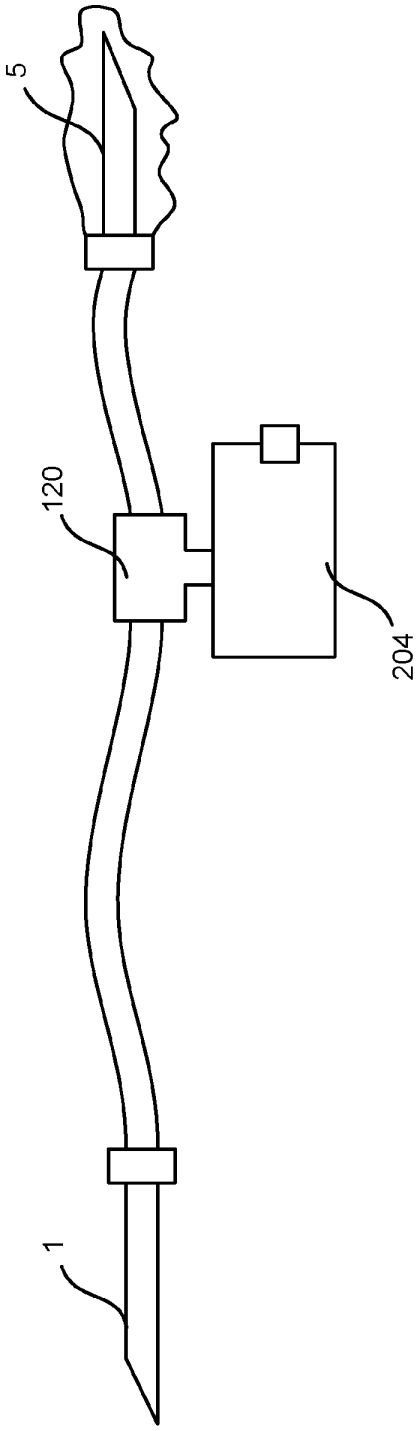


FIG. 5

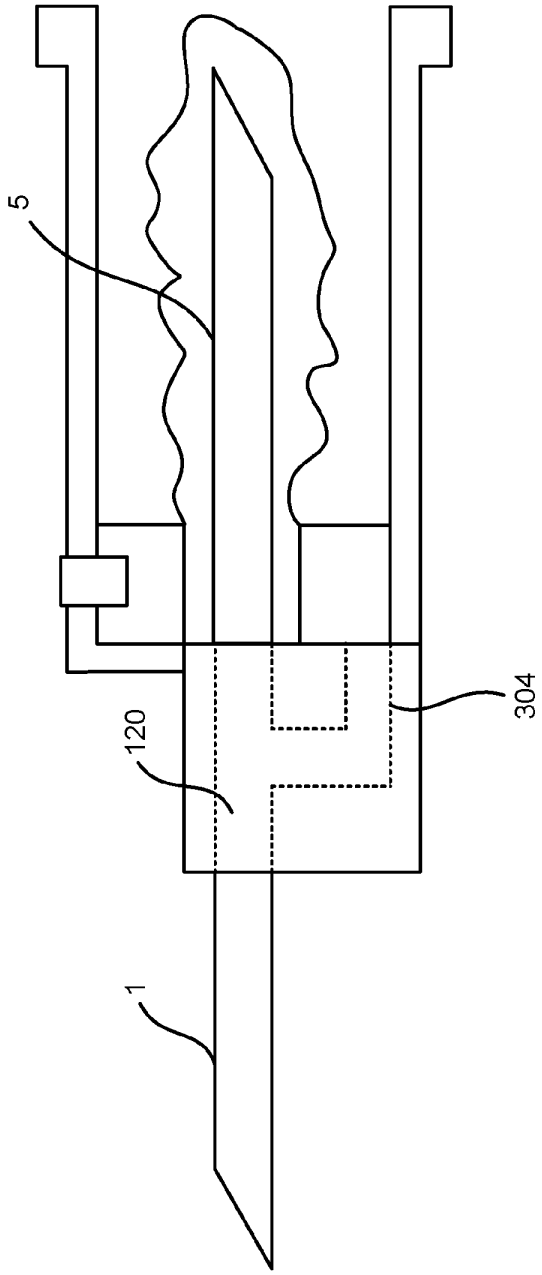


FIG. 6

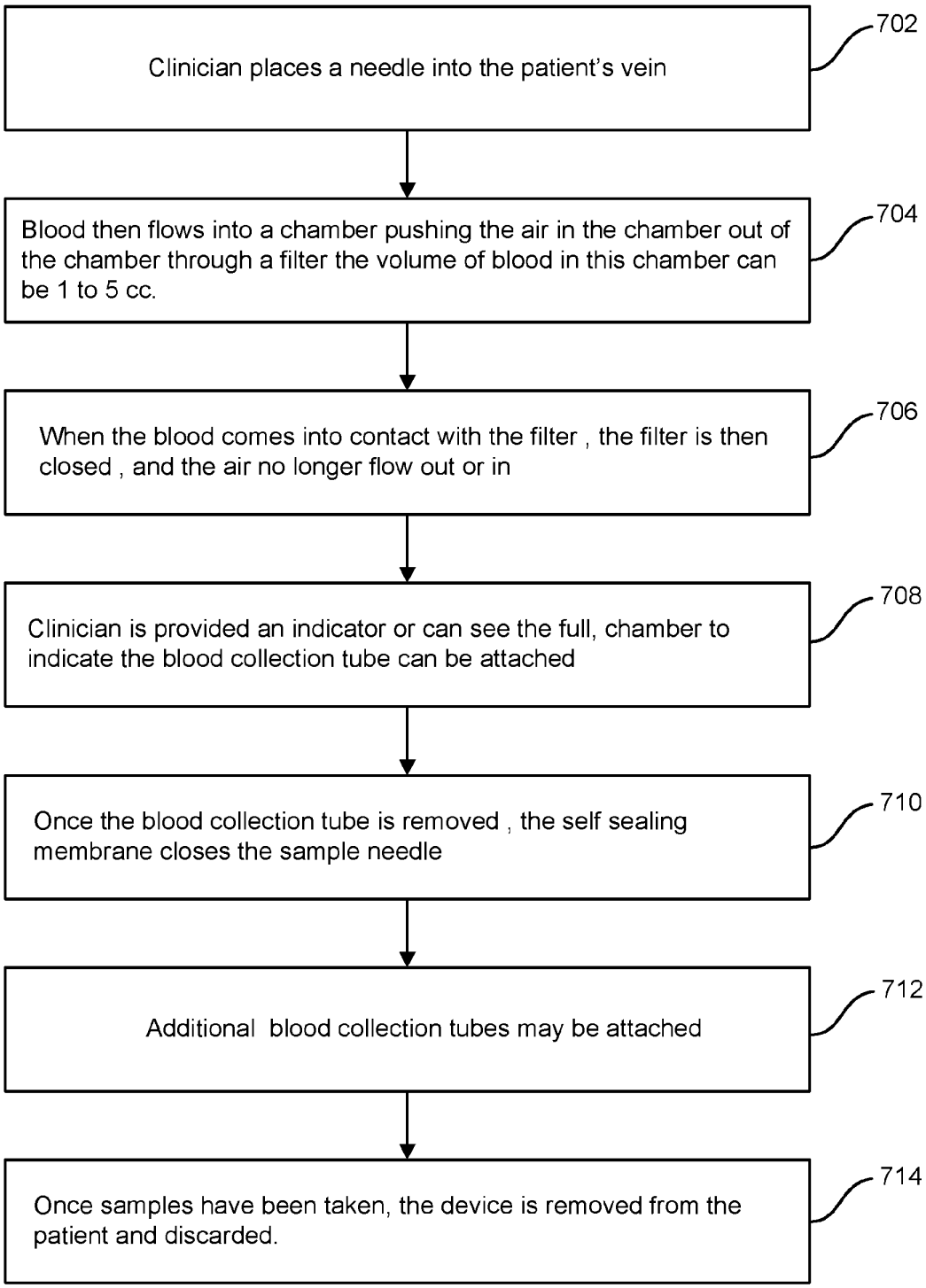

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air no longer flow out or in
706
Clinician is provided an indicator or can see the full, chamber to indicate the blood collection tube can be attached
708
Once the blood collection tube is removed , the self sealing membrane closes the sample needle
710
Additional blood collection tubes may be attached
712
Once samples have been taken, the device is removed from the patient and discarded.
714

FIG. 7

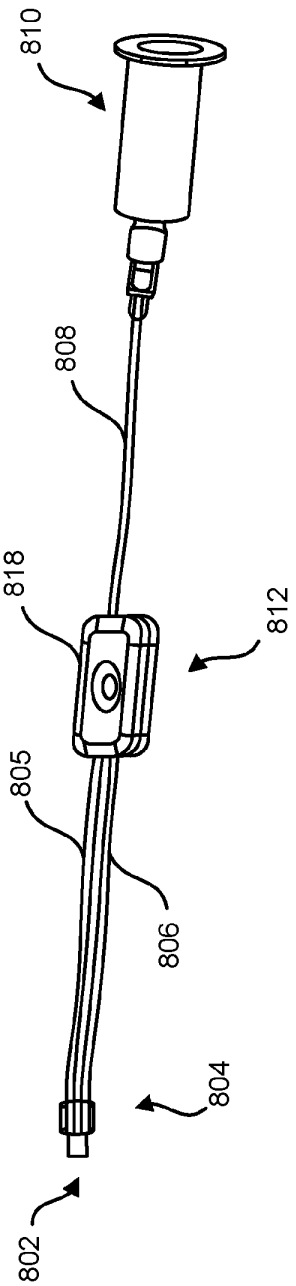


FIG. 8A

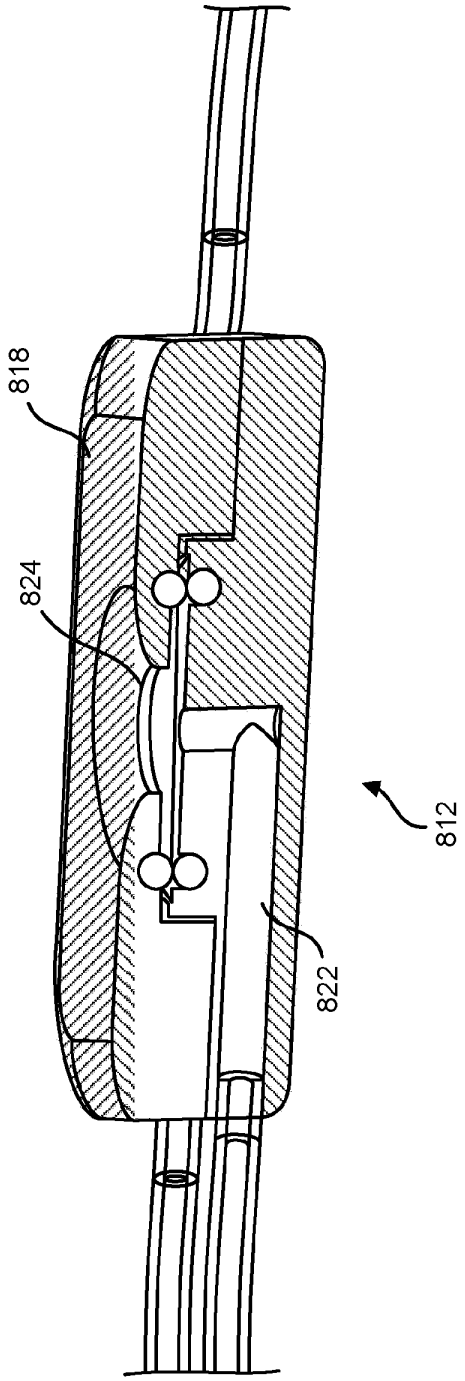


FIG. 8B

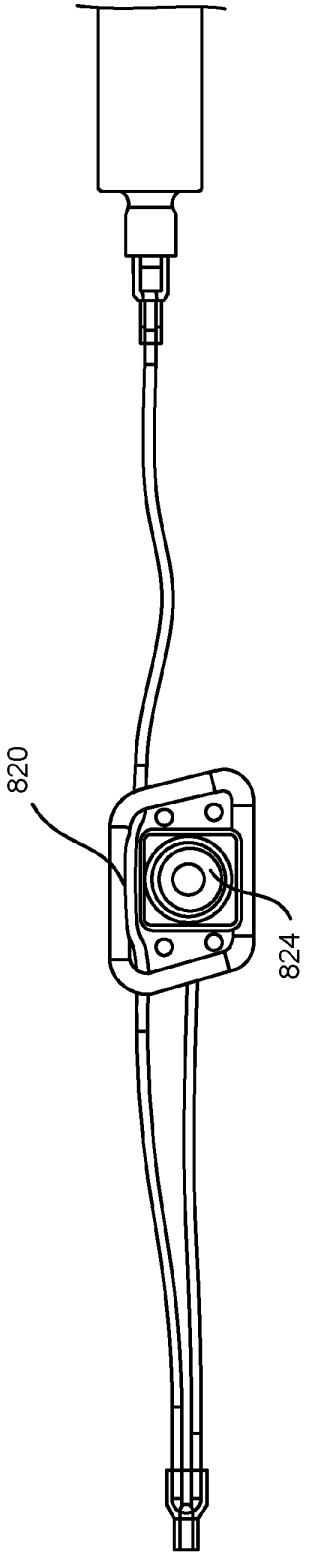


FIG. 8C

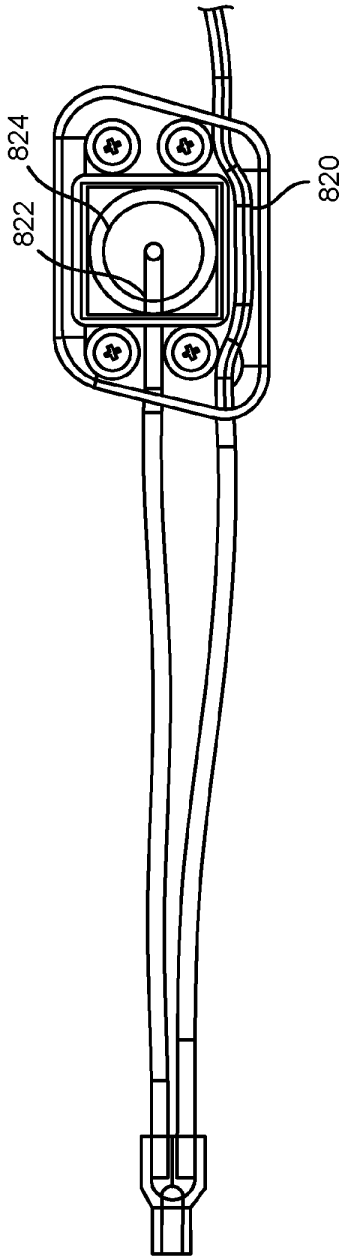


FIG. 8D

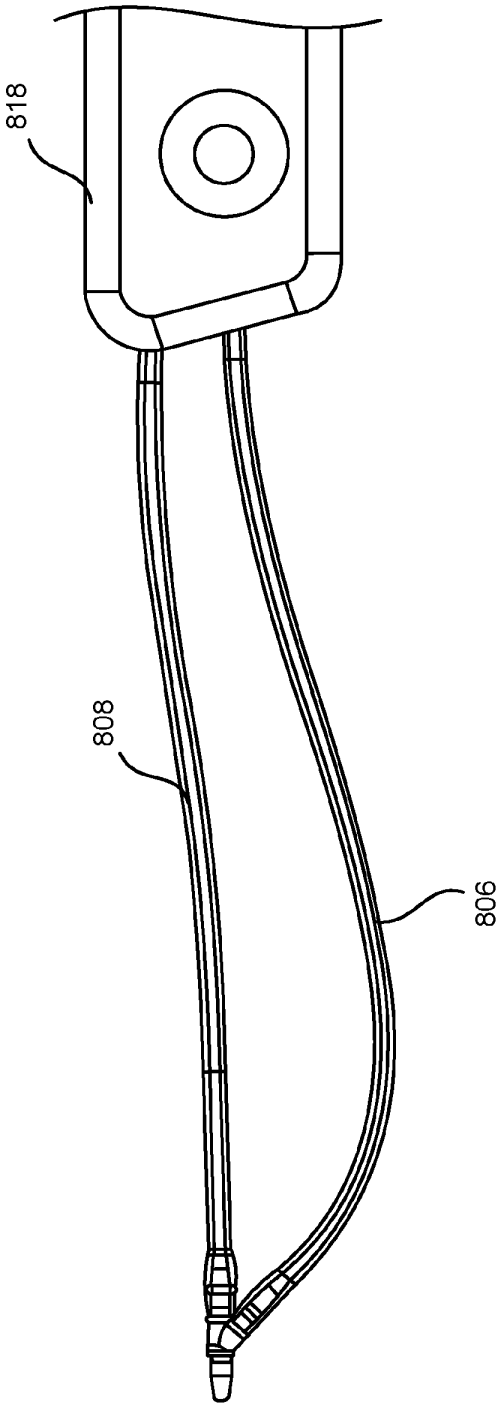


FIG. 8E

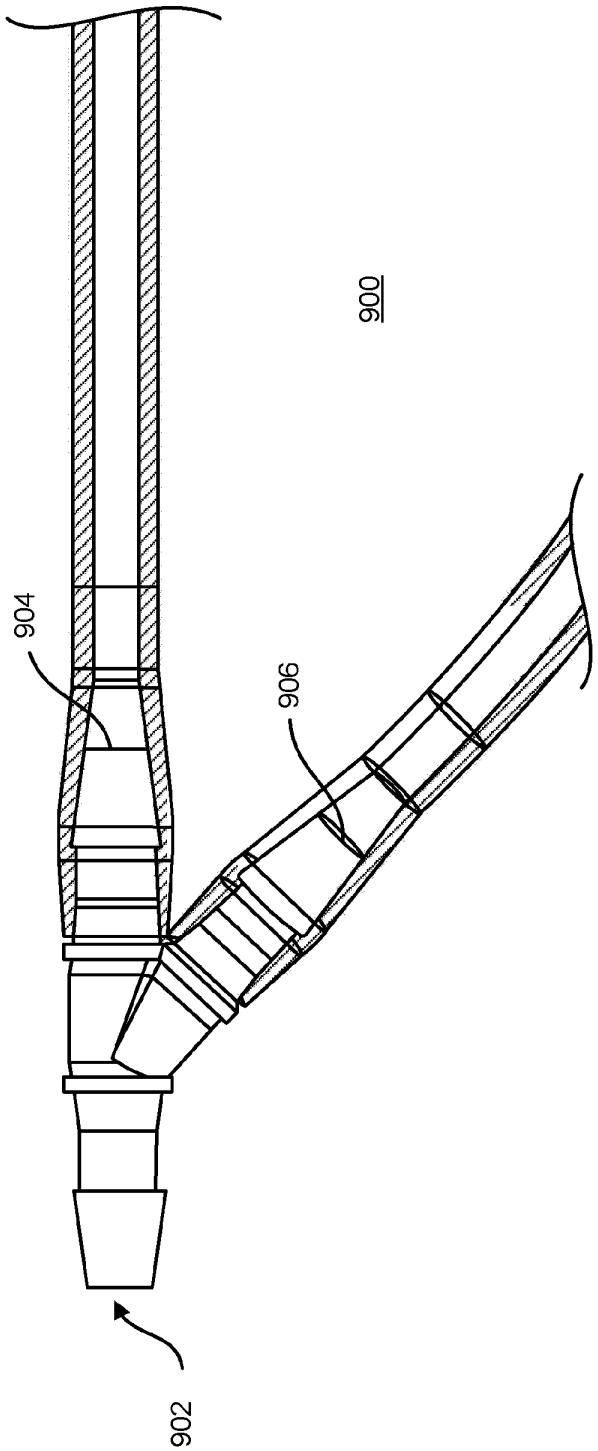


FIG. 9

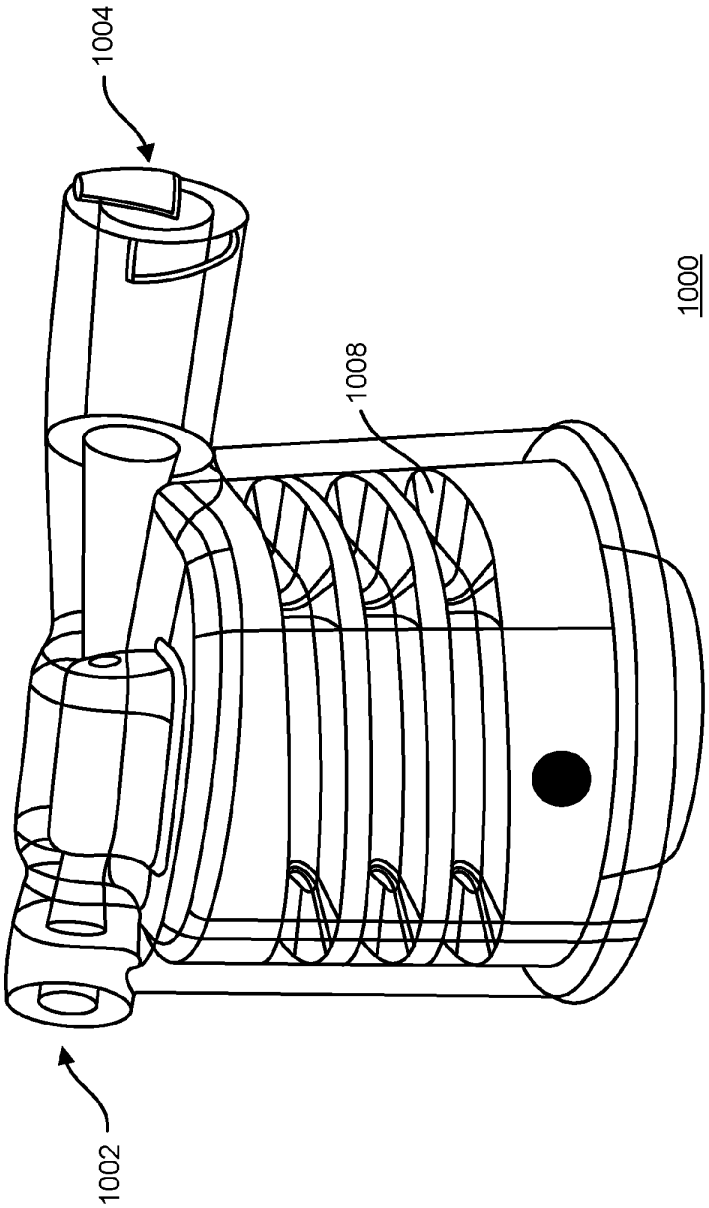


FIG. 10A

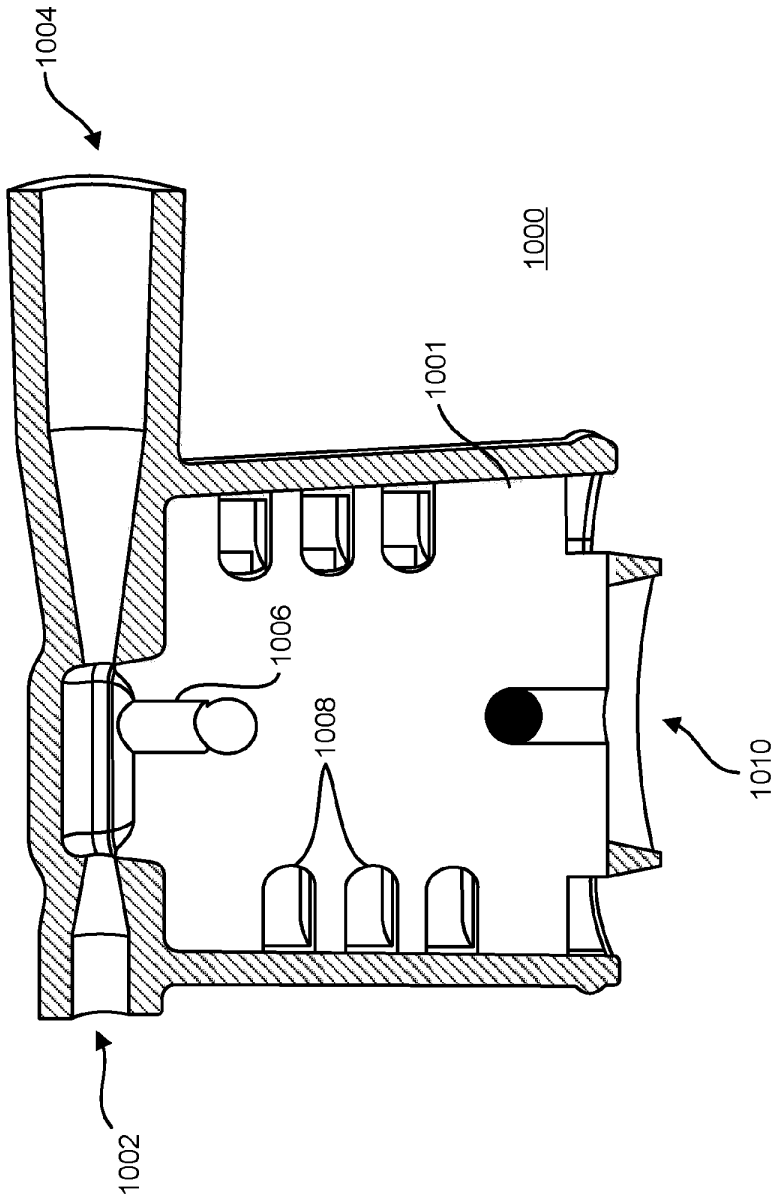


FIG. 10B

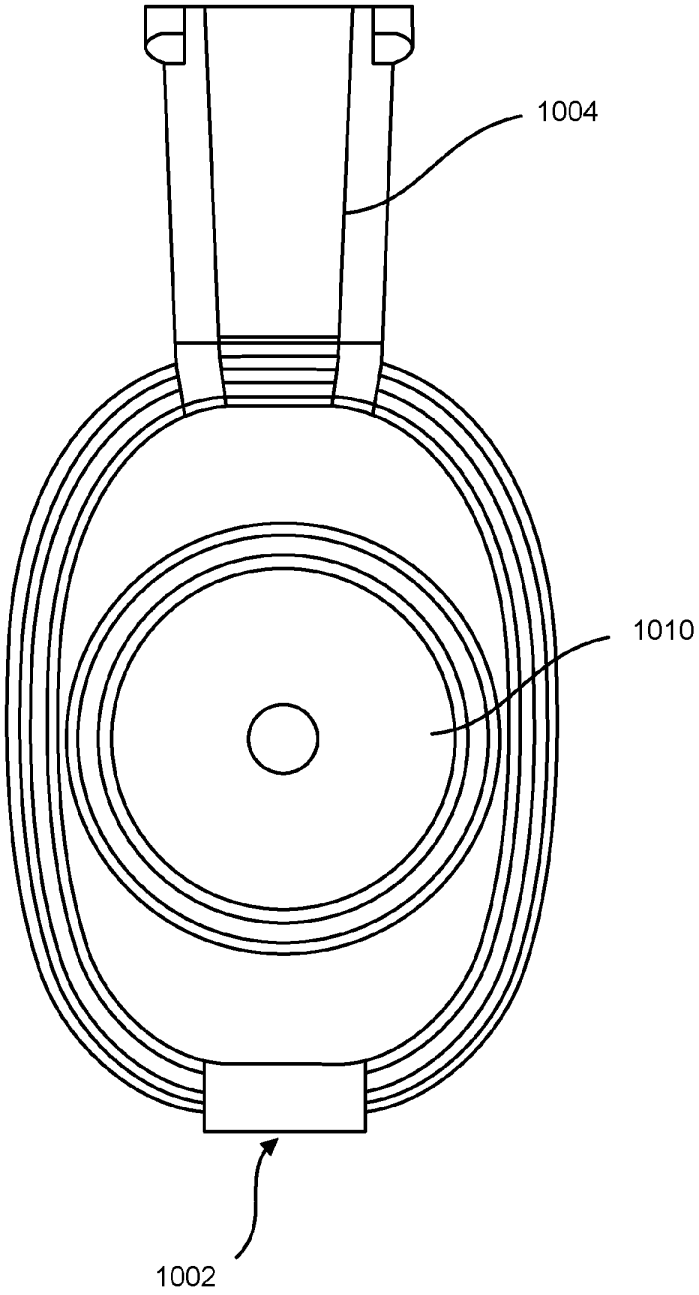


FIG. 10C

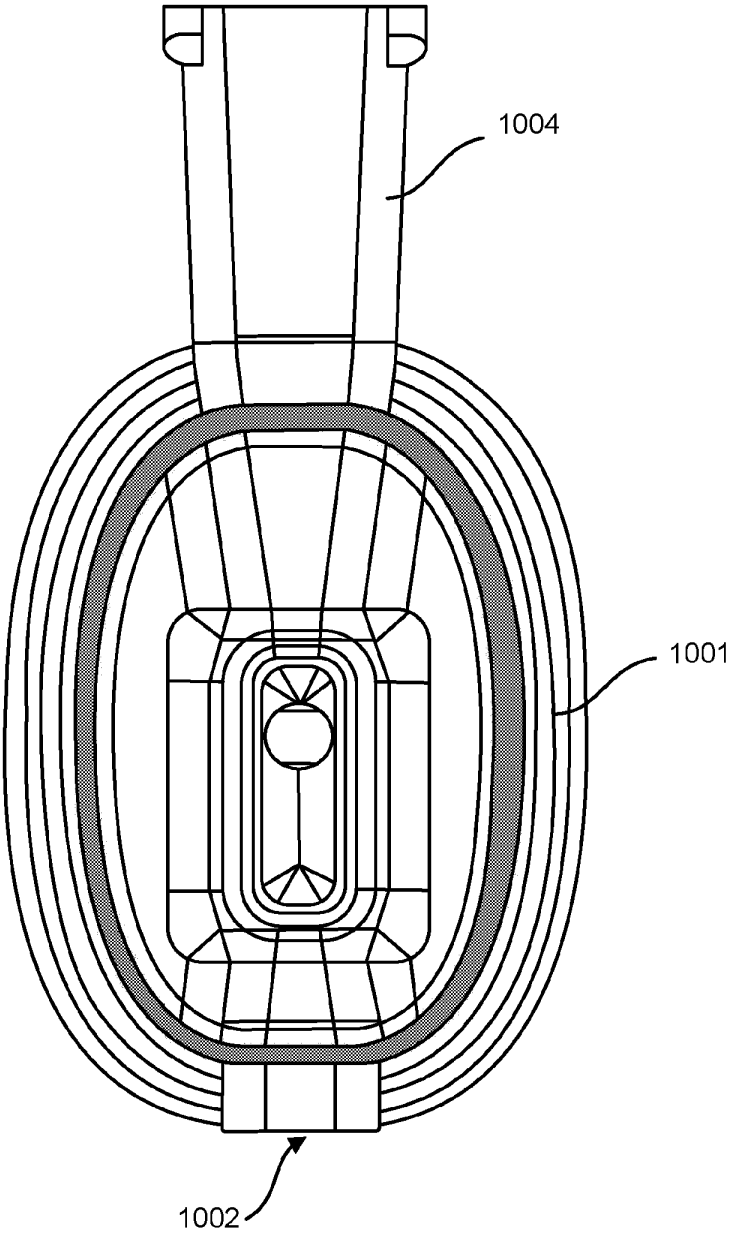


FIG. 10D

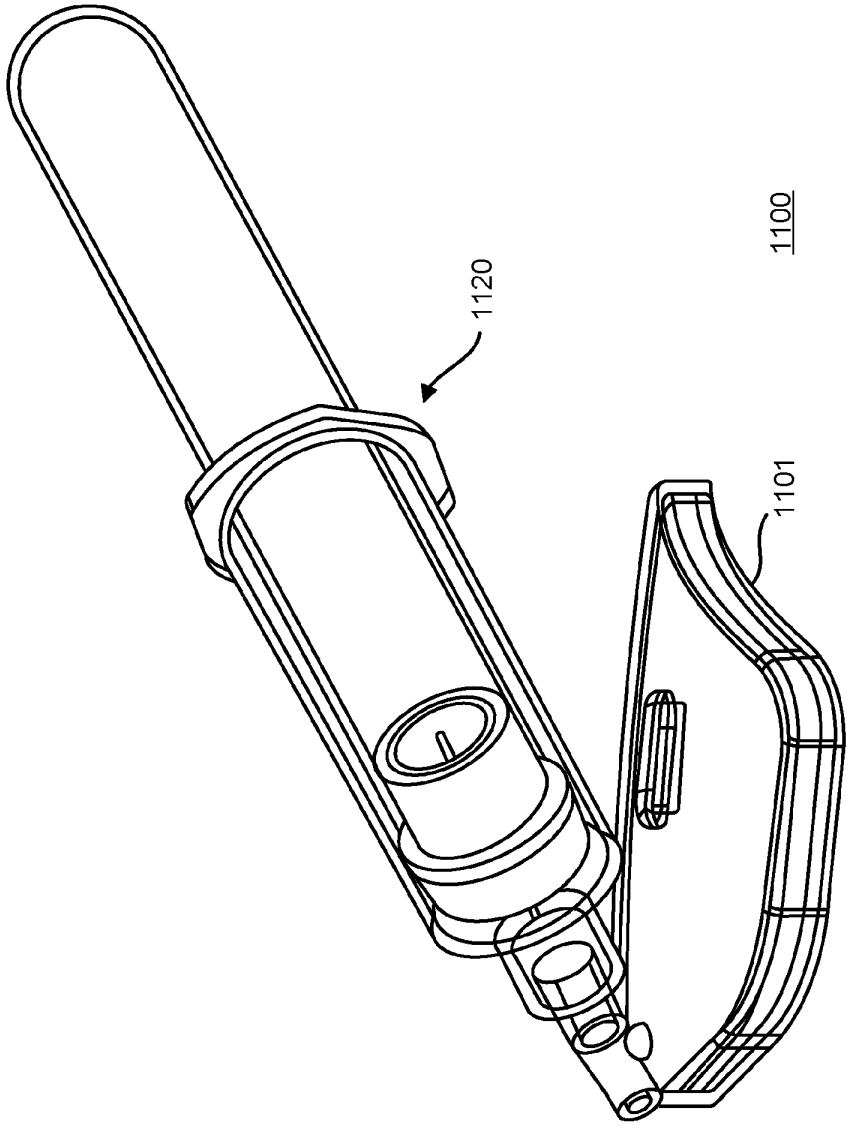


FIG. 11A

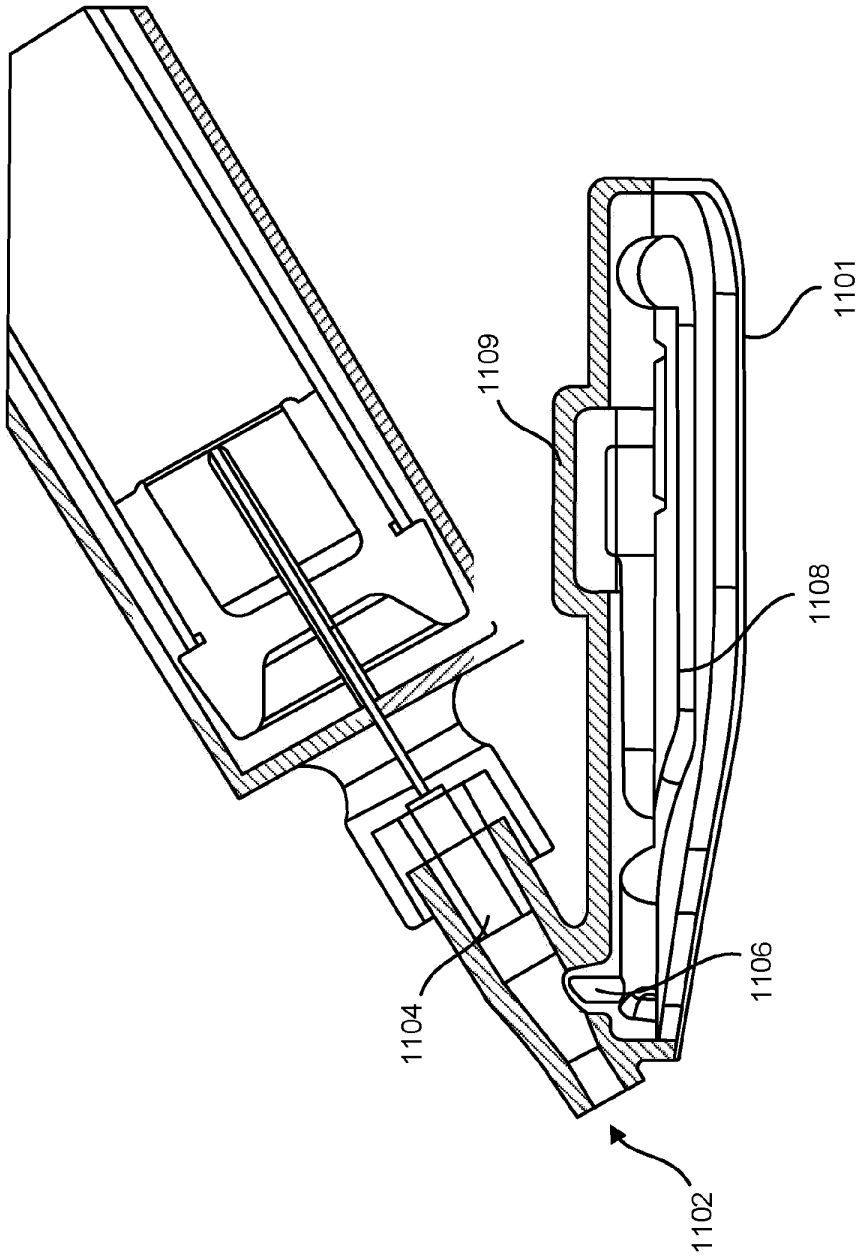


FIG. 11B

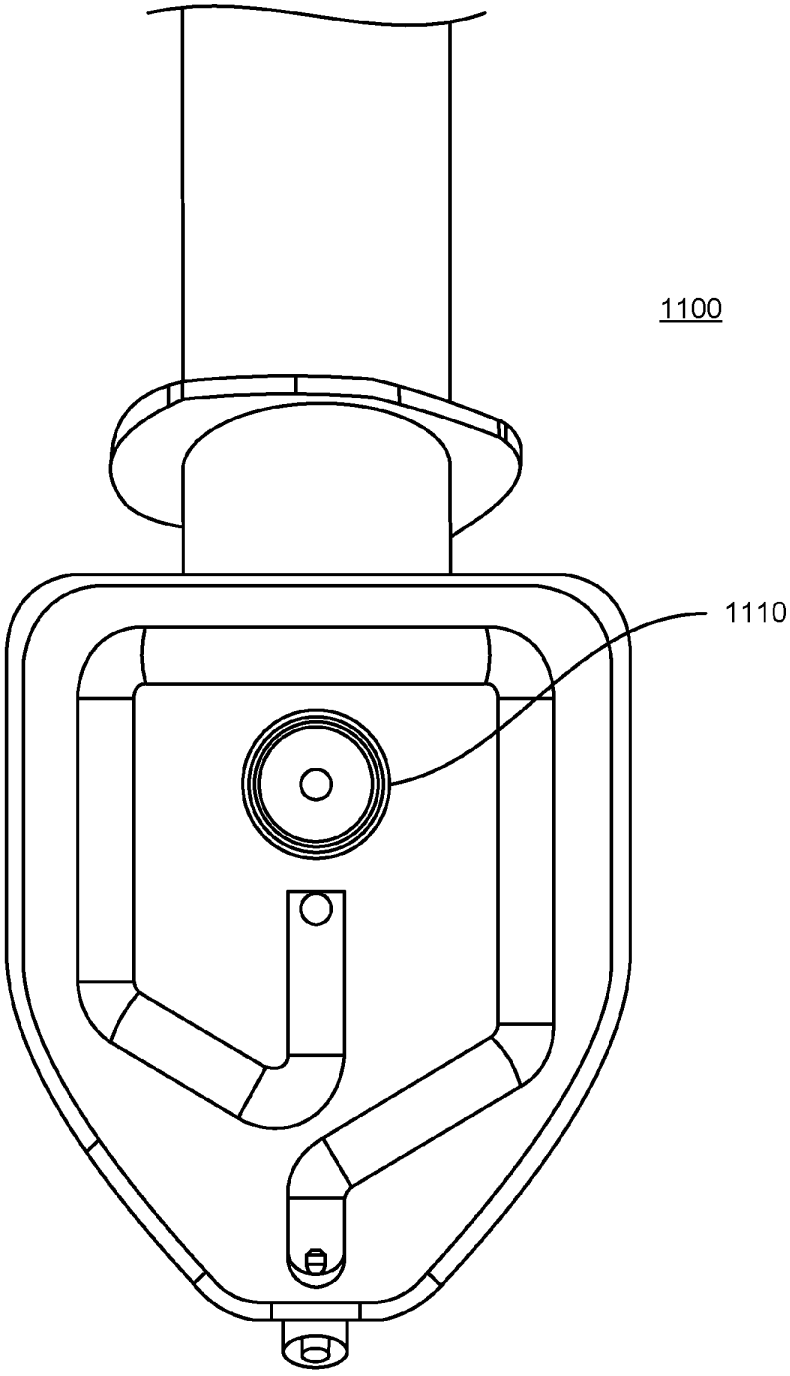


FIG. 11C

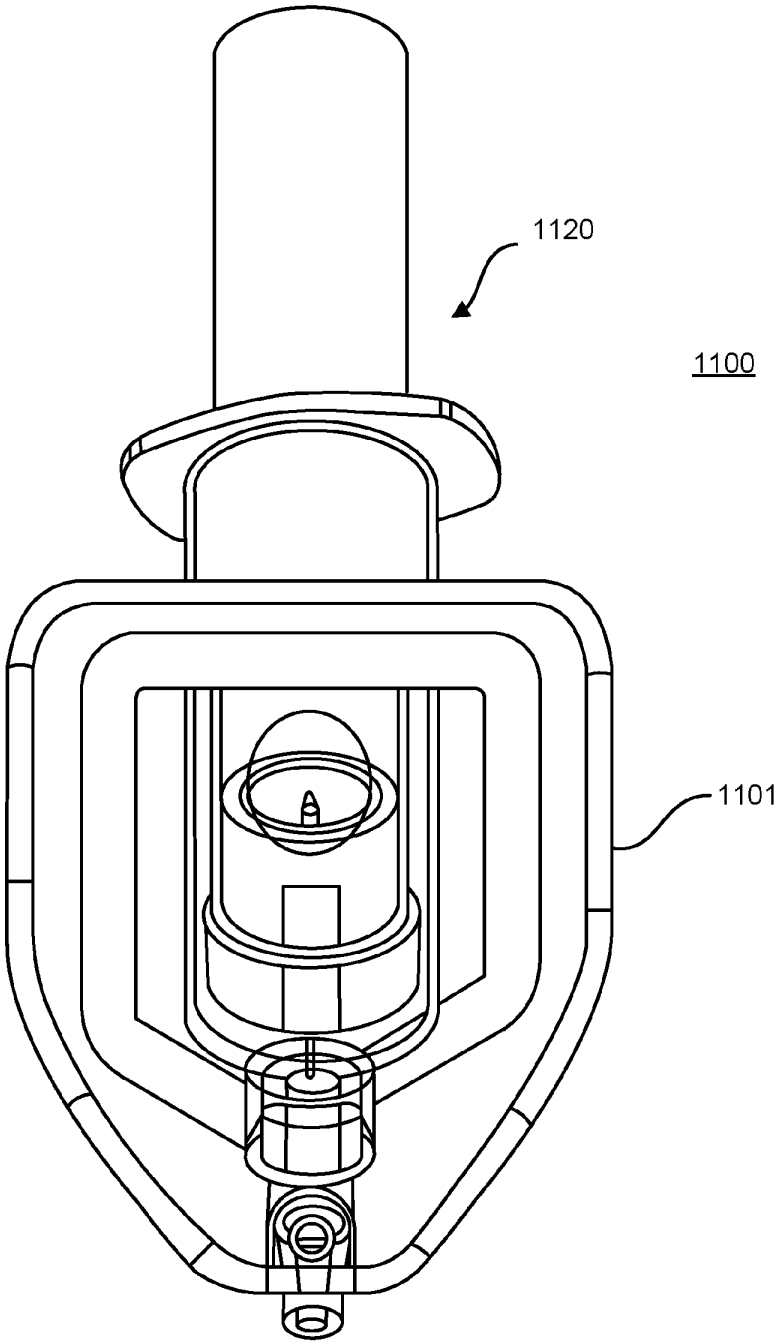


FIG. 11D

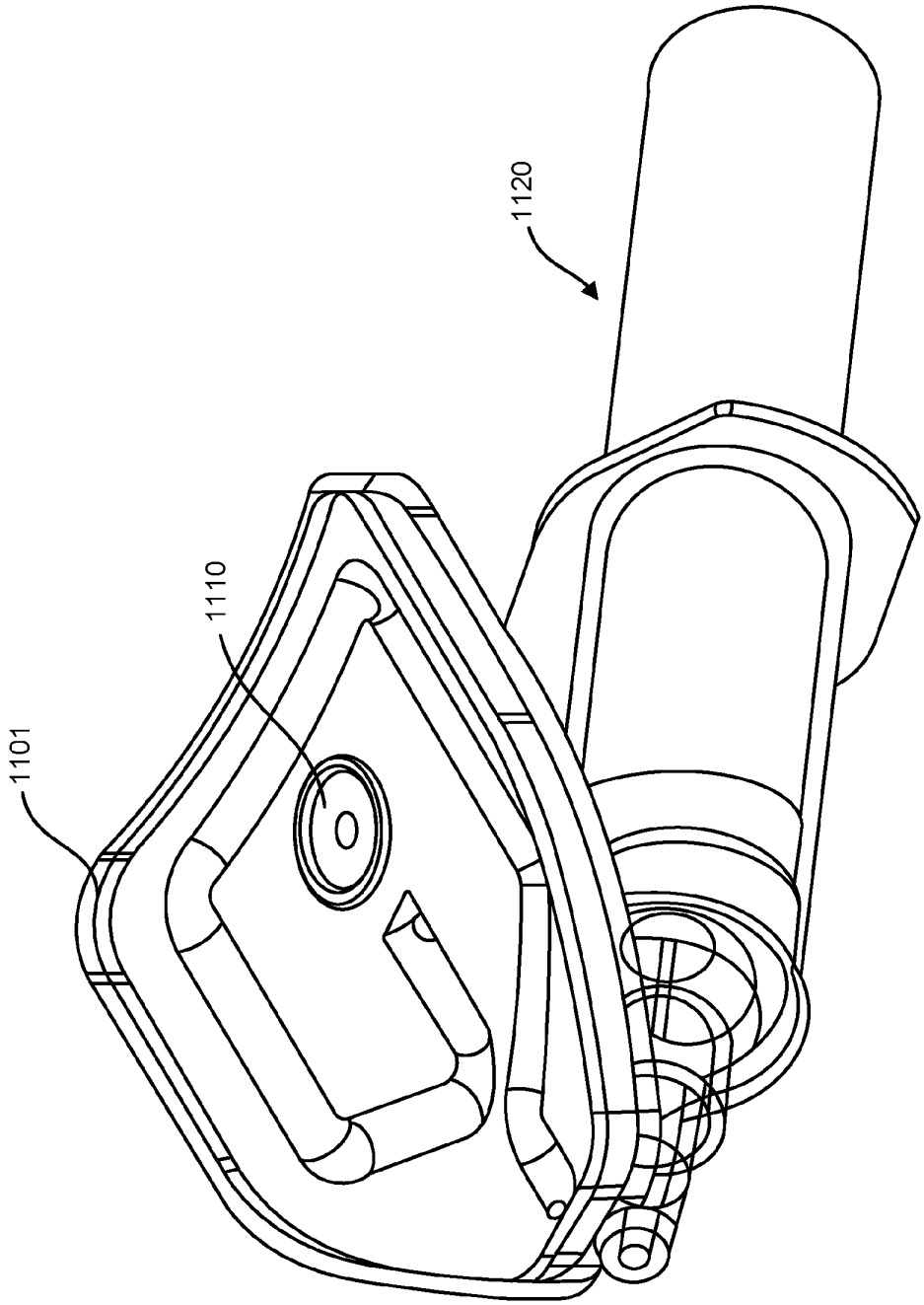


FIG. 11E

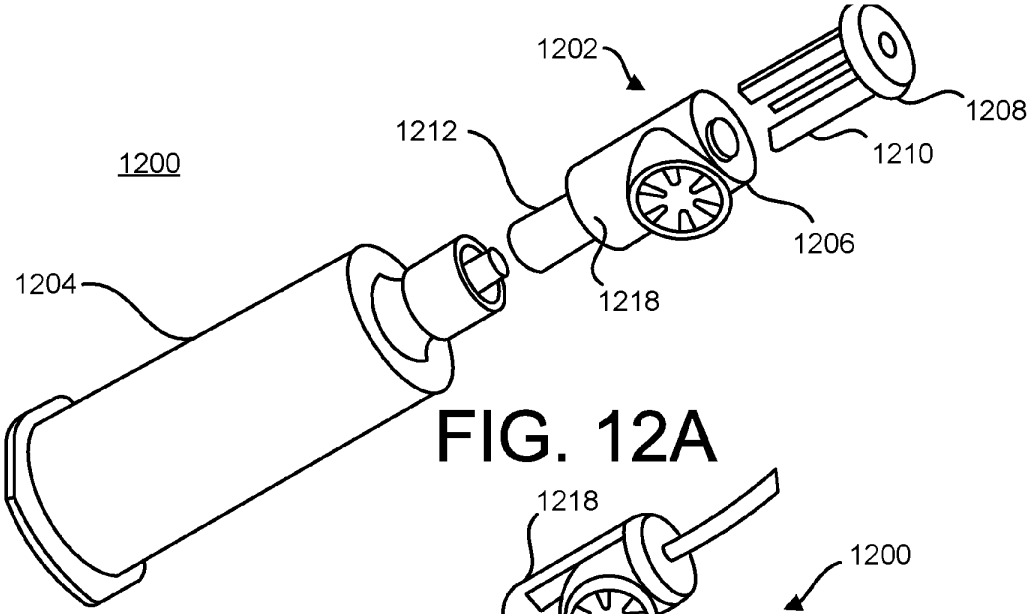


FIG. 12A

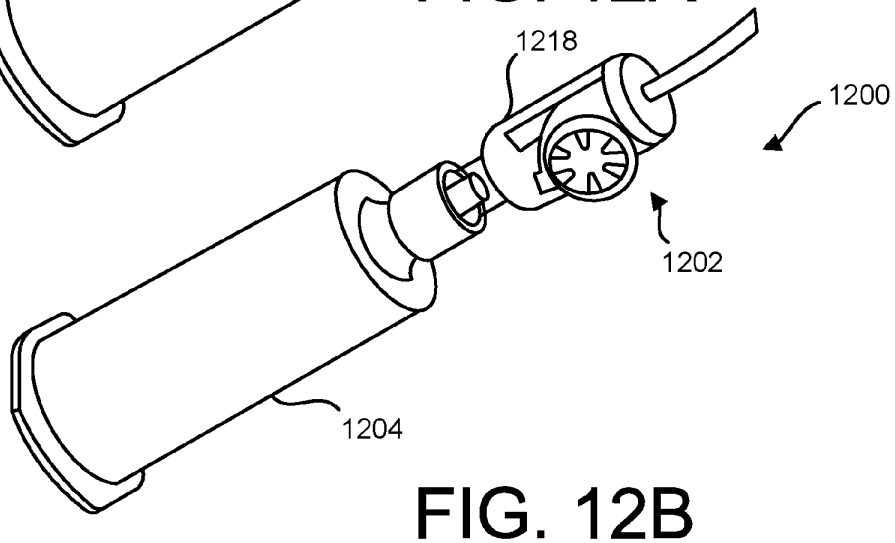


FIG. 12B

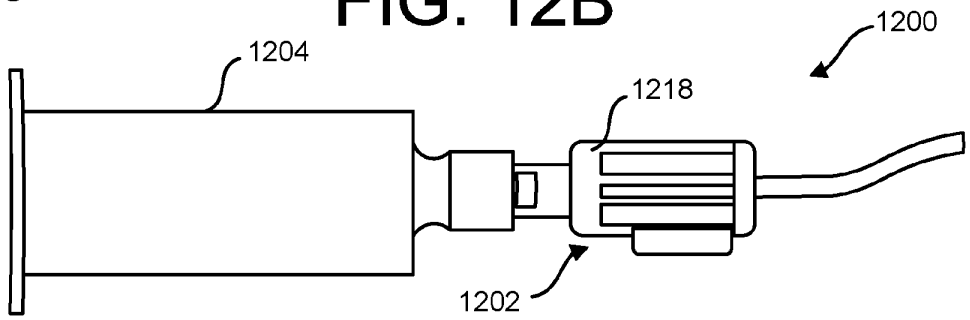


FIG. 12C

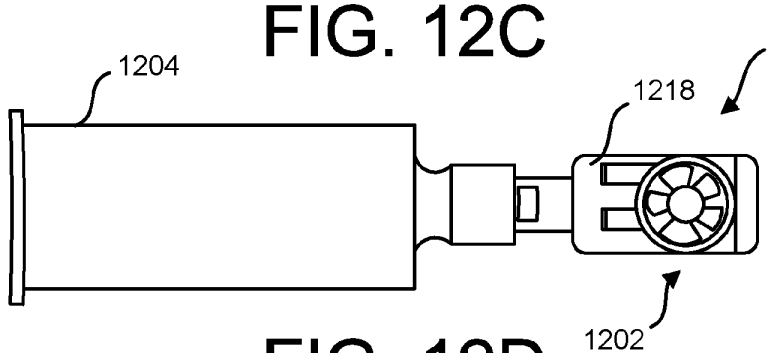


FIG. 12D

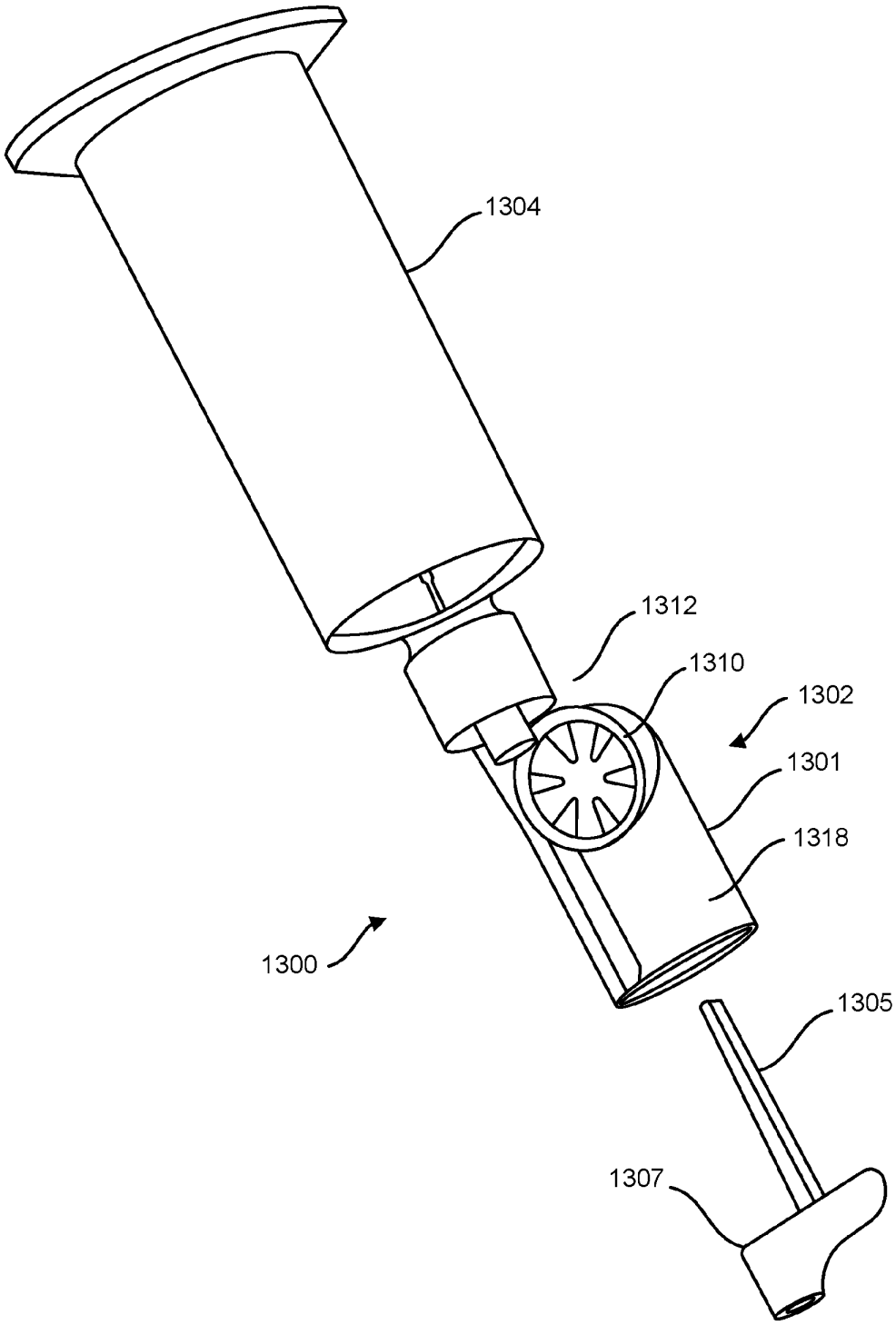


FIG. 13A

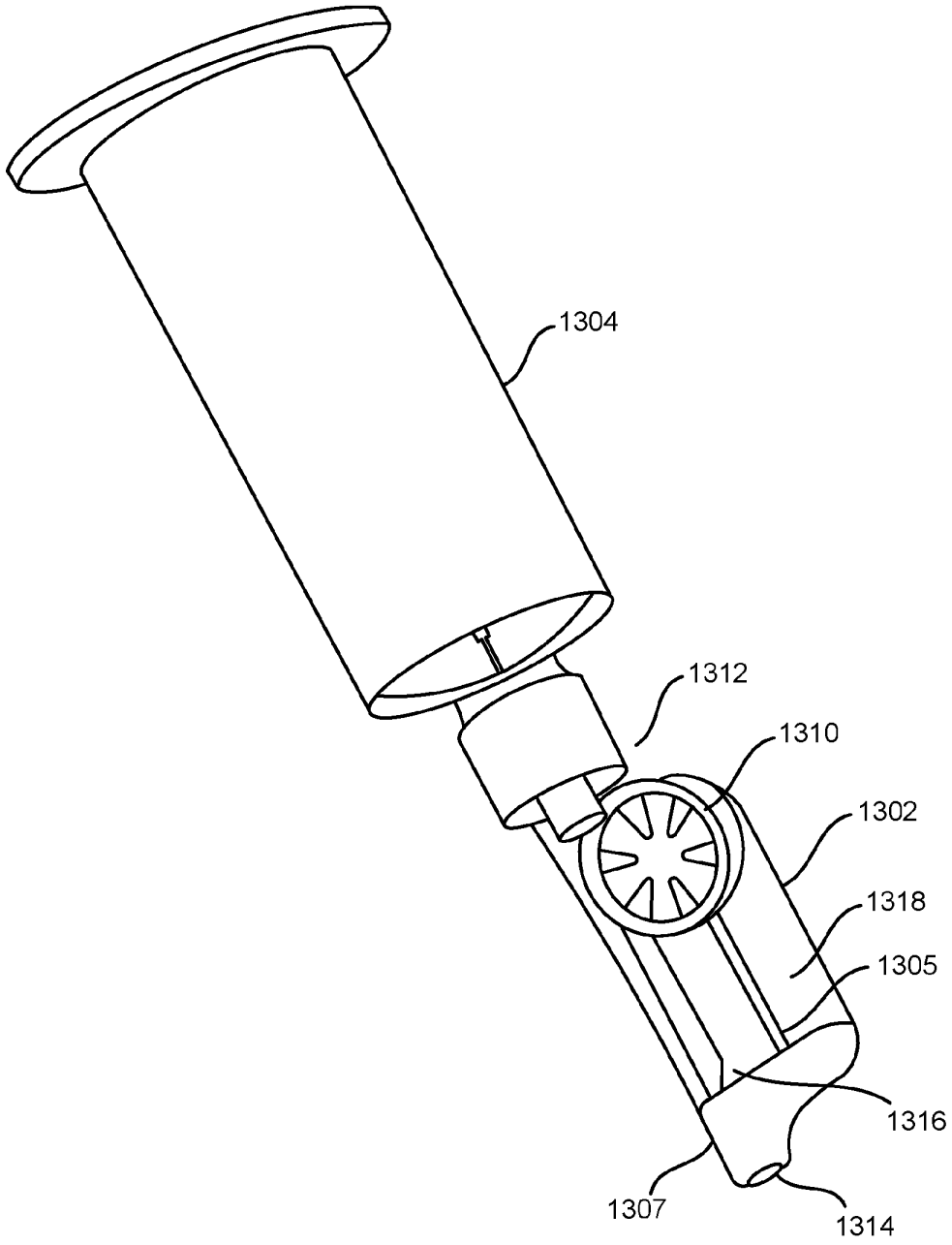


FIG. 13B

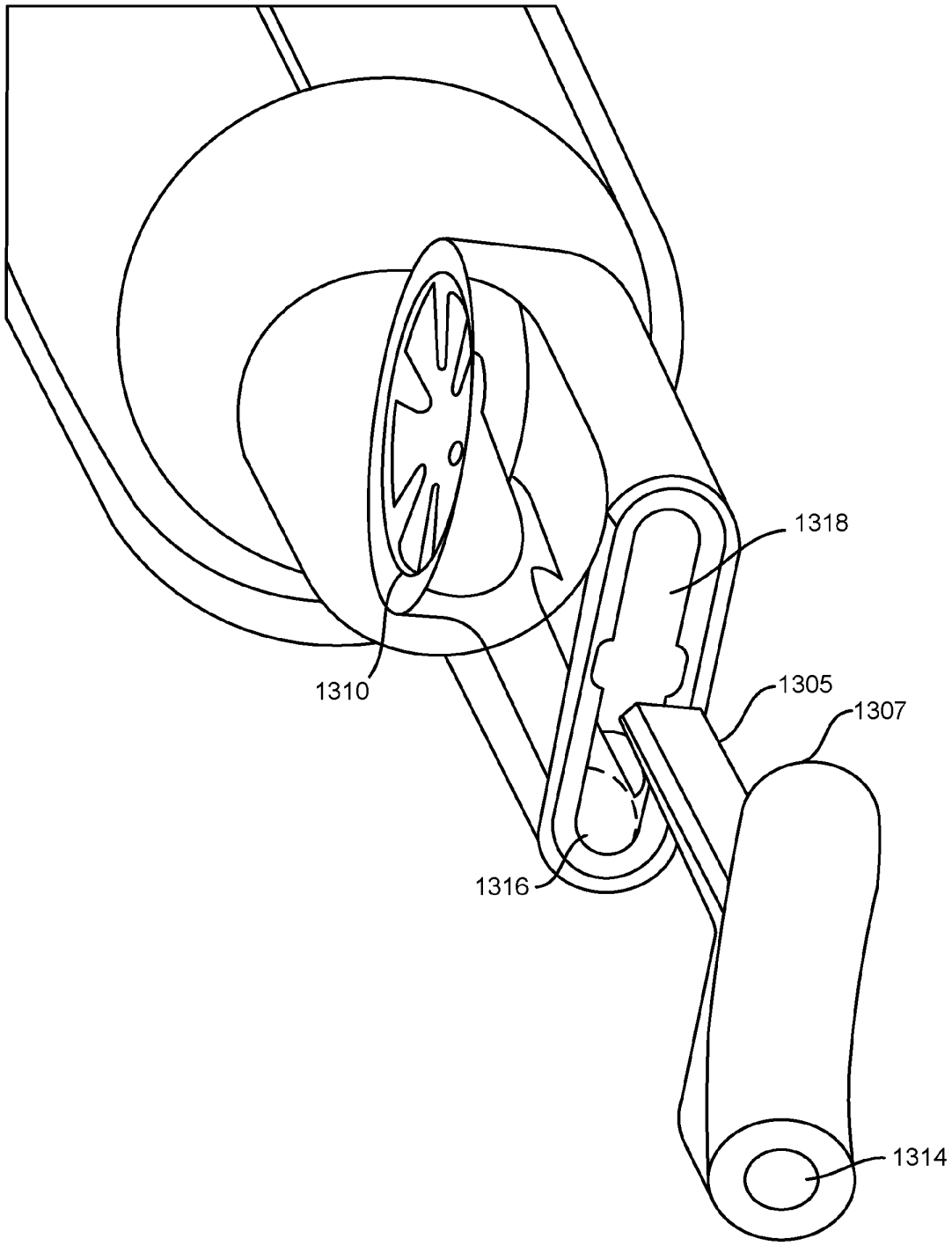


FIG. 13C

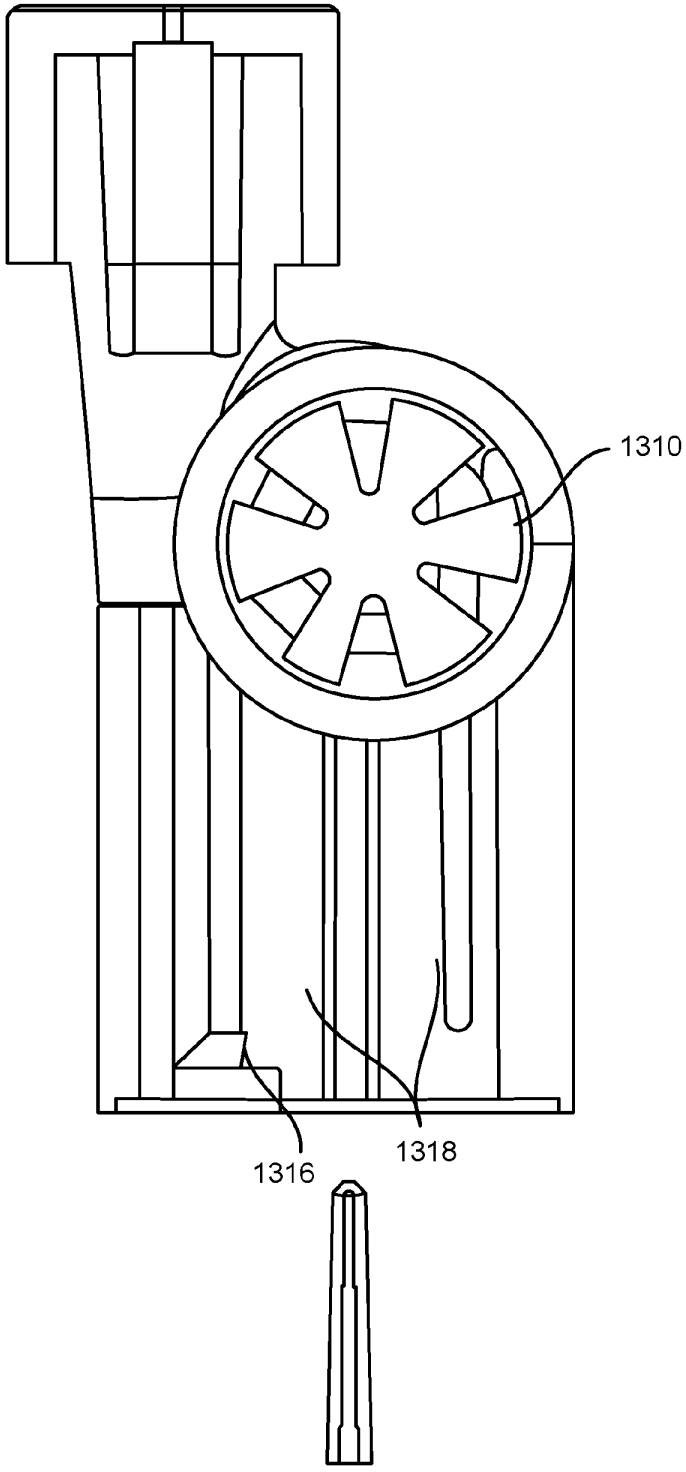


FIG. 13D

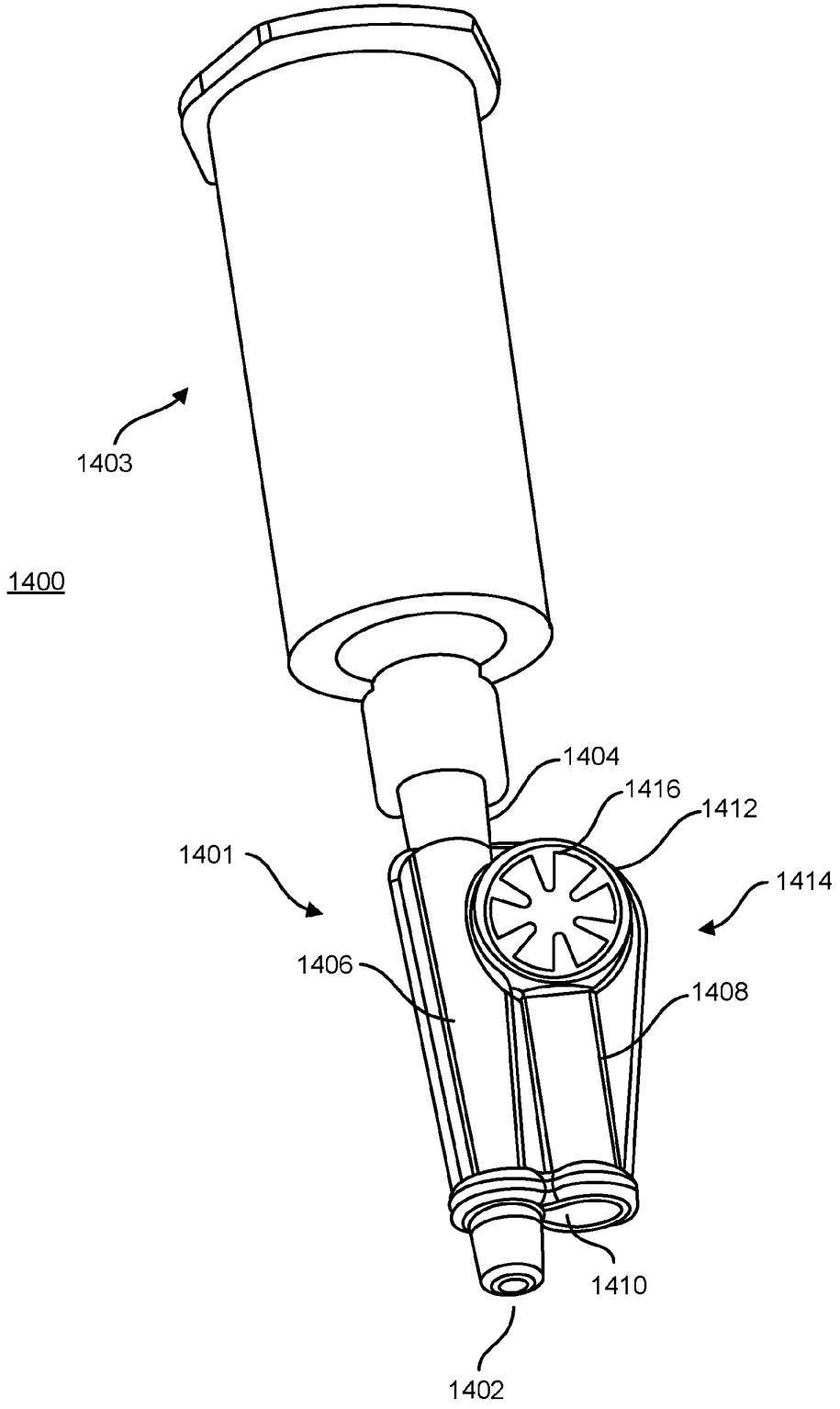


FIG. 14A

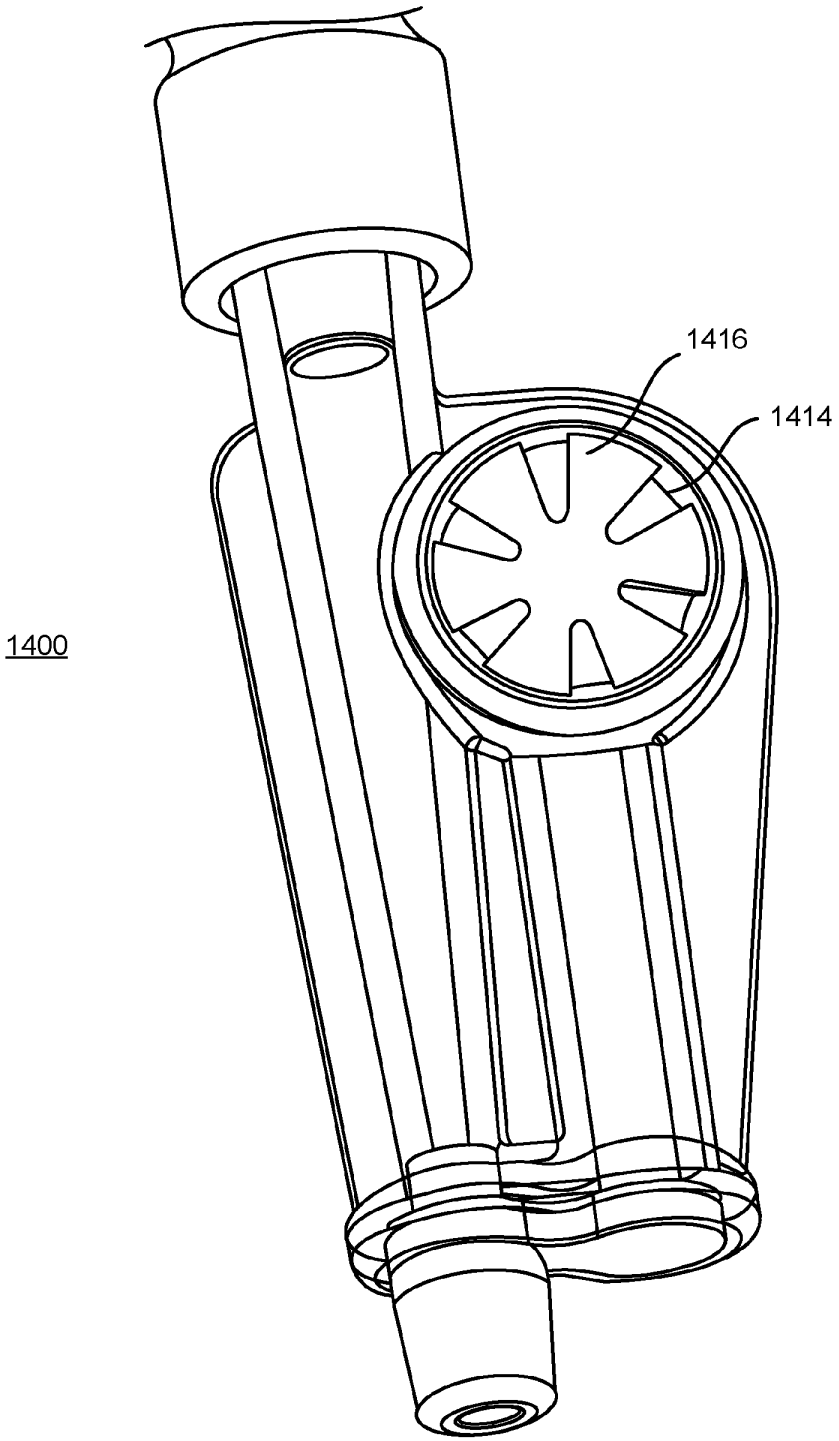


FIG. 14B

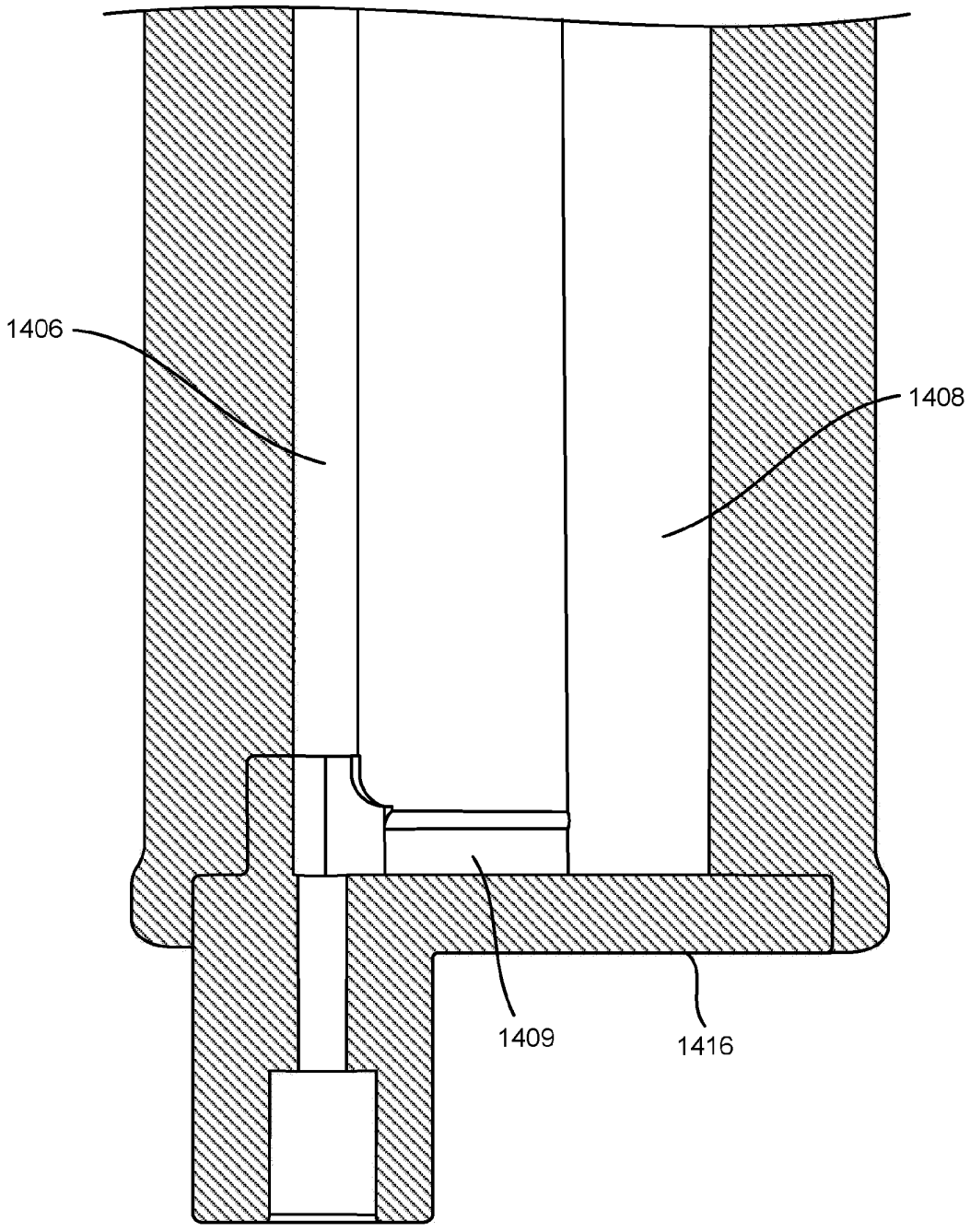


FIG. 14C

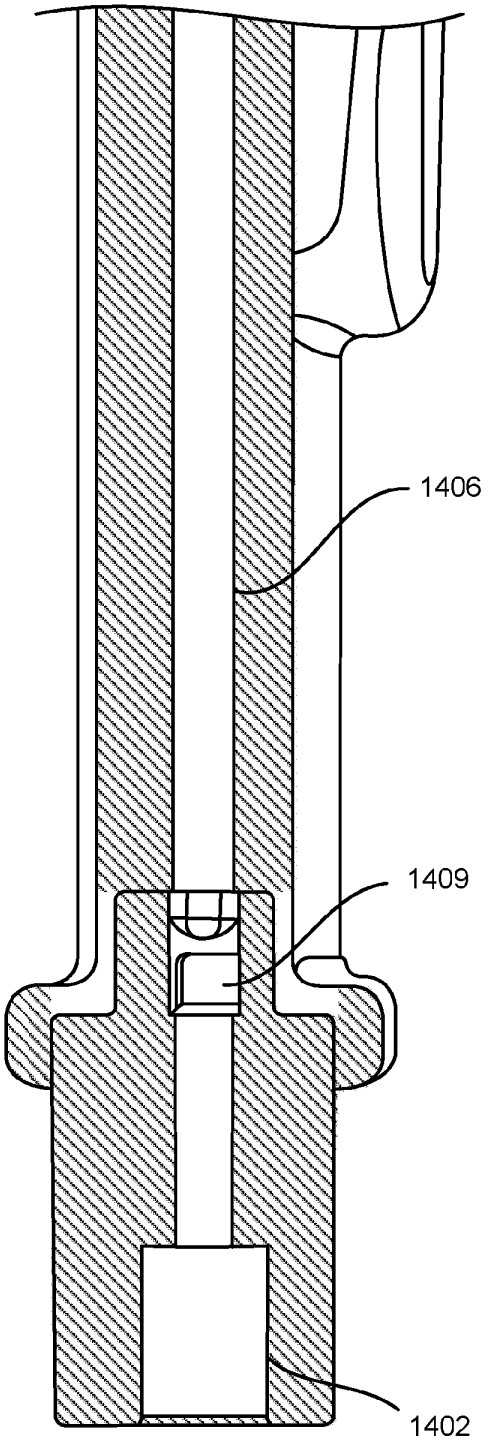


FIG. 14D

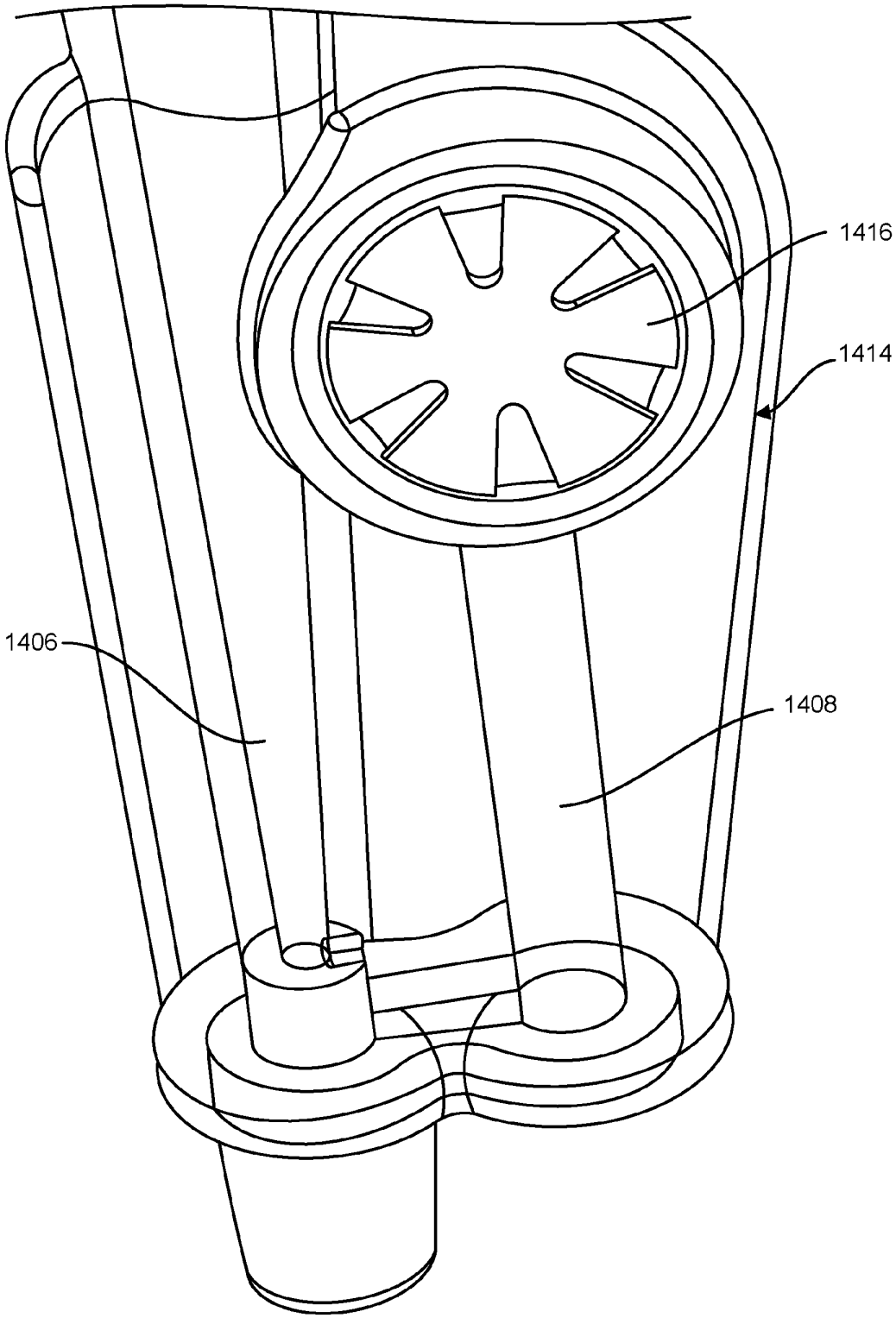


FIG. 14E

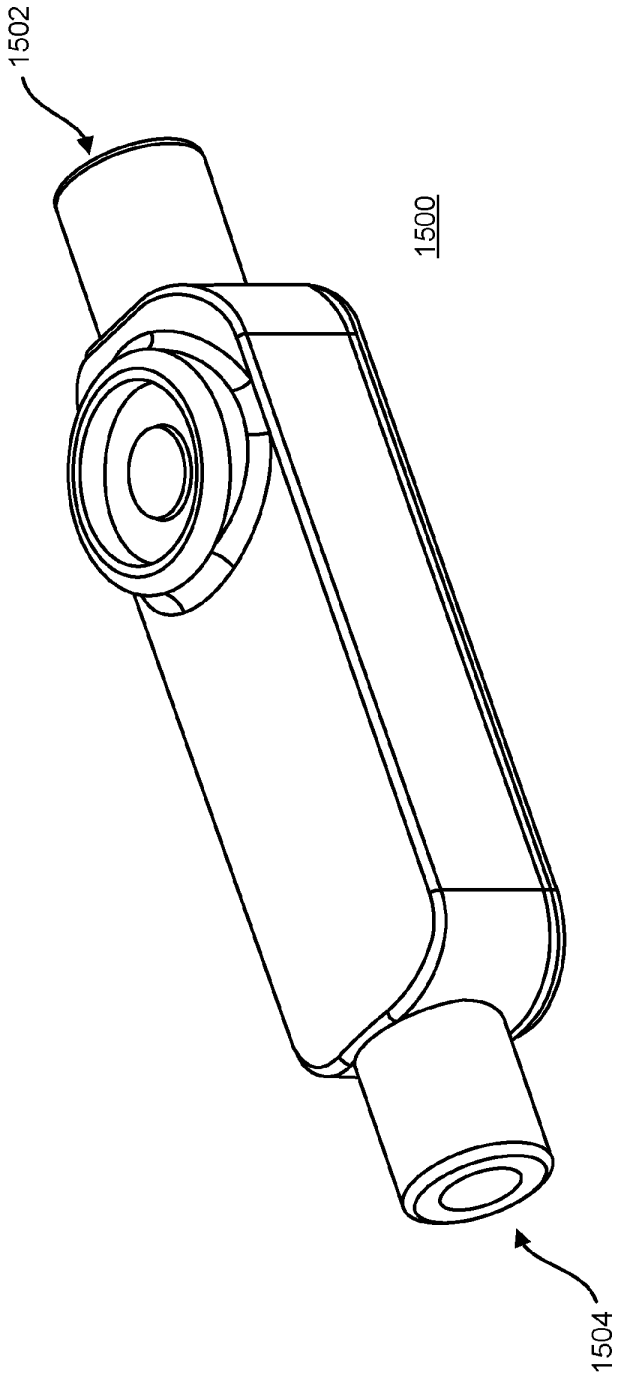


FIG. 15A

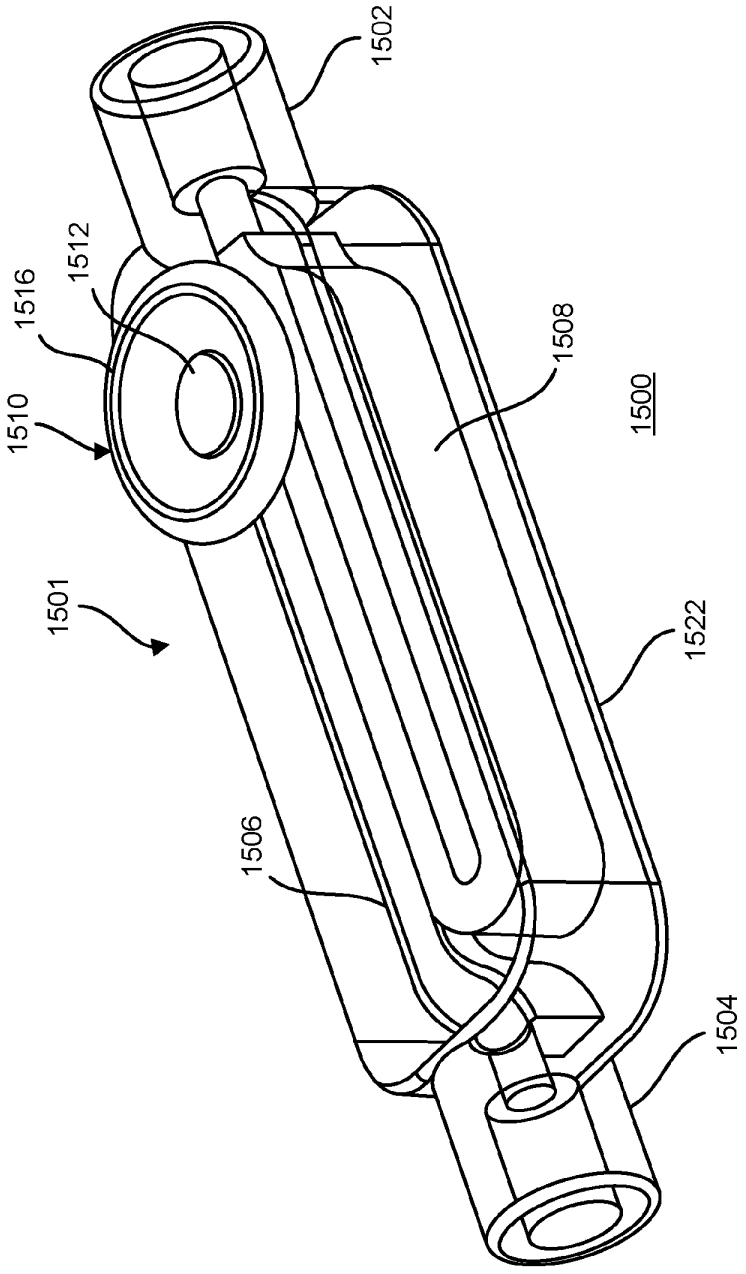


FIG. 15B

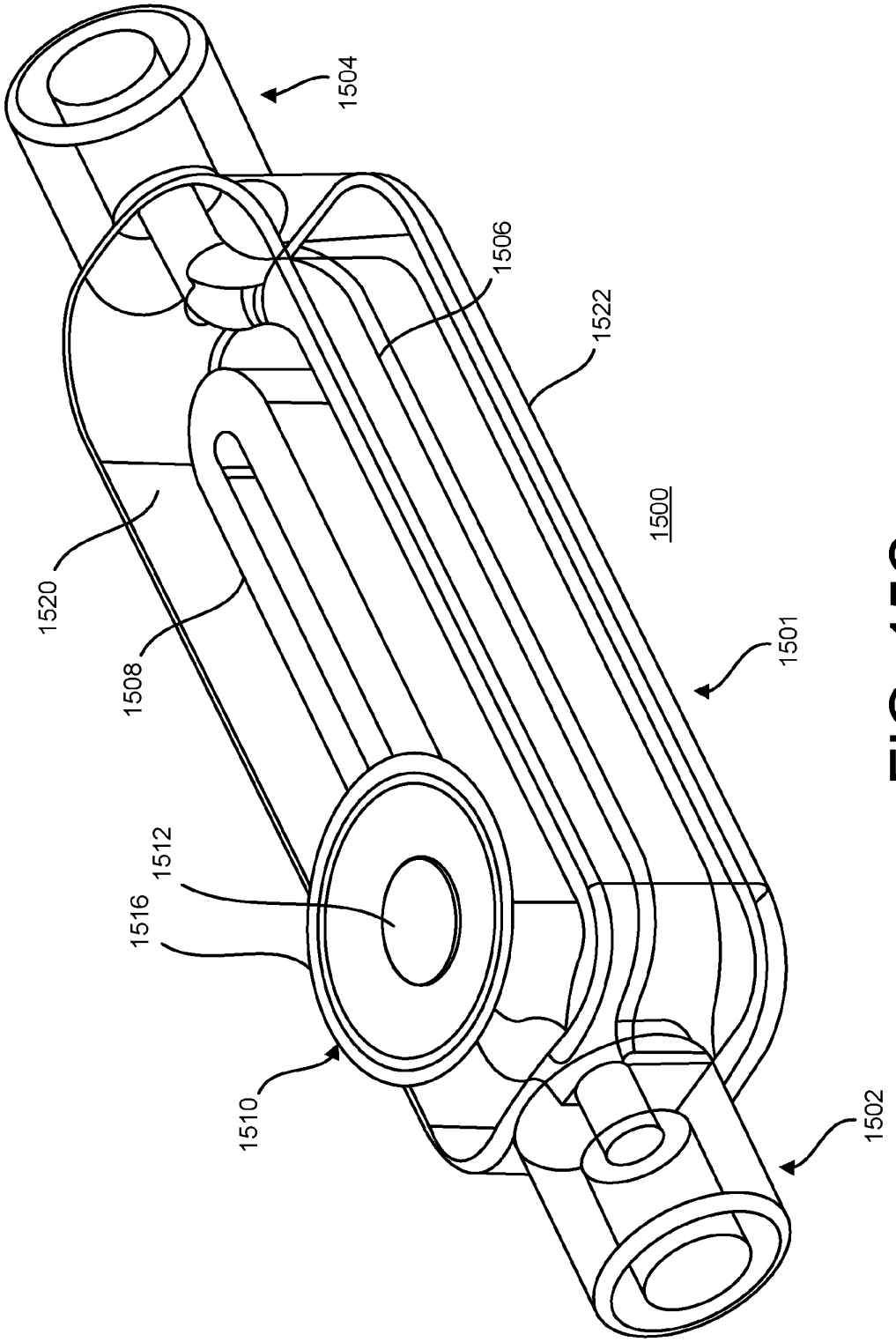


FIG. 15C

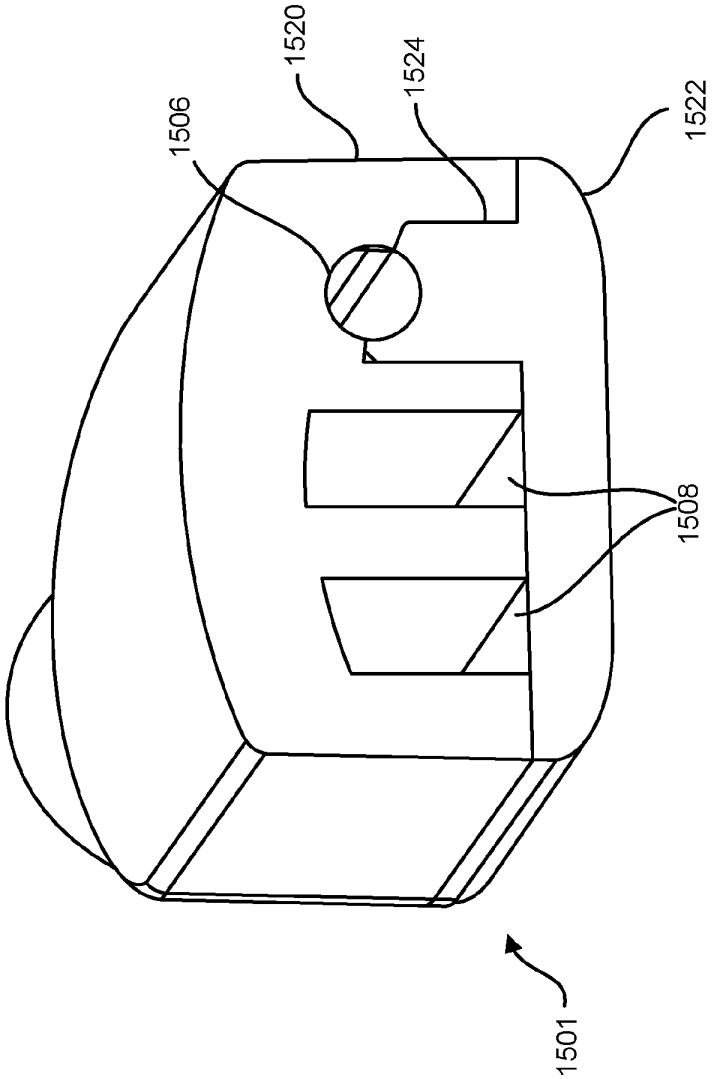


FIG. 15D

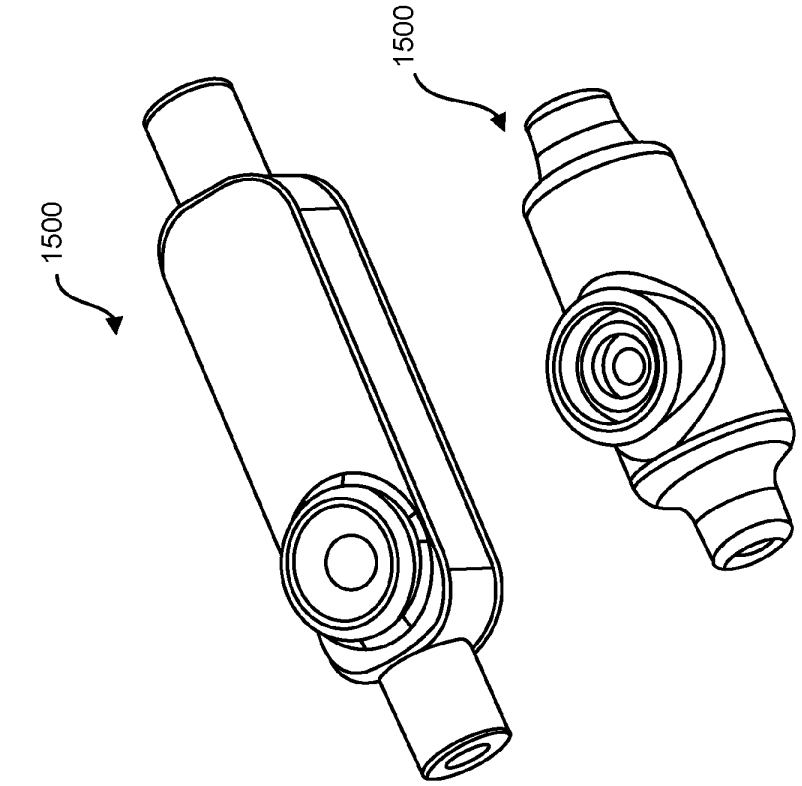


FIG. 15F

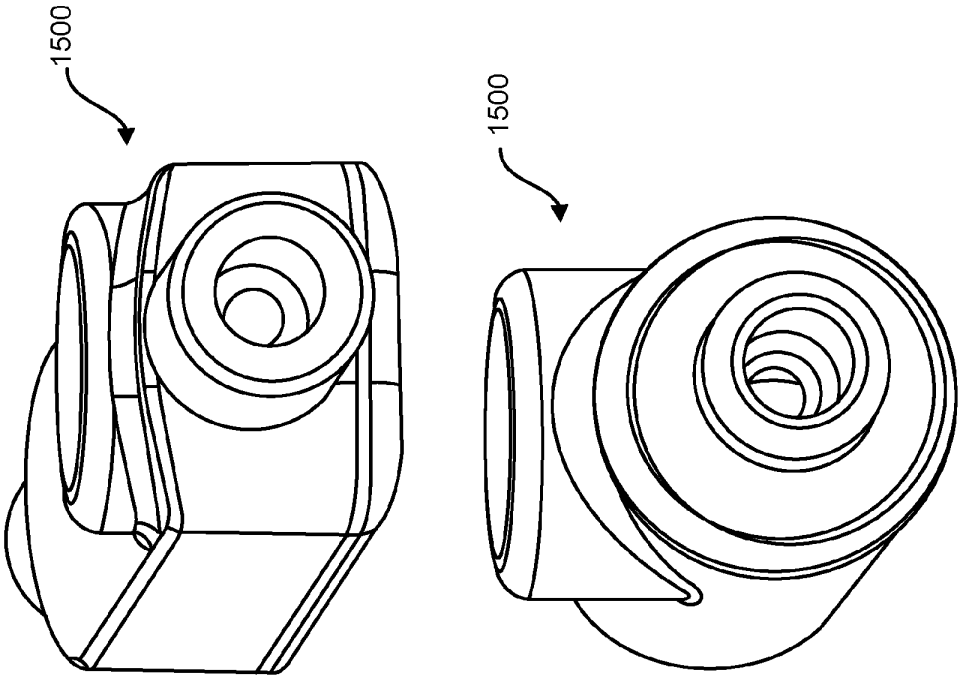


FIG. 15E

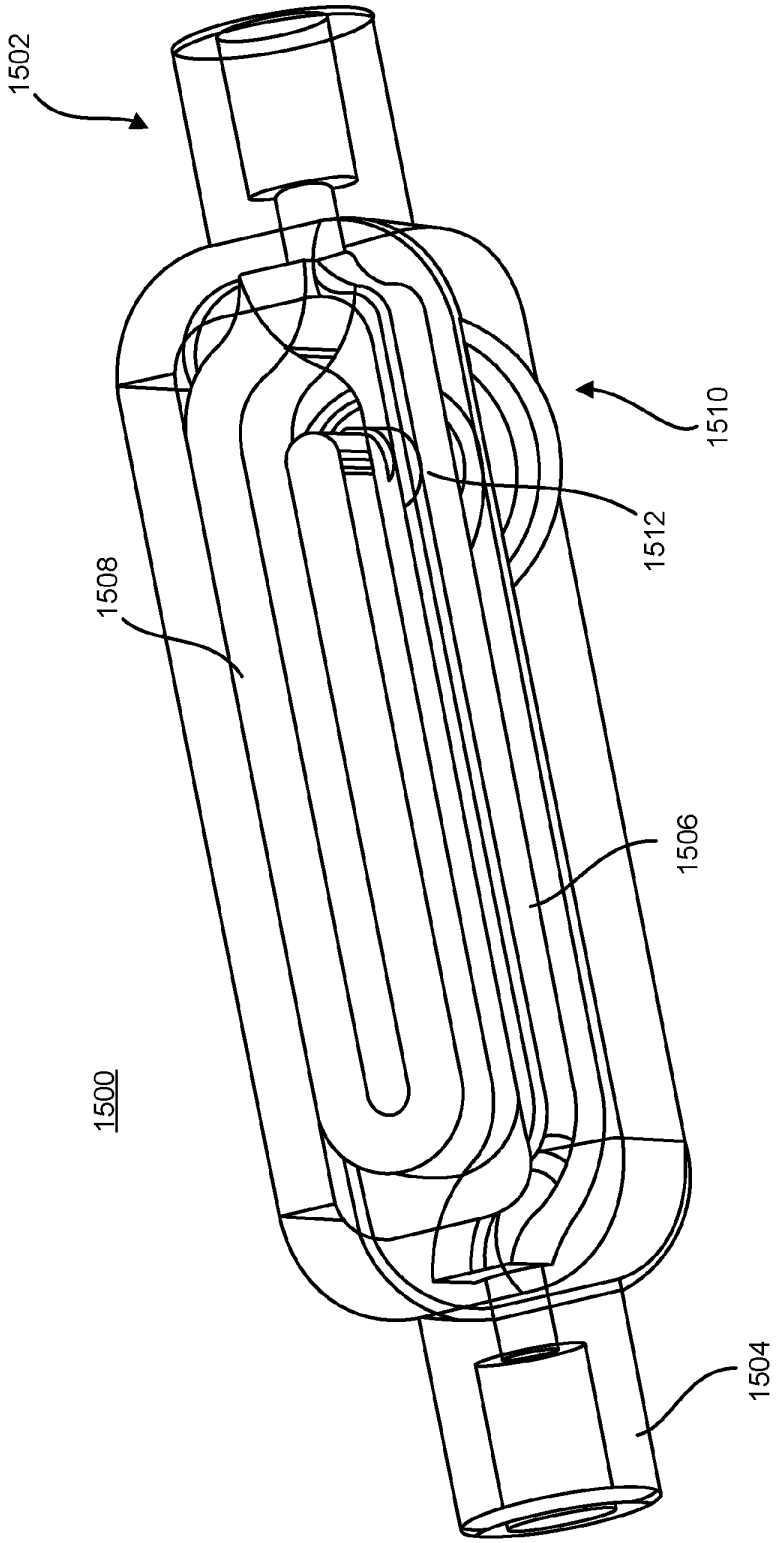


FIG. 15G

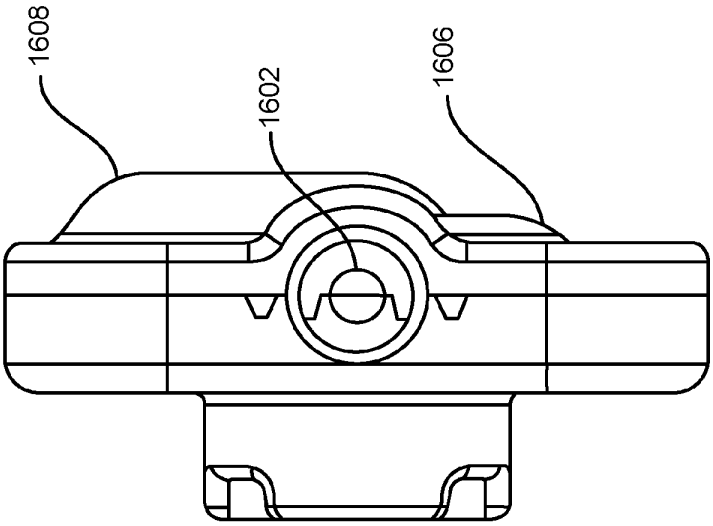


FIG. 16C

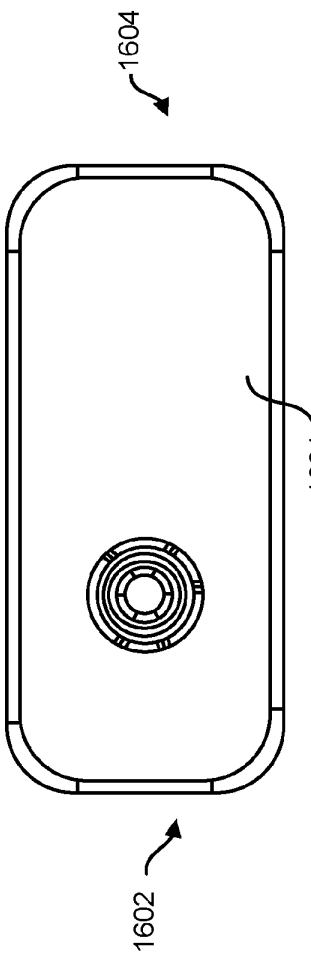


FIG. 16A

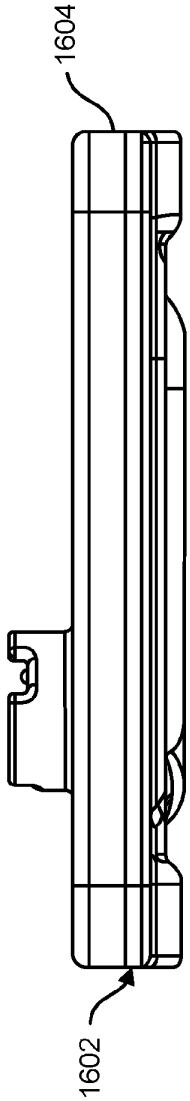


FIG. 16B

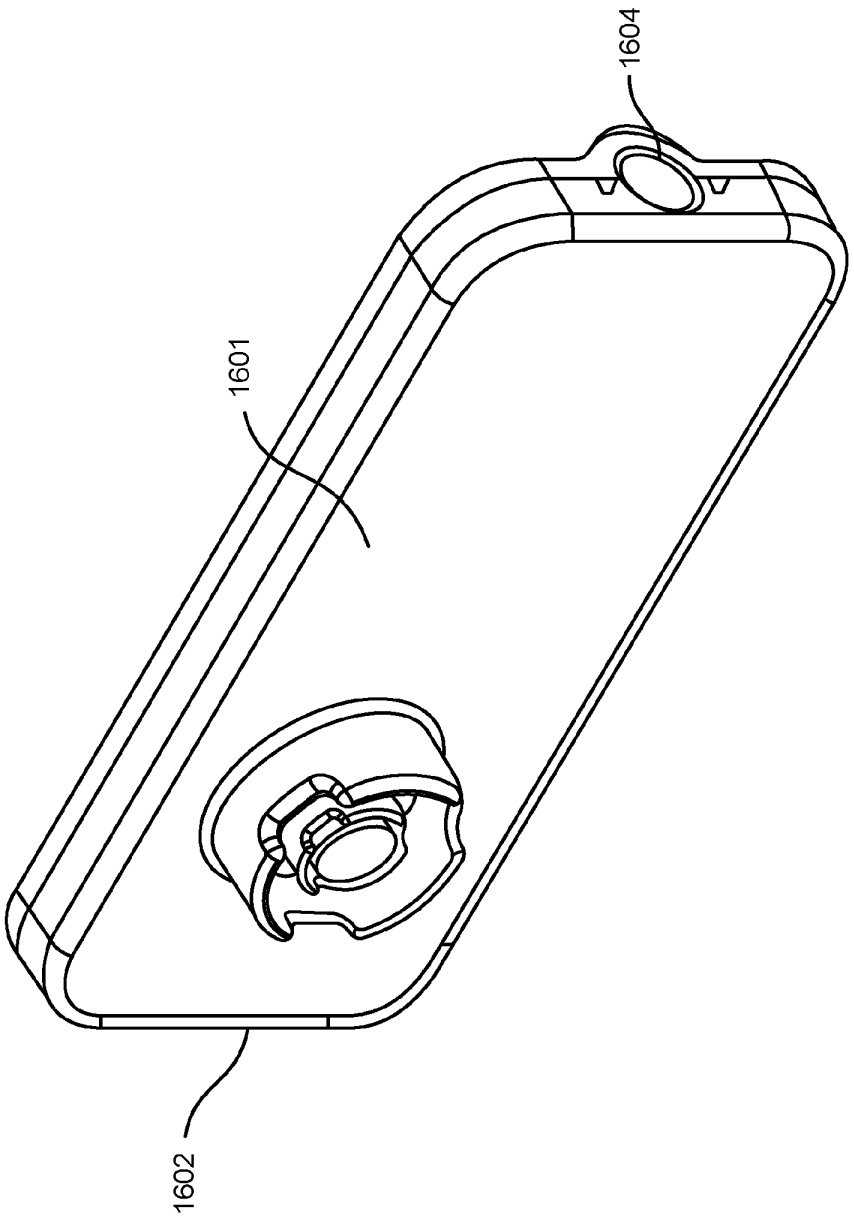


FIG. 16D

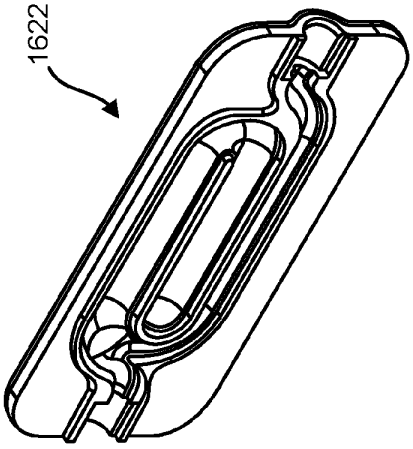


FIG. 17B



FIG. 17E

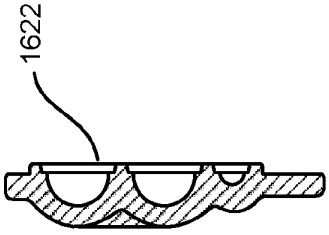


FIG. 17D

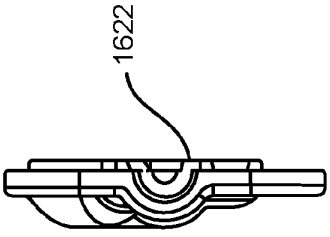


FIG. 17C

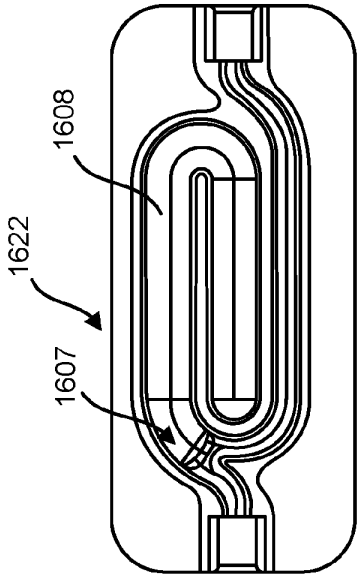


FIG. 17A

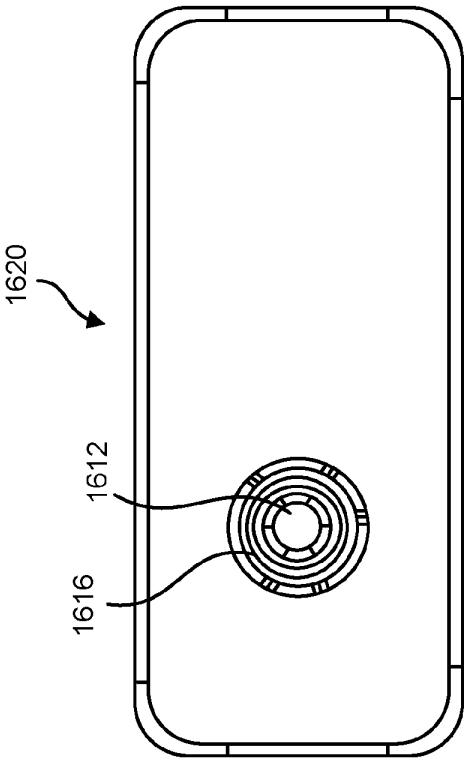


FIG. 18A

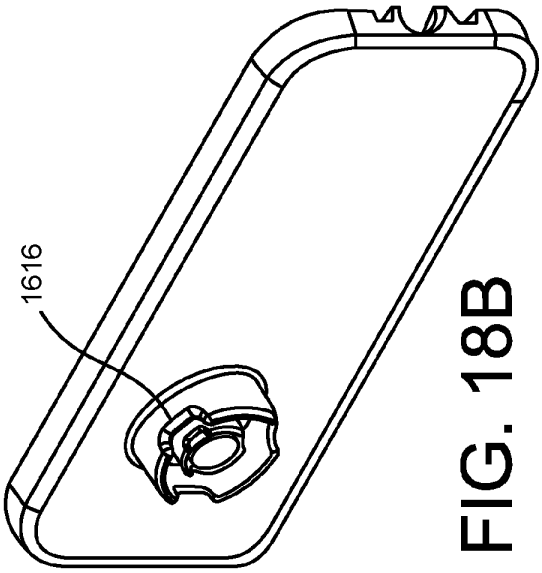


FIG. 18B



FIG. 18C

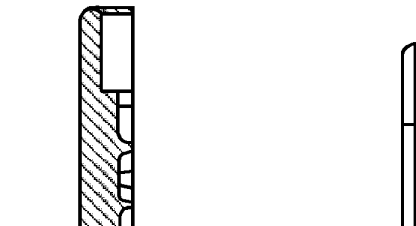


FIG. 18F

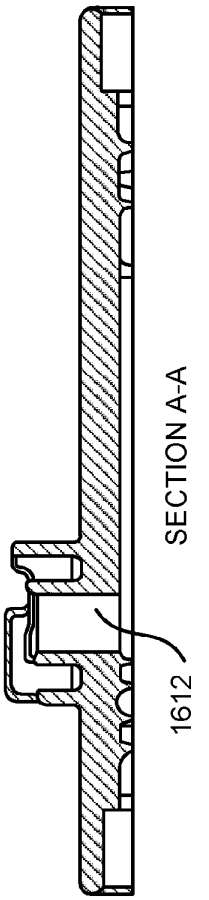


FIG. 18D

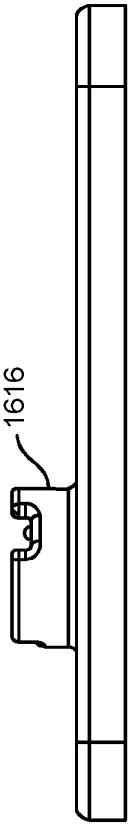


FIG. 18E

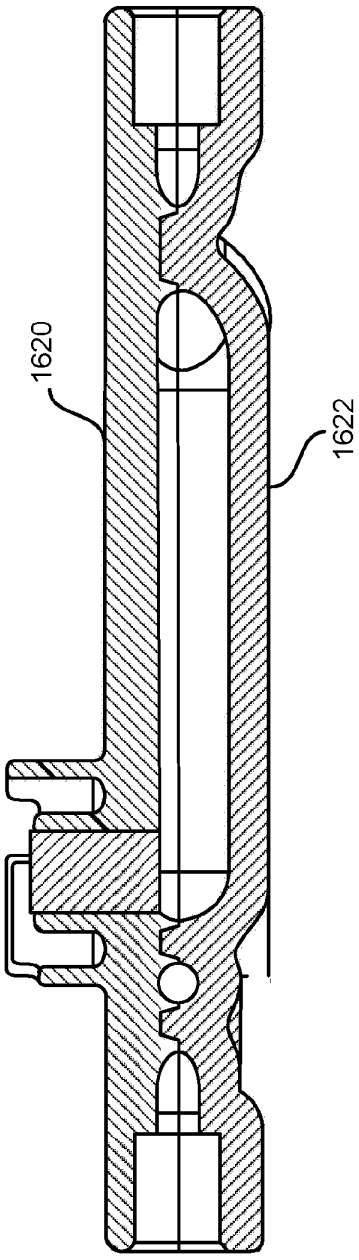


FIG. 19A

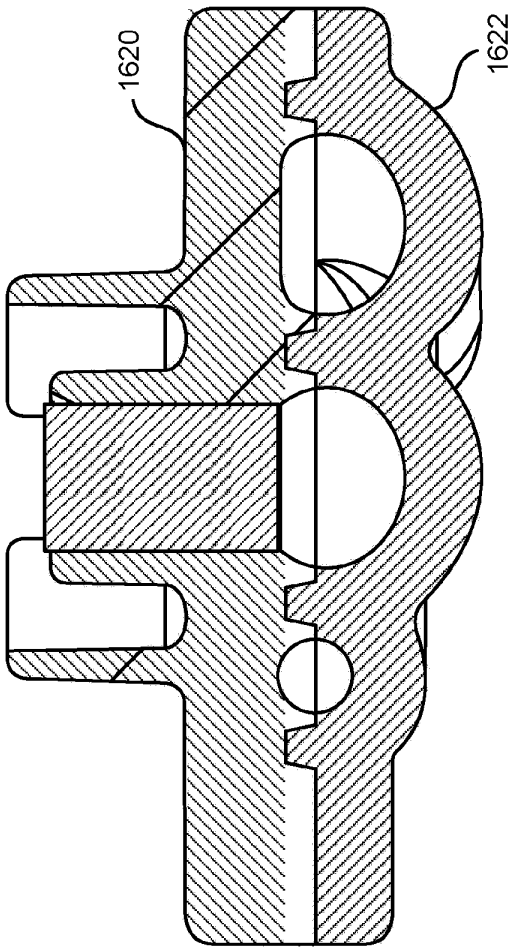


FIG. 19B

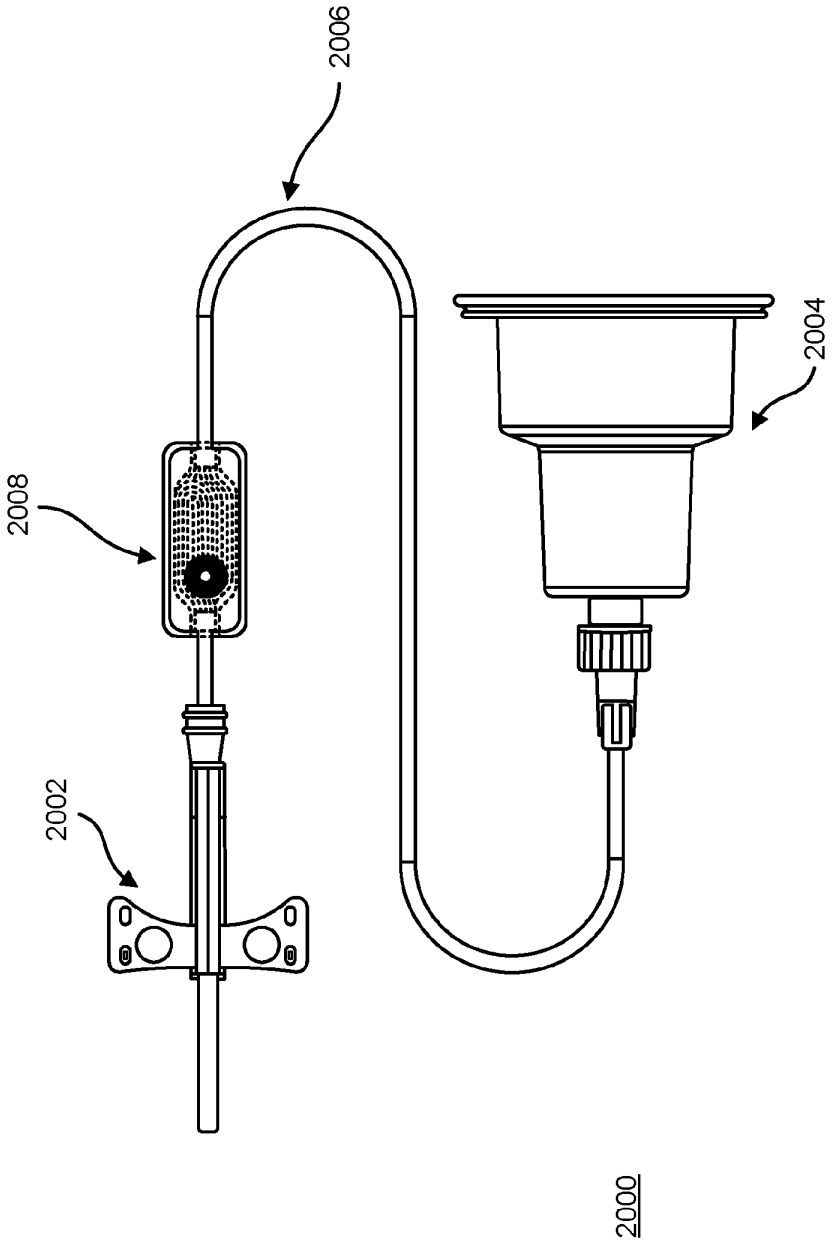


FIG. 20

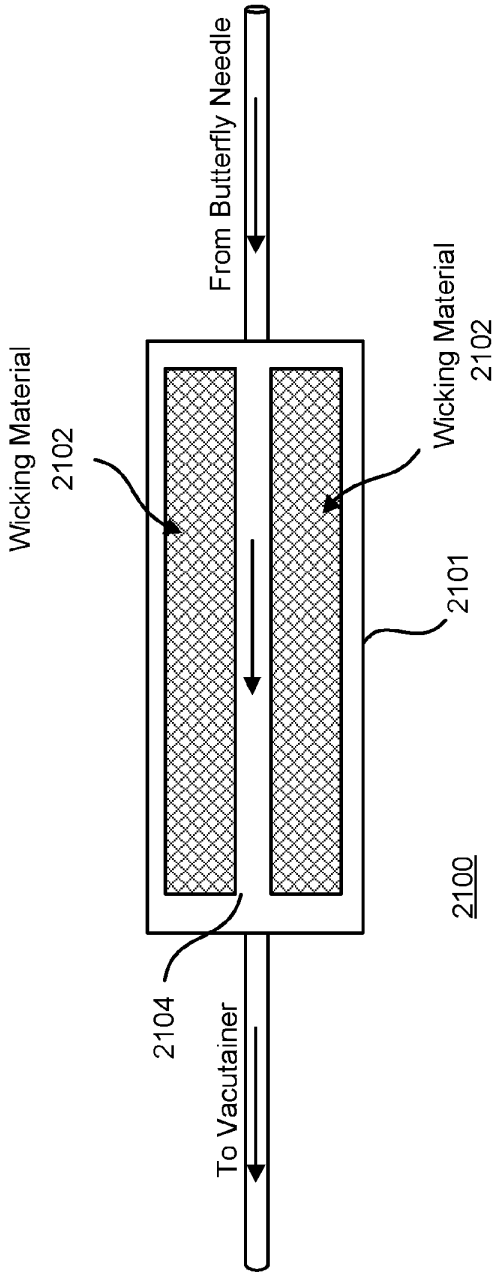

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

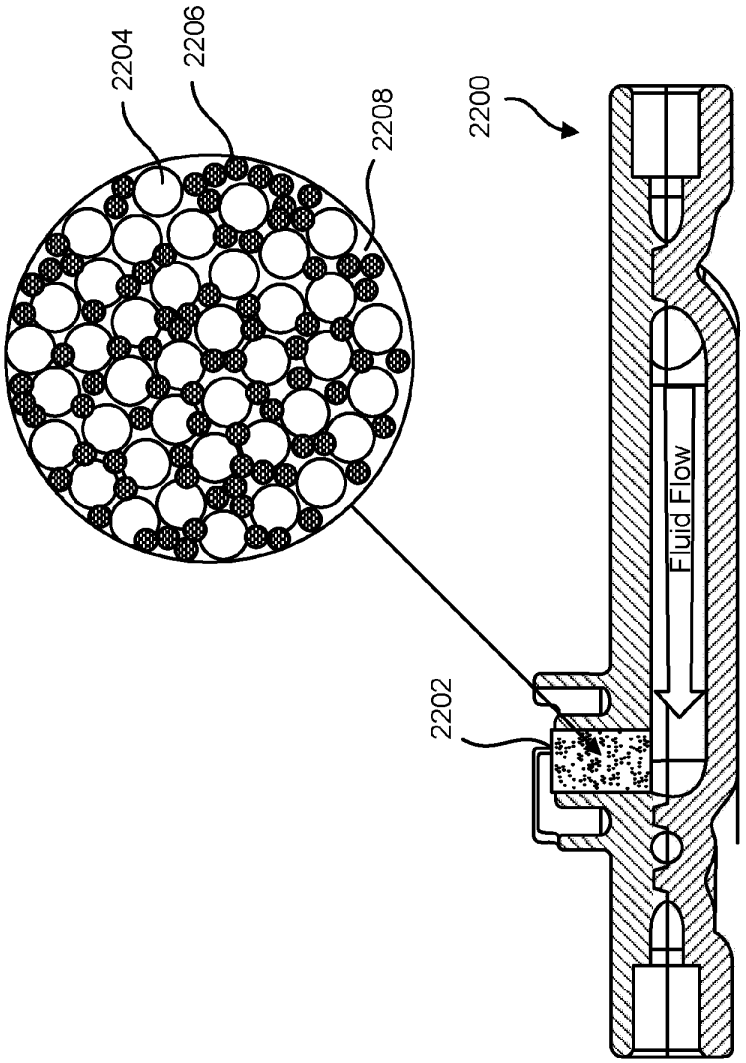


FIG. 22A

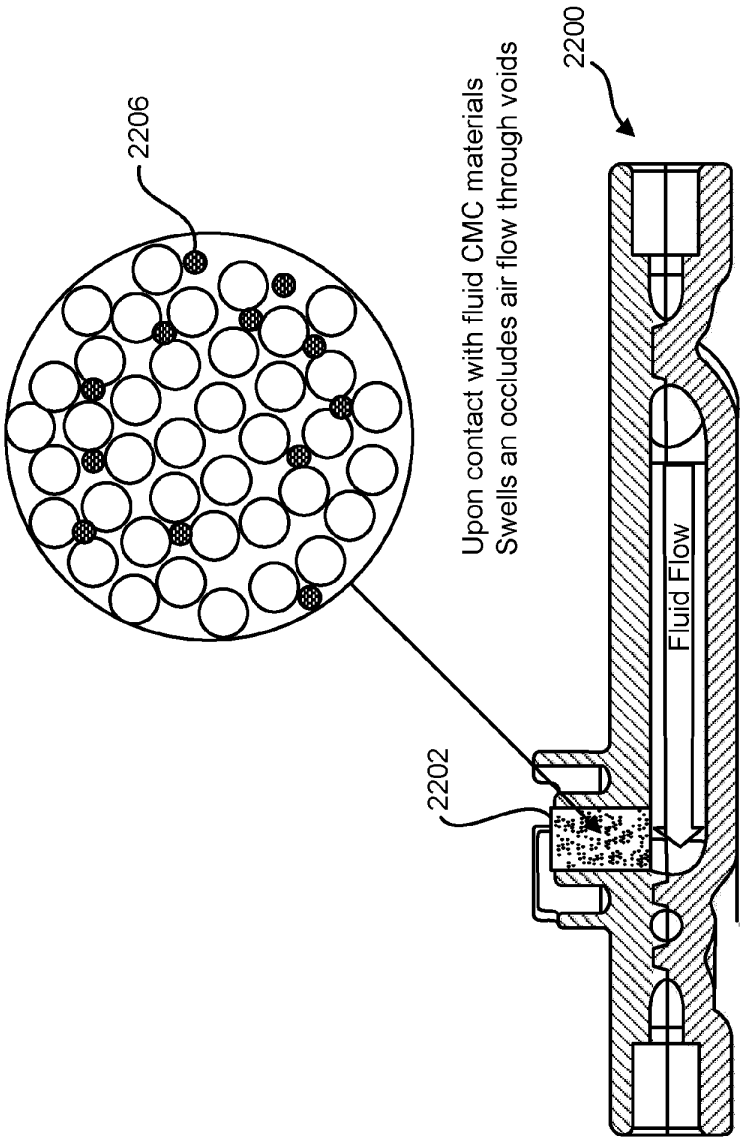

2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2200
2202
Fluid Flow

FIG. 22B

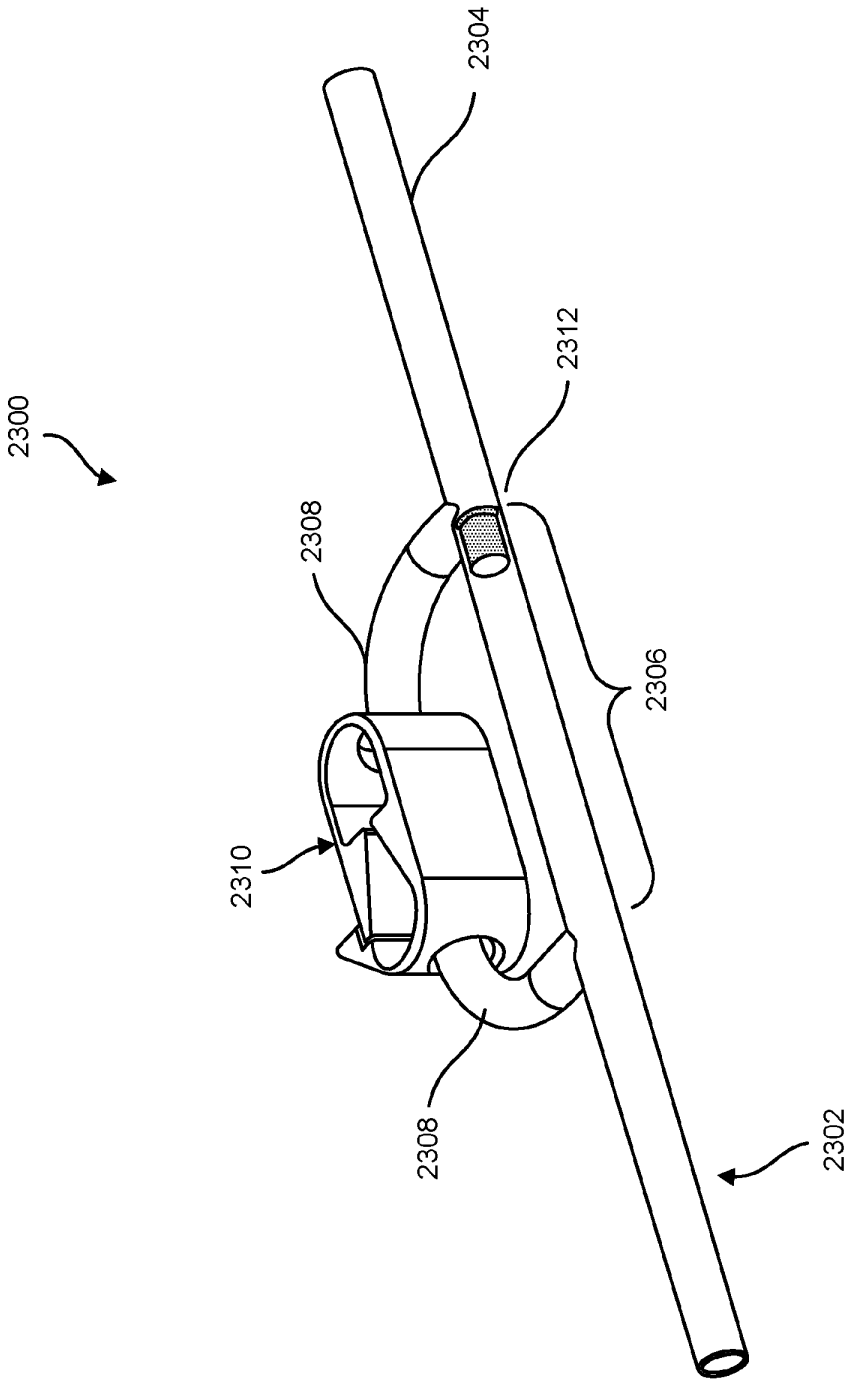


FIG. 23A

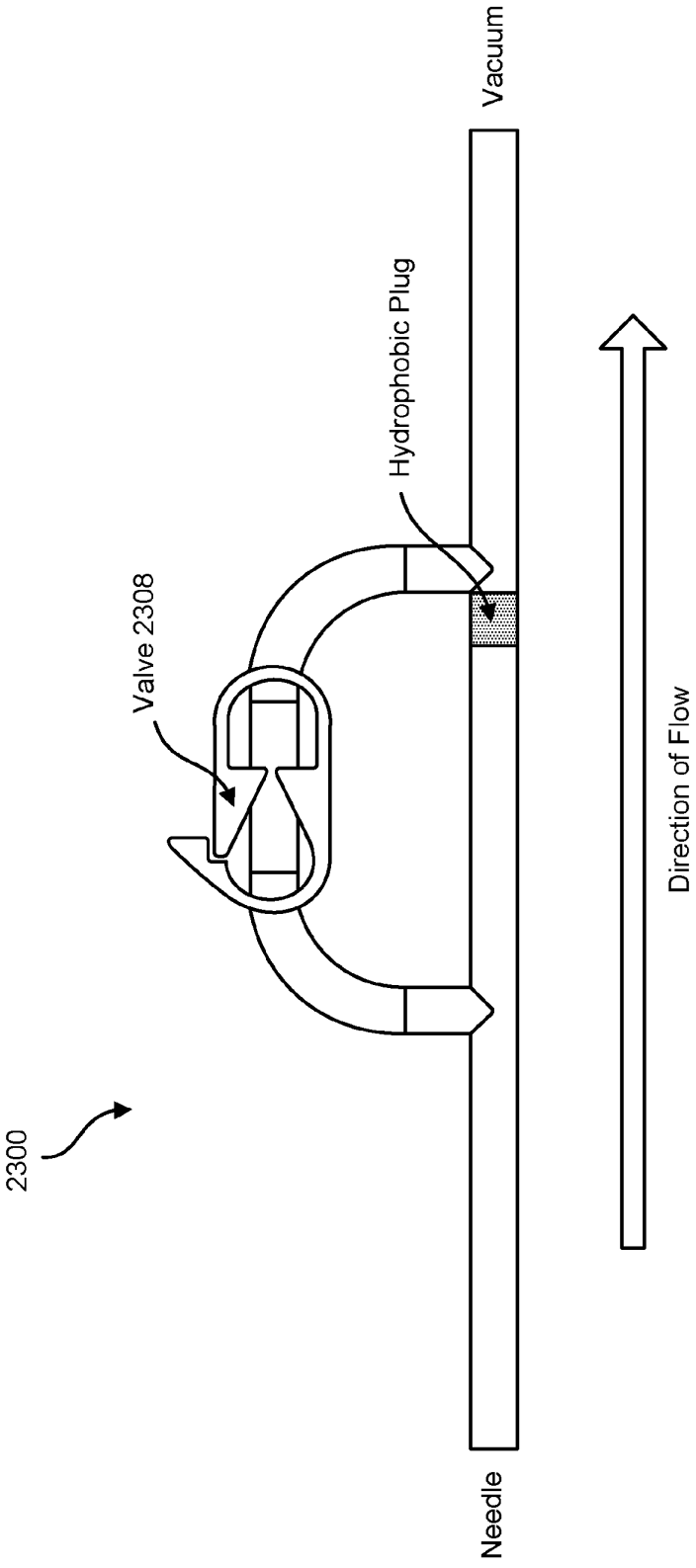

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US]; FISCHEL LLOYD [US]; BR) 29 December 2011 (2011-12-29)	1-5, 7-13, 15-20
A	paragraph [0070] figure 15 abstract	6,14
A	US 2009/227953 A1 (TAN CHEE LEONG [SG] ET AL) 10 September 2009 (2009-09-10) the whole document	1-20
A	JP H08 257018 A (NISSHO KK) 8 October 1996 (1996-10-08) abstract; figures	1-20

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2016	19/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schultz, Ottmar

2

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 416 290 A (LUTKOWSKI LAWRENCE [US]) 22 November 1983 (1983-11-22) abstract; figures	1-20
A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) abstract; figures	1-20
A	EP 1 665 986 A1 (BECTON DICKINSON CO [US]) 7 June 2006 (2006-06-07) figures 13,14	1-20
A	US 4 056 101 A (GEISSLER ULRICH C ET AL) 1 November 1977 (1977-11-01) abstract; figures	1-20
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) paragraphs [0084] - [0094] figures 16-18	1-20

2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043709

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Hypodermic needle blood taking device - has valves at needle end and at attachable evacuated chamber connection

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Abstract of DE2541494 (A1)

The blood-taking device is of the type where a hypodermic needle is inserted into a blood vessela nd one or more evacuated containers in successions are connected to the needle for collecting blood samples. The device has two valves. The first valve closes the proximal end of the needle section when a container is not connected to it and the second valve makes it possible to control the difference of pressure utilized for drawing blood from a subject. The second valve can be closed rapidly in the event it is discovered that the needle lies in tissue exterior to a blood vessel rather than in a blood vessel itself, thereby preventing extravasation and haematoma.

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DESCRIPTION DE2541494A1

[0001]

13 blood collection device

[0002]

17 The invention relates to a blood sampling device for draining blood from a blood vessel.

[0003]

21 It is routine in modern hospitals to draw blood samples from patients by sequentially inserting one or more evacuated test tubes into a holder having a double-tipped cannula; one pointed end of the kanttle pierces the patient's vein and the other pointed end pierces the stopper of the evacuated test tube, thereby allowing blood to flow from the vein into the evacuated tube.

[0004]

28 However, vacuum tube holders are relatively expensive and therefore not disposable; they are also bulky devices subject to contamination (see U.S. Patent 3,520,292).

30 Unless dual-tipped cannulas are already installed in the holders, they must be attached to the holders by a user.

32 However, handling these double-tipped cannulas is dangerous because the user could prick their fingers or infect the cannula.

34 In addition, double-ended needles do not readily permit the injection of soluble drugs into the vein. In medical practice, however, it is sometimes desirable to inject drugs after the blood has been drawn through the cannula in order to save the patient the pain of re-inserting a vein. Another disadvantage of using double-pointed cannulas is that when the tube is withdrawn,

some blood from the vein will flow back through the cannula to its inner end and soil the surrounding area. Of particular note when vacuum tubes are used with double-pointed cannulas is the risk that if the outer tip is not in a vein but in tissue, puncture of the inner tip of the cannula through the tube will result in blood leaking from the vein and a hematoma is coming. Then the user must pull out the cannula as quickly as possible. Even then, the user cannot grasp the situation quickly enough to avoid damage because the full pressure differential is applied to the outer tip of the cannula when the stopper of the evacuated tube is punctured.

[0005]

48 The conventional device has a holder surrounding the proximal end of the double-pointed cannula to receive the plugged end of the evacuated tube.

50 The diameter of the holder part is so large that the cannula penetrates the skin at a relatively acute angle, which increases the risk that the cannula will also puncture the other wall of the blood vessel, so that the tip of the cannula will then be in the tissue rather than in the blood vessel comes to rest. Even without an evacuated reservoir attached to the proximal end of the cannula, blood can clot at the tip, making the device inoperable if another sample is to be taken.

[0006]

58 The invention seeks to provide an improved blood sampling device that avoids the above deficiencies.

60 With the device according to the invention, it should be possible to take a plurality of blood samples with a single puncture of a cannula in a blood vessel without the risk of blood clotting in the space between the successive blood withdrawals. Furthermore, the angle at which the cannula penetrates the patient's skin should be determined by the device itself.

[0007]

67 In order to achieve this, the invention provides a blood sampling device as described in the characterizing part of the first claim.

[0008]

72 The device according to the invention has two valves.

73 The first valve closes the proximal end of the needle part when no container is connected; the second valve makes it possible to control the pressure difference used to aspirate blood from the patient.

76 The second valve can be quickly closed if it is discovered that the needle is not in a blood vessel but outside of it in the tissue. In this way, leakage of blood into the environment and a flamatoma are avoided.

[0009]

82 The device according to the invention consists of two composable parts; the first part comprises a cannula and a holder, the second part comprises an evacuated container closed with a stopper through which an axially slidable and rotatable tube passes.

85 The first and second parts, hereinafter referred to as the holder part and the container part, can be firmly joined together to form a continuous channel for blood to flow through the cannula, holder part and tube into the container. In the holder part is arranged the first valve, which is usually closed, so that when the tube and the container part are not connected to the holder part, the blood trapped in the holder part does not come into contact with air and thus possible infection is avoided. A second valve is mounted in the reservoir portion to allow control of the pressure differential acting across the distal tip of the cannula and to shut off negative pressure from the tip if the cannula is improperly seated in a blood vessel from which blood is being drawn to avoid the risk of a hematoma. The second valve is operated by rotating the container around the tube.

[0010]

98 The distal end of the tube can be inserted into the proximal end of the holder member so that a continuous channel is formed.

100 In one embodiment the distal end of the tube is provided with a protruding flange which opens the first valve when the container part and the holder part are connected to each other. In a second embodiment, the distal end of the tube itself opens the first valve and the container part can be detached from the holder part only when the second valve is closed.

[0011]

107 The invention thus has the advantage, among other things, that the negative pressure at the tip of a cannula is shut off by a valve if the cannula is not correctly positioned in a blood vessel.

109 The invention also eliminates the need for a holder and double-pointed needles by providing a novel vacuum container stopper and hypodermic applicator.

[0012]

114 The hypodermic applicator allows both the injection of soluble drugs into a blood vessel and the collection of blood samples without splashing back blood.

[0013]

119 Assembling the cannula containing part with the container part automatically opens the valve in the holder part so that a continuous and unobstructed channel is formed from the tip of the cannula to the proximal end of the tube which opens into the container.

122 Controlling the negative pressure applied to a vein can prevent the vein from collapsing.

[0014]

126 Further details and advantages of the invention result from the following description of exemplary embodiments with reference to the accompanying drawings.

128 1 shows a side view of a device according to the invention, in which the part containing the cannula is separated from the container part; Figure 2 shows a side elevation of the device according to the invention, in which the two parts are ready for assembly; Figure 3 is a side elevation showing the two parts of the device connected together and showing the valve in the container part closed; Figure 4 is a side elevation similar to Figure 3 but with the valve in the container part open; Figure 5 is a sectional view taken along line 5-5 of Figure 4; Figure 6 is a sectional view taken along line 6-6 of Figure 4; Figure 7 is a side perspective view of a second embodiment of the invention; Figure 8 is a partially sectioned view of the two parts of the second embodiment of the invention separated; Figure 9 is a view similar to Figure 8 but showing the two parts combined; Figure 10 shows the same two parts of the second embodiment but with the container advanced so that the second valve is open; Figure 11 is a view taken along line 11-11 of Figure 10; Figure 12 is a view taken along line 12-12 of Figure 10; and FIG. 13 is a sectional view taken along line 13-13 of FIG.

[0015]

144 The blood sampling device according to the invention consists of two parts that can be joined together, a holder part and a container part, which are shown separately from one another in FIG.

147 A cannula 23 has a tip 24 for piercing a blood vessel through a patient's skin.

148 The proximal end 25 (FIG. 2) of the cannula 23 is fastened in a holder part 22 through which a channel 26 runs. A flexible walled plug 27 sits in the end 28 of the channel. A flexible wall of the ben lies across an opening 29 so that the plug 27 simultaneously seals the opening 29 and the end 28 of the channel.

[0016]

155 The holder part 22 has a projection 30 which serves to hold the holder part at a certain distance from the patient's skin, thereby adjusting the angle at which the cannula 23 penetrates the skin and the manipulation of the holder part and the cannula is facilitated.

[0017]

161 A container 12 is closed with a stopper 10 having a flange 11 seated on the open end of the container 12 .

163 The plug 10 is penetrated by an axial passage in which is inserted a tube 14 which fits tightly

enough in the plug 10 to prevent air from entering between the tube 14 and the axial passage in the plug 10, yet is loose enough That they can move or rotate in the plug 10 in the axial direction.

[0018]

170 The tube 14 is closed at its proximal end, preferably with a disc cemented or otherwise secured onto the end of the tube 14 after the tube 14 is inserted into the stopper 10.

172 The washer 15 performs the dual function of sealing the end of the tube 14 and at the same time limiting the axial movement of the tube 14 away from the container 12.

174 The tube 14 also has a rigidly attached or molded stop 18 at a location such that the movement of the tube 14 axially toward the container 12 is limited.

[0019]

179 The tube 14 is provided with a side opening 16 located a small distance from the sealed tube end.

181 As shown in Figure 2, the opening 16 lies within the passage through the stopper 10 so that the container 12 is protected against ingress of air during evacuation. In a convenient embodiment, the axial passage through the plug 10 is threaded from its outer part to just short of where the orifice 16 comes to rest when the disc 15 is brought into contact with the plug 10. In this case, of course, the tube 14 must also be equipped with a suitable thread.

[0020]

189 Figure 2 shows the container part of the device being assembled with the holder part.

190 The connection is made by inserting the distal end 19 of the tube 14 into a socket 29. The tube end and socket are shaped to fit flush and prevent air from entering between them. A flange 20 is attached to the tube end 19 which bears against the flexible wall 29' of the plug 27 when the two parts are joined together. When the tube end 19 is pushed into the receptacle 29, the flange 20 pushes aside the top of the stopper 27 so that a continuous channel is established between the tip of the cannula 23 and the interior of the tube 14. This can be seen in Figure 3 where the top wall of the flexible plug 27 is depressed by the flange 20. The appearance of the holder portion of the device after insertion of the tube end 19 into the socket 29 is shown in the sectional views of Figs.

[0021]

202 When a blood sample is to be taken, the container 12 is gently rotated in the direction indicated by the arrow in FIG.

204 The axial movement of the container 12 towards the stop 18 results from the fact that the tube 14 is provided with a thread 13 which engages with a threaded part 13' of the stopper 10.

[0022]

209 It should be noted that the plug 10 has an unthreaded portion at its proximal end which ensures a tight seal when the opening 16 is within the plug 10.

[0023]

214 If blood does not flow through opening 16 into container 12 substantially immediately, the container 12 is rotated in the opposite direction to bring opening 16 back into stopper 10, thereby avoiding the full pressure differential being applied to the tissue in where the cannula must lie.

218 This avoids extravasation of blood and the resulting hematoma.

219 The cannula can then be pulled out and properly inserted again so that its tip comes to rest in a blood vessel.

[0024]

224 Then the container 12 is turned again according to FIG. 4 in order to start again with the blood collection.

226 If blood flows through the opening 16, the container 12 is rotated further until the stopper 10 hits the stop 18 on the holder part 22. The container then remains in this position until the desired amount of blood has been aspirated or until the container is filled.

[0025]

232 A second embodiment of the invention is shown in FIGS.

233 Again the device consists of two parts, a holder part, generally designated 221, containing the cannula, and a container part, generally designated 351. The container part 351 has a container 121 which is closed with a stopper 101 in which a through hole is made. A tube 141 having a threaded portion 131 is mounted in the bore of plug 101 . The tube 141 has two parts 141a and 141b which form an angle with each other. A passage 161a through tube 141 is closed at its end by a conical portion 151 which fits into a corresponding portion 151a of the bore in plug 101. A lateral opening 161 is provided in the channel 161a near the conical part 151 . The threaded portion 131 of the tube 141 terminates short of the side opening 161 so that when the container 121 is in a position such that the conical portion 151 is snugly received in section 151a, the opening 161 passes through the cylindrical portion of the stopper 101 is tightly closed.

[0026]

247 To assemble the holder portion and container portion of the device, end 191 of tube 141 is

inserted into a receptacle 291 in holder portion 221, lugs 301a slide into grooves 301b in holder portion 221, and rotation of container portion 351 establishes a bayonet fitting between lugs 301a and 301a grooves 301b.

251 In addition, the receptacle 29a has a spherical portion 311b which mates with a corresponding spherical portion 311a on the tube 141 to provide a tight seal between the holder portion and the container portion.

[0027]

257 When the tube end 191 is inserted into the socket 291 and the bayonet fitting is made, the pointed tube end 191 pushes down the top of a flexible plug 271 which is preferably hollow.

259 In doing so, the pointed end of the tube itself serves as a means to push the upper part 271' of the plug 271 aside. This displacement creates an uninterrupted line between the channel 161a in the container part and the cannula 23. The hollow plug 271 closes the end of the socket 291 and acts as a valve upon insertion of the tube end 191 due to the depressed top plug wall 271'. A portion 401 of the tube end is preferably received in a snug fit in receptacle 29a so that a seal is formed between these portions.

[0028]

268 When the container 121 is rotated in the direction indicated by an arrow in Fig. 10, it moves distally as shown in Fig. 10 and communicates the side opening 161 with the container interior; so that a connection is made from the cannula 23 to the container.

271 If the container is evacuated before the two parts are joined, then blood will flow through the cannula and through the associated channels into the container 121 after the side opening 161 enters the conical portion of the bore in the stopper 101. The range of movement of the container in a distal direction - the threads on the tube 141 are right-hand in this case - is restricted by the contact between the plug 101 and the rear part 321 of the border of the holder part 221.

[0029]

280 Conveniently, the plug 271 carries a ridge 271a which nests in a groove 271b in the retainer portion 221 to help hold the plug 271 in place.

[0030]

285 The manner in which the lugs 301a are fixed in the grooves 301b can be clearly seen from FIGS.

287 The path by which liquid enters the container 121 from the cannula is clear from FIGS. 10 and 12.

[0031]

292 Once the container is filled, the tip 191 of the tube 141 is removed from the channel, i. pulled out of the socket 29a and the flexible wall of the plug 27a springs back so that it blocks a channel 261 in the holder part 221.

295 This process can be repeated any number of times, each time using a new container to collect a sample.

[0032]

300 The distance between the border 321 of the holder part 221 and the outer surface 38a of the plug 101 is chosen so that the container part cannot lift off the corner 361 until the conical part 151 seals tightly in the bore portion 151a, and this sealing engagement is achieved by Turning the container 351 produced with simultaneous displacement of the same in the proximal direction.

305 The dashed curve shows how the distance at which the tip 371 of the plug 101 clears the corner 361 is determined.

307 The purpose of this arrangement is to ensure that the container is properly sealed before container portion 351 is removed from holder portion 221.

[0033]

312 The container portion can then be handled separately without risk of contamination of its contents.

[0034]

317 It should be noted that the seal between the tube end portion 401 and the receptacle 291 prevents air ingress when unlocking the bayonet fitting if unlocking is attempted when the container portion 351 at the side opening 161 is only partially closed.

[0035]

323 If desired, a soluble drug can be injected without causing pain to the patient by drawing the drug into an ordinary syringe fitted with a thin gauge needle and piercing the stopper 271 through an opening 28a with the needle tip of the syringe.

326 The drug is then injected into the channel 26a and from there goes to the cannula 23, to its tip 24 and finally into the patient's blood vessel, provided that the passageway serving as receptacle 291 remains sealed.

329 A new reservoir portion can be attached to the holder portion 221 that remains in place to aspirate more blood, or the cannula 23 can be withdrawn from the blood vessel and then discarded.

332 The filled part of the container is sent to an appropriate biochemical laboratory, where the valve of the side opening 161 is first opened, after which the plug 101 can be easily removed, the tests can be carried out and the whole unit can then be destroyed.

[0036]

338 Since receptacle 291 is blocked each time a container is removed, blood cannot continue to ooze out of channel 261, nor is it drawn back into the blood vessel.

[0037]

343 The object of the invention is thus fulfilled.

344 Modifications are possible with respect to the exemplary embodiments described.

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CLAIMS DE2541494A1

1.

13 L n 8 p r u c h e 9 Blood extraction device for draining blood from a blood vessel, characterized in that it consists of a holder part (22, 221) and a container part (351), that the holder part has a cannula (23) with a pointed distal end (24) and a proximal end (25) and is traversed by a channel (26, 261), in whose distal end the proximal end (25) of the cannula is received in a sealed manner and which communicates with an opening (29, 291) of the holder part and that a first valve (27, 271) is seated in the proximal end of the duct (26, 261) to close the duct, normally blocking communication between the opening (29, 291) and the duct, that further the container part has an evacuatable container (12, 121), the opening of which is closed by a stopper (10, 101), and that a tube (14, 141) is provided, the proximal end of which passes through the stopper (10, 101). and is connected at its distal end to the opening (29, 291) in the holder part in such a way that a sealing connection can be established between the tube and the holder part at this opening, and that at the distal end of the tube an actuating element (20, 191) is provided which opens the first valve (27, 271) thereby connecting the orifice (29, 291) to the channel (26, 261) when the tube (14, 141) is attached to the holder part (22, 221) with the plug (10,101) being attached to the container (12,121) so that it is movable with the container relative to the tube but is sufficiently tight in the container opening to prevent air ingress between the two prevent sharing.

2.

33 Device according to Claim 1, characterized in that the first valve consists of a flexible plug (27, 271) which fits into the proximal end (28, 281) of the channel (26, 261) and closes this end (28, 281). and which extends across the opening (29, 291) and completely seals this opening when the tube (14, 141) is not connected to the holder part (22, 221).

3.

40 Apparatus according to claim 2 characterized in that the actuator on the tube (14) is a flange (20) projecting from the distal end of the tube and positioned to engage that portion (29) of the hollow flexible plug (27) blocking the opening (29), pushing aside and thereby establishing communication with the channel (26) so that blood can flow through the holder part (22) into the tube (14).

4.

48 Apparatus according to any one of the preceding paragraphs characterized in that the opening (29, 291) is shaped as a socket and the distal end of the tube (14, 141) is receivable in the socket-shaped opening with a snug fit.

5.

54 Device according to one of the preceding claims, characterized in that the holder part is provided with a projection (30) which can be placed on the surface into which the cannula (2#) is to be inserted and thus defines the angle under which the cannula is inserted into the surface, and also maintains the holder portion at a distance from the surface and provides a means for more conveniently retaining the holder portion.

6.

62 Device according to any one of the preceding claims, characterized in that the plug (10, 101) is traversed by an axial channel in which the tube (14, 141) fits tightly enough to permit a flow of fluid between the tube and the channel wall preventing, and that the tube (14, 141) is closed at its proximal end and has an opening (16, 161) in its side wall near the proximal end, and that the container (12, 121) relative to this proximal end of the tube is axially movable sufficiently so that in a first position the opening (16, 161) is within the container and communicates between the tube and the container and in a second position within the channel in the stopper (10, 101) and thus the container is sealed against the ingress of air or liquid from the tube into the container, the opening (16, 161) in the side wall of the tube constituting a second valve.

7.

74 Device according to claim 6, characterized in that the distal end of the channel in the stopper (10, 101) and the proximal end of the tube are externally provided with mating threads (13, 13'; 131, 131') so that through Rotating the container around the tube gradually establishes a connection between the tube and the container or the connection can be broken.

8.

81 Device according to claim 6 or 7, characterized in that the tube (14) is provided on both sides of the stopper (10) with protruding parts (18, 15) serving as stops to limit the relative axial freedom of movement of the container and the stopper to limit the tube.

9.

87 A device according to any one of claims 6 to 8, characterized in that the proximal end of the tube and the proximal end of the channel in the stopper are shaped to match each other so that a seal is formed between the two parts when the tube is inserted into the channel.

10.

93 Apparatus according to claim 9, characterized in that the mating parts (151, 151a) of the tube and duct are conically shaped.

11.

98 Apparatus according to any one of the preceding claims characterized in that the first valve is a hollow plug (27, 271) through which a hypodermic needle can be inserted to inject fluid into a patient once the patient's skin has been punctured for blood collection .

12.

104 Device according to one of claims 6 to 11, characterized in that the axial range of movement of the container (121) relative to the tube (141) in the proximal direction is determined by the contact of the proximal end (151) of the tube with the stopper (101) and in the distal Direction is limited by the contact of the plug (101) with the holder part (221).

13.

111 Device according to Claim 12, characterized in that the distance between the holder part (221) and the stopper (101) is selected in such a way that the container part (351) can only be removed from the holder part (221) if the container has reached the am position furthest from the holder part, which position corresponds to the limit of movement of the container in the proximal direction, thereby ensuring that the second valve (161) is closed.

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DT 25 41 494 A 1

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Ansprüche

1. Blutentnahmevorrichtung zum Abzapfen von Blut aus einem Blutgefäß, dadurch gekennzeichnet, daß sie aus einem Halterteil (22, 221) und einem Behälterteil (351) besteht, daß der Halterteil eine Kanüle (23) mit einem zugespitzten distalen Ende (24) und einem proximalen Ende (25) aufweist und von einem Kanal (26, 261) durchzogen ist, in dessen distalem Ende das proximale Ende (25) der Kanüle dichtend aufgenommen ist und der mit einer Öffnung (29, 291) des Halterteils in Verbindung steht, und daß ein erstes Ventil (27, 271) in dem proximalen Ende des Kanals (26, 261) sitzt, um den Kanal zu schließen, das normalerweise die Verbindung zwischen der Öffnung (29, 291) und dem Kanal sperrt, daß ferner der Behälterteil einen evakuierbaren Behälter (12, 121) aufweist, dessen Öffnung durch einen Stöpsel (10, 101) verschlossen ist, und daß eine Röhre (14, 141) vorgesehen ist, die mit ihrem proximalen Ende durch den Stöpsel (10, 101) tritt und an ihrem distalen Ende derart mit der Öffnung (29, 291) in dem Halterteil verbunden ist, daß an dieser Öffnung eine abdichtende Verbindung zwischen der Röhre und dem Halterteil herstellbar ist, und daß an dem distalen Ende der Röhre ein Betätigungselement (20, 191) vorgesehen ist, das das erste Ventil (27, 271) öffnet und dabei die Öffnung (29, 291) mit dem Kanal (26, 261) verbindet, wenn die Röhre (14, 141) an den Halterteil (22, 221) angeschlossen wird, wobei der Stöpsel (10, 101) derart an dem Behälter (12, 121) angebracht ist, daß er mit dem Behälter relativ zur Röhre bewegbar ist, aber fest genug in der Behälteröffnung sitzt, um ein Eindringen von Luft zwischen den beiden Teilen zu verhindern.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß das erste Ventil aus einem flexiblen Stopfen (27, 271) besteht, der in dem proximalen Ende (28, 281) des Kanals (26, 261) sitzt und dieses Ende (28, 281) verschließt und der sich quer über die Öffnung (29, 291) erstreckt und die-

se Öffnung vollständig abdichtet, wenn die Röhre (14, 141) nicht mit dem Halterteil (22, 221) verbunden ist.

3. Vorrichtung nach Anspruch 2, dadurch gekennzeichnet, daß das Betätigungselement an der Röhre (14) ein Flansch (20) ist, der vom distalen Ende der Röhre absteht und eine solche Lage hat, daß er denjenigen Teil (29) des hohlen flexiblen Stopfens (27), der die Öffnung (29) versperrt, beiseitedrückt und dadurch eine Verbindung mit dem Kanal (26) herstellt, so daß Blut durch den Halterteil (22) in die Röhre (14) fließen kann.

4. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß die Öffnung (29, 291) als Muffe geformt ist und das distale Ende der Röhre (14, 141) im Paßsitz in der muffenförmigen Öffnung aufnehmbar ist.

5. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß der Halterteil mit einem Vorsprung (30) versehen ist, der an der Oberfläche, in die die Kanüle (23) eingeführt werden soll, aufsetzbar ist und damit den Winkel festlegt, unter dem die Kanüle in die Oberfläche eingeführt wird, und zudem den Halterteil in einem Abstand von der Oberfläche hält und ein Mittel zum bequemeren Festhalten des Halterteils darstellt.

6. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß der Stöpsel (10, 101) von einem axialen Kanal durchzogen ist, in dem die Röhre (14, 141) fest genug sitzt, um einen Fluß von Fluid zwischen der Röhre und der Kanalwand zu verhindern, und daß die Röhre (14, 141) an ihrem proximalen Ende verschlossen ist und in ihrer Seitenwand nahe dem proximalen Ende eine Öffnung (16, 161) hat, und daß der Behälter (12, 121) relativ zu diesem proximalen Ende der Röhre in Achsrichtung weit genug bewegbar ist, so daß die Öffnung (16, 161) in einer

ersten Stellung sich in dem Behälter befindet und eine Verbindung zwischen der Röhre und dem Behälter herstellt und in einer zweiten Stellung innerhalb des Kanals in dem Stöpsel (10, 101) liegt und damit der Behälter gegen das Eindringen von Luft oder Flüssigkeit aus der Röhre in den Behälter abgedichtet ist, wobei die Öffnung (16, 161) in der Seitenwand der Röhre ein zweites Ventil darstellt.

7. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß das distale Ende des Kanals im Stöpsel (10, 101) und das proximale Ende der Röhre auf der Außenseite mit zusammenpassenden Gewinden (13, 13'; 131, 131') versehen sind, so daß durch Drehen des Behälters um die Röhre allmählich eine Verbindung zwischen der Röhre und dem Behälter herstellbar ist bzw. die Verbindung unterbrechbar ist.

8. Vorrichtung nach Anspruch 6 oder 7, dadurch gekennzeichnet, daß die Röhre (14) zu beiden Seiten des Stöpsels (10) mit vorstehenden Teilen (18, 15) versehen ist, die als Anschläge dienen, um den axialen Bewegungsspielraum des Behälters und des Stöpsels relativ zur Röhre zu begrenzen.

9. Vorrichtung nach einem der Ansprüche 6 bis 8, dadurch gekennzeichnet, daß das proximale Ende der Röhre und das proximale Ende des Kanals im Stöpsel zueinander passend geformt sind, so daß beim Einsetzen der Röhre in den Kanal eine Abdichtung zwischen beiden Teilen zustandekommt.

10. Vorrichtung nach Anspruch 9, dadurch gekennzeichnet, daß die zusammenpassenden Teile (151, 151a) von Röhre und Kanal konisch geformt sind.

11. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß das erste Ventil ein hohler Stopfen (27, 271) ist, durch den eine Injektionsnadel eingeführt werden kann, um Fluid einem Patienten zu injizieren,

wenn die Haut des Patienten zur Blutentnahme bereits einmal durchstochen ist.

12. Vorrichtung nach einem der Ansprüche 6 bis 11, dadurch gekennzeichnet, daß der axiale Bewegungsspielraum des Behälters (121) relativ zur Röhre (141) in proximaler Richtung durch den Kontakt des proximalen Endes (151) der Röhre mit dem Stöpsel (101) und in distaler Richtung durch den Kontakt des Stöpsels (101) mit dem Halterteil (221) begrenzt ist.

13. Vorrichtung nach Anspruch 12, dadurch gekennzeichnet, daß der Abstand zwischen dem Halterteil (221) und dem Stöpsel (101) so gewählt ist, daß ein Wegnehmen des Behälterteils (351) vom Halterteil (221) nur dann möglich ist, wenn der Behälter die am weitesten von dem Halterteil entfernte Lage einnimmt, wobei diese Lage der Bewegungsgrenze des Behälters in proximaler Richtung entspricht, wodurch sichergestellt ist, daß das zweite Ventil (161) geschlossen ist.

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Blutentnahmevorrichtung

Die Erfindung betrifft eine Blutentnahmevorrichtung zum Abzapfen von Blut aus einem Blutgefäß.

In modernen Krankenhäusern gehört es zur Routine, von Patienten Blutproben zu entnehmen, indem man eine oder mehrere evakuierte Teströhren nacheinander in einen Halter einsetzt, der eine Kanüle mit zwei Spitzen hat; das eine zugespitzte Ende der Kanüle sticht in die Vene des Patienten ein und das andere spitze Ende durchsticht den Stöpsel der evakuierten Teströhre, um auf diese Weise Blut aus der Vene in die evakuierte Röhre fließen zu lassen.

Halter für Vakuumröhren sind jedoch verhältnismäßig teuer und daher keine Wegwerfartikel; außerdem sind sie unhandliche Geräte, die einer Verunreinigung ausgesetzt sind (siehe US-PS 3 520 292). Wenn in den Haltern nicht bereits Kanülen mit zwei Spitzen eingebaut sind, müssen sie von einem Benützer an den Haltern angebracht werden. Die Handhabung dieser Kanülen mit zwei Spitzen ist jedoch gefährlich, weil der Benützer sich in die Finger stechen oder die Kanüle infizieren kann. Außerdem erlauben doppelseitig zugespitzte Kanülen nicht ohne weiteres die Injektion von löslichen Arzneimitteln in die Vene. In der medizinischen Praxis ist es jedoch manchmal erwünscht, nach der Blutentnahme durch die Kanüle Arzneimittel zu injizieren,

weil man so dem Patienten den Schmerz beim nochmaligen Einstechen in eine Vene erspart. Ein weiterer Nachteil in der Verwendung doppelt zugespitzter Kanülen ist, daß beim Herausziehen der Röhre etwas Blut aus der Vene durch die Kanüle zu deren innerem Ende zurückfließt und die Umgebung beschmutzt. Besonders beachtlich ist bei der Verwendung von Vakuumröhren zusammen mit doppelt zugespitzten Kanülen die Gefahr, daß, wenn die äußere Spitze nicht in einer Vene sondern im Gewebe liegt, es beim Durchstechen der inneren Spitze der Kanüle durch die Röhre zu einem Blutaustritt aus der Vene und einem Hämatom kommt. Dann muß der Benützer die Kanüle so rasch wie möglich herausziehen. Selbst dann kann der Benützer die Situation nicht schnell genug erfassen, um Schaden zu vermeiden, weil der volle Druckunterschied an die äußere Spitze der Kanüle angelegt wird, wenn der Stöpsel der evakuierten Röhre durchstochen wird.

Das herkömmliche Gerät hat einen Halter, der das proximale Ende der doppelt zugespitzten Kanüle umgibt, um das zugestöpselte Ende der evakuierten Röhre aufzunehmen. Der Durchmesser des Halterteils ist so groß, daß die Kanüle in die Haut unter einem verhältnismäßig spitzen Winkel eindringt, was die Gefahr erhöht, daß die Kanüle auch noch die andere Wand des Blutgefäßes durchsticht, so daß die Spitze der Kanüle dann im Gewebe statt im Blutgefäß zu liegen kommt. Auch wenn auf dem proximalen Ende der Kanüle kein evakuierter Behälter angebracht ist, kann es an der Spitze zu einer Blutgerinnung kommen, wodurch die Funktion des Gerätes gestört ist, wenn eine weitere Probe entnommen werden soll.

Die Erfindung will eine verbesserte Blutentnahmevorrichtung schaffen, die die obigen Mängel vermeidet. Mit der erfindungsgemäßen Vorrichtung sollen mit einem einzigen Einstich einer Kanüle in ein Blutgefäß mehrere Blutproben entnommen werden können, ohne daß die Gefahr einer Blutgerinnung in dem Zwischenraum zwischen den aufeinanderfolgenden Blutentnahmen besteht. Ferner soll der Winkel, unter dem die Kanüle in die

Haut des Patienten eindringt, durch das Gerät selbst festgelegt sein.

Um dies zu erreichen, sieht die Erfindung eine Blutentnahmevorrichtung vor, wie sie im kennzeichnenden Teil des ersten Anspruchs beschrieben ist.

Die erfindungsgemäße Vorrichtung hat zwei Ventile. Das erste Ventil schließt das proximale Ende des Nadelteils, wenn kein Behälter angeschlossen ist; das zweite Ventil macht es möglich, den Druckunterschied, der zum Absaugen von Blut aus dem Patienten genützt wird, zu steuern. Das zweite Ventil kann rasch geschlossen werden, falls man entdeckt, daß die Nadel nicht in einem Blutgefäß sondern außerhalb desselben im Gewebe liegt. Auf diese Weise wird ein Blutaustritt in die Umgebung und ein Hämatom vermieden.

Die erfindungsgemäße Vorrichtung besteht aus zwei zusammensetzbaren Teilen; der erste Teil umfaßt eine Kanüle und einen Halter, der zweite Teil umfaßt einen evakuierten Behälter, der mit einem Stöpsel geschlossen ist, durch den eine axial verschiebbare und drehbare Röhre tritt. Der erste und zweite Teil, die nachstehend als der Halterteil und der Behälterteil bezeichnet werden, können fest miteinander vereinigt werden, so daß ein durchgehender Kanal für das fließende Blut durch die Kanüle, den Halterteil und die Röhre in den Behälter gebildet ist. In dem Halterteil ist das erste Ventil angeordnet, das gewöhnlich geschlossen ist, so daß, wenn die Röhre und der Behälterteil nicht mit dem Halterteil verbunden sind, das in dem Halterteil eingeschlossene Blut nicht mit Luft in Berührung kommt und somit eine mögliche Infizierung vermieden ist. In dem Behälterteil ist ein zweites Ventil angebracht, das die Steuerung der Druckdifferenz, die an der distalen Spitze der Kanüle wirksam wird, ermöglicht und den Unterdruck von der Spitze absperren kann, falls die Kanüle nicht ordnungsgemäß in einem Blutgefäß liegt, aus dem Blut entnommen werden soll, um so die Gefahr eines Hämatoms auszuschließen. Das zweite Ven-

til wird durch Drehung des Behälters um die Röhre betätigt. Das distale Ende der Röhre kann in das proximale Ende des Halterteils eingesetzt werden, so daß ein durchgehender Kanal gebildet wird. In einer Ausführungsform ist das distale Ende der Röhre mit einem vorstehenden Flansch versehen, der das erste Ventil öffnet, wenn der Behälterteil und der Halterteil miteinander verbunden werden. In einer zweiten Ausführungsform öffnet das distale Ende der Röhre selbst das erste Ventil und der Behälterteil kann von dem Halterteil nur dann abgenommen werden, wenn das zweite Ventil geschlossen ist.

Die Erfindung hat also u.a. den Vorteil, daß der Unterdruck an der Spitze einer Kanüle von einem Ventil abgesperrt wird, falls die Kanüle nicht richtig in einem Blutgefäß liegt. Die Erfindung macht außerdem durch einen neuartigen Stöpsel für einen Vakuumbehälter und einen neuartigen hypodermischen Applikator einen Halter und doppelt zugesptitze Kanülen überflüssig. Der hypodermische Applikator erlaubt sowohl die Injizierung löslicher Arzneimittel in ein Blutgefäß als auch das Entnehmen von Blutproben, ohne ein Verspritzen von rückschießendem Blut. Durch das Zusammensetzen des die Kanüle enthaltenden Teils mit dem Behälterteil wird automatisch das Ventil in dem Halterteil geöffnet, so daß ein durchgehender und unbehinderter Kanal von der Kanülenspitze bis zum proximalen Ende der Röhre, das in den Behälter mündet, gebildet ist. Durch die Steuerung des an eine Vene angelegten Unterdruckes kann ein Kollaps der Vene vermieden werden.

Weitere Einzelheiten und Vorzüge der Erfindung ergeben sich aus der nachfolgenden Beschreibung von Ausführungsbeispielen anhand der beigefügten Zeichnungen. Darin zeigen:

Fig.1 eine Seitenansicht einer erfindungsgemäßen Vorrichtung, in der der die Kanüle enthaltende Teil von dem Behälterteil getrennt ist;

Fig.2 einen Seitenriß der erfindungsgemäßen Vorrichtung, in dem die beiden Teile in der Lage zum Zusammensetzen sind;

Fig.3 einen Seitenriß, der die zwei Teile der Vorrichtung miteinander verbunden zeigt und in dem das Ventil im Behälterteil geschlossen dargestellt ist;

Fig.4 einen der Fig.3 ähnlichen Seitenriß, bei dem jedoch das Ventil im Behälterteil offen ist;

Fig.5 eine Schnittansicht nach der Linie 5-5 der Fig.4;

Fig.6 eine Schnittansicht nach der Linie 6-6 der Fig.4;

Fig.7 eine perspektivische Seitenansicht einer zweiten Ausführungsform der Erfindung;

Fig.8 eine teilweise geschnittene Ansicht der beiden Teile der zweiten Ausführungsform der Erfindung im getrennten Zustand;

Fig.9 eine der Fig.8 ähnliche Ansicht, in der jedoch die beiden Teile vereinigt sind;

Fig.10 die gleichen beiden Teile der zweiten Ausführungsform, wobei jedoch der Behälter vorgeschoben ist, so daß das zweite Ventil offen ist;

Fig.11 eine Ansicht nach der Linie 11-11 der Fig.10;

Fig.12 eine Ansicht nach der Linie 12-12 der Fig.10; und

Fig.13 eine Schnittansicht nach der Linie 13-13 der Fig.9.

Die erfindungsgemäße Blutentnahmevorrichtung besteht aus zwei zusammenfügbaren Teilen, einem Halterteil und einem Behälterteil, die in Fig.1 getrennt voneinander dargestellt sind. Eine Kanüle 23 hat eine Spitze 24 zum Einstechen in ein Blutgefäß durch die Haut eines Patienten. Das proximale Ende 25 (Fig.2) der Kanüle 23 ist in einem Halterteil 22 befestigt, der von einem Kanal 26 durchzogen ist. Ein Stopfen 27 mit flexiblen Wänden sitzt im Ende 28 des Kanals. Eine flexible Wand desselben liegt quer über einer Öffnung 29, so daß der Stopfen 27 zugleich die Öffnung 29 und das Ende 28 des Kanals abdichtet. Der Halterteil 22 hat einen Vorsprung 30, der dazu dient, den Halterteil in einem bestimmten Abstand von der Haut des Patien-

ten zu halten, wodurch der Winkel eingestellt wird, unter dem die Kanüle 23 in die Haut eindringt, und die Handhabung des Halterteils und der Kanüle erleichtert wird.

Ein Behälter 12 ist mit einem Stöpsel 10 verschlossen, der einen auf dem offenen Ende des Behälters 12 aufsitzenden Flansch 11 hat. Der Stöpsel 10 ist von einem axialen Kanal durchzogen, in dem eine Röhre 14 steckt, die fest genug in dem Stöpsel 10 sitzt, um ein Eindringen von Luft zwischen die Röhre 14 und den axialen Kanal im Stöpsel 10 zu verhindern, aber andererseits doch so locker, daß sie sich im Stöpsel 10 in Achsrichtung verschieben oder drehen kann.

Die Röhre 14 ist an ihrem proximalen Ende verschlossen, vorzugsweise mit einer Scheibe, die auf dem Ende der Röhre 14 festgekittet oder sonstwie befestigt wird, nachdem die Röhre 14 in den Stöpsel 10 eingeführt ist. Die Scheibe 15 erfüllt eine doppelte Aufgabe, nämlich das Ende der Röhre 14 abzudichten und zugleich den axialen Bewegungsspielraum der Röhre 14 von dem Behälter 12 weg zu begrenzen. Die Röhre 14 hat auch noch einen starr angebrachten oder angeformten Anschlag 18 an einer solchen Stelle, daß der Bewegungsspielraum der Röhre 14 in axialer Richtung zum Behälter 12 hin begrenzt wird.

Die Röhre 14 ist mit einer seitlichen Öffnung 16 versehen, die in einem kleinen Abstand von dem abgedichteten Röhrenende angeordnet ist. Wie in Fig.2 gezeigt, liegt die Öffnung 16 innerhalb des den Stöpsel 10 durchziehenden Kanals, so daß der Behälter 12 gegen ein Eindringen von Luft beim Evakuieren geschützt ist. In einer zweckmäßigen Ausführungsform ist der axiale Kanal durch den Stöpsel 10 von seinem äußeren Teil bis kurz vor die Stelle, wo die Öffnung 16 zu liegen kommt, wenn die Scheibe 15 mit dem Stöpsel 10 in Kontakt gebracht ist, mit einem Gewinde versehen. Selbstverständlich ist in diesem Fall auch die Röhre 14 mit einem passenden Gewinde auszustatten.

Fig.2 zeigt den Behälterteil der Vorrichtung gerade beim Zu-

sammenfügen mit dem Halterteil. Die Verbindung wird in der Weise hergestellt, daß das distale Ende 19 der Röhre 14 in eine Aufnahme 29 eingesetzt wird, Das Röhrenende und die Aufnahme sind so geformt, daß sie bündig zusammenpassen und keine Luft zwischen ihnen eindringen kann. An dem Röhrenende 19 ist ein Flansch 20 angebracht, der sich gegen die flexible Wand 29' des Stopfens 27 anlegt, wenn die beiden Teile miteinander vereinigt sind. Wenn das Röhrenende 19 in die Aufnahme 29 eingeschoben wird, drückt der Flansch 20 den oberen Teil des Stopfens 27 beiseite, so daß ein durchgehender Kanal zwischen der Spitze der Kanüle 23 und dem Inneren der Röhre 14 hergestellt wird. Dies ist in Fig.3 zu sehen, in der die obere Wand des flexiblen Stopfens 27 von dem Flansch 20 niedergedrückt ist. Das Aussehen des Halterteils der Vorrichtung nach dem Einführen des Röhrenendes 19 in die Aufnahme 29 ist in den Schnittansichten der Fig.5 und 6 gezeigt.

Wenn eine Blutprobe entnommen werden soll, wird der Behälter 12 vorsichtig in der durch den Pfeil in Fig.4 angegebenen Richtung gedreht, bis die Öffnung 16 eben von dem proximalen Ende des Stöpsels 10 freikommt. Die axiale Bewegung des Behälters 12 in Richtung zum Anschlag 18 ergibt sich aus der Tatsache, daß die Röhre 14 mit einem Gewinde 13 versehen ist, das mit einem Gewindeteil 13' des Stöpsels 10 im Eingriff ist. Zu beachten ist, daß der Stöpsel 10 an seinem proximalen Ende einen gewindefreien Teil hat, wodurch eine feste Abdichtung sichergestellt ist, wenn sich die Öffnung 16 innerhalb des Stöpsels 10 befindet.

Wenn nicht praktisch sofort Blut durch die Öffnung 16 in den Behälter 12 fließt, wird der Behälter 12 in der entgegengesetzten Richtung gedreht, um die Öffnung 16 wieder in den Stöpsel 10 zurückzubringen, wodurch man vermeidet, daß die volle Druckdifferenz auf das Gewebe einwirkt, in dem die Kanüle liegen muß. Auf diese Weise werden eine Extravasation von Blut und das dabei entstehende Hämatom vermieden. Die Kanüle kann dann herausgezogen und noch einmal richtig eingestochen wer-

den, so daß ihre Spitze in einem Blutgefäß zu liegen kommt. Dann wird der Behälter 12 wieder gemäß Fig.4 gedreht, um noch einmal mit der Blutentnahme zu beginnen. Falls Blut durch die Öffnung 16 fließt, wird der Behälter 12 weitergedreht, bis der Stöpsel 10 auf den Anschlag 18 am Halterteil 22 trifft. In dieser Lage bleibt dann der Behälter, bis die gewünschte Blutmenge abgesaugt ist oder bis der Behälter gefüllt ist.

In den Fig.7-12 ist eine zweite Ausführungsform der Erfindung dargestellt. Wieder besteht die Vorrichtung aus zwei Teilen, einem die Kanüle enthaltenden Halterteil, der insgesamt mit 221 bezeichnet ist, und einem insgesamt mit 351 bezeichneten Behälterteil. Der Behälterteil 351 weist einen Behälter 121 auf, der mit einem Stöpsel 101 verschlossen ist, in dem eine durchgehende Bohrung angebracht ist. Eine Röhre 141, die einen Gewindeteil 131 hat, ist in der Bohrung des Stöpsels 101 angebracht. Die Röhre 141 hat zwei Teile 141a und 141b, die miteinander einen Winkel bilden. Ein die Röhre 141 durchziehender Kanal 161a ist an seinem Ende mit einem konischen Teil 151 verschlossen, das in einen entsprechenden Abschnitt 151a der Bohrung im Stöpsel 101 paßt. In dem Kanal 161a ist nahe dem konischen Teil 151 eine seitliche Öffnung 161 vorgesehen. Der Gewindeteil 131 der Röhre 141 hört kurz vor der seitlichen Öffnung 161 auf, so daß, wenn der Behälter 121 eine solche Lage hat, daß das konische Teil 151 im Paßsitz im Abschnitt 151a aufgenommen ist, die Öffnung 161 durch den zylindrischen Teil des Stöpsels 101 dichtend verschlossen ist.

Um den Halterteil und den Behälterteil der Vorrichtung zusammenzufügen, wird das Ende 191 der Röhre 141 in eine Aufnahme 291 im Halterteil 221 eingeführt. Nasen 301a schieben sich in Nuten 301b im Halterteil 221 und eine Drehung des Behälterteils 351 stellt einen Bajonettverschluß zwischen den Nasen 301a und Nuten 301b her. Außerdem hat die Aufnahme 29a einen kugeligen Teil 311b, der mit einem entsprechenden kugeligen Teil 311a an der Röhre 141 zusammenpaßt, so daß eine feste Abdich-

tung zwischen dem Halterteil und dem Behälterteil zustande kommt.

Wenn das Röhrenende 191 in die Aufnahme 291 eingeschoben und der Bajonettverschluß hergestellt ist, drückt das zugespitzte Röhrenende 191 den oberen Teil eines flexiblen Stopfens 271 nach unten, der vorzugsweise hohl ist. Dabei dient das zugespitzte Röhrenende selbst als ein Mittel, um den oberen Teil 271' des Stopfens 271 beiseite zu schieben. Durch diese Verlagerung entsteht eine ununterbrochene Leitung zwischen dem Kanal 161a im Behälterteil und der Kanüle 23. Der hohle Stopfen 271 schließt das Ende der Aufnahme 291 und wirkt beim Einführen des Röhrenendes 191 als Ventil infolge der herabgedrückten oberen Stopfenwand 271'. Ein Teil 401 des Röhrenendes ist vorzugsweise im Paßsitz in der Aufnahme 29a aufgenommen, so daß zwischen diesen Teilen eine Abdichtung hergestellt ist.

Wenn der Behälter 121 in der durch einen Pfeil in Fig.10 angedeuteten Richtung gedreht wird, bewegt er sich gemäß Fig.10 in distaler Richtung und verbindet die seitliche Öffnung 161 mit dem Behälterinnenraum; damit ist eine Verbindung von der Kanüle 23 zum Behälter hergestellt. Falls der Behälter vor dem Vereinigen der beiden Teile evakuiert ist, fließt dann Blut durch die Kanüle und durch die verbundenen Kanäle in den Behälter 121, nachdem die seitliche Öffnung 161 in den konischen Abschnitt der Bohrung im Stöpsel 101 gelangt ist. Der Bewegungsspielraum des Behälters in distaler Richtung - das Gewinde an der Röhre 141 ist in diesem Fall rechtsgängig - wird durch den Kontakt zwischen dem Stöpsel 101 und dem hinteren Teil 321 der Begrenzung des Halterteils 221 eingeschränkt.

Zweckmäßigerweise trägt der Stopfen 271 einen Wulst 271a, der sich in eine Nut 271b im Halterteil 221 einbettet, um dazu beizutragen, daß der Stopfen 271 in seiner Lage gehalten wird.

Auf welche Weise die Nasen 301a sich in den Nuten 301b festsetzen, ist deutlich aus den Fig.11 und 12 ersichtlich. Der

Weg, auf dem Flüssigkeit von der Kanüle in den Behälter 121 gelangt, wird aus den Fig.10 und 12 deutlich.

Sobald der Behälter gefüllt ist, wird die Spitze 191 der Röhre 141 von dem Kanal, d.i. aus der Aufnahme 29a herausgezogen und die flexible Wand des Stopfens 27a schnellt zurück, so daß sie einen Kanal 261 im Halterteil 221 versperrt. Dieser Vorgang kann beliebig oft wiederholt werden, wobei man jedesmal einen neuen Behälter zum Entnehmen einer Probe verwendet.

Der Abstand zwischen der Begrenzung 321 des Halterteils 221 und der Außenfläche 38a des Stöpsels 101 ist so gewählt, daß der Behälterteil von der Ecke 361 nicht abheben kann, bevor nicht das konische Teil 151 fest in dem Bohrungsabschnitt 151a abdichtet, und diese dichtende Anlage wird durch Drehen des Behälters 351 mit gleichzeitiger Verschiebung desselben in proximaler Richtung hergestellt. Die gestrichelte Kurve zeigt, wie der Abstand, bei dem die Spitze 371 des Stöpsels 101 von der Ecke 361 freikommt, bestimmt wird. Zweck dieser Anordnung ist es, sicherzustellen, daß der Behälter gut abgedichtet ist, bevor der Behälterteil 351 vom Halterteil 221 weggenommen wird. Der Behälterteil kann dann getrennt gehandhabt werden, ohne daß die Gefahr einer Verunreinigung seines Inhalts besteht.

Zu beachten ist, daß die Abdichtung zwischen dem Röhrenendenteil 401 und der Aufnahme 291 ein Eindringen von Luft beim Entriegeln des Bajonettverschlusses verhindert, falls ein Entriegeln versucht wird, wenn der Behälterteil 351 an der seitlichen Öffnung 161 nur teilweise verschlossen ist.

Nach Wunsch kann ein lösliches Arzneimittel ohne Schmerzen für den Patienten injiziert werden, indem man das Arzneimittel in eine übliche Spritze aufzieht, an der eine dünnkalibrige Nadel angesetzt ist, und den Stopfen 271 durch eine Öffnung 28a hindurch mit der Nadelspitze der Spritze durchsticht. Das Arzneimittel wird dann in den Kanal 26a eingespritzt und geht

von dort zur Kanüle 23, zu deren Spitze 24 und schließlich in das Blutgefäß des Patienten, vorausgesetzt, daß der als Aufnahme 291 dienende Durchgang abgedichtet bleibt. An den am Ort bleibenden Halterteil 221 kann ein neuer Behälterteil angesetzt werden, um mehr Blut abzusaugen, oder es kann auch die Kanüle 23 aus dem Blutgefäß herausgezogen und dann weggeworfen werden. Der gefüllte Behälterteil wird an ein entsprechendes biochemisches Labor geschickt, wo das Ventil der seitlichen Öffnung 161 zuerst geöffnet wird, worauf der Stöpsel 101 ohne weiteres entfernt, die Untersuchungen vorgenommen und die ganze Einheit dann vernichtet werden kann.

Da die Aufnahme 291 jedesmal versperrt wird, wenn ein Behälter weggenommen wird, kann Blut weder weiter aus dem Kanal 261 aussickern, noch wird es in das Blutgefäß zurückgesaugt.

Die der Erfindung gestellt Aufgabe ist somit erfüllt. Gegenüber den beschriebenen Ausführungsbeispielen sind Abänderungen möglich.

17.

FIG. 1

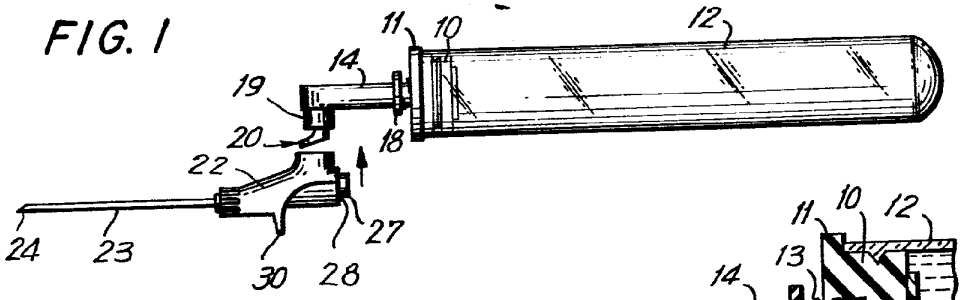


FIG. 2

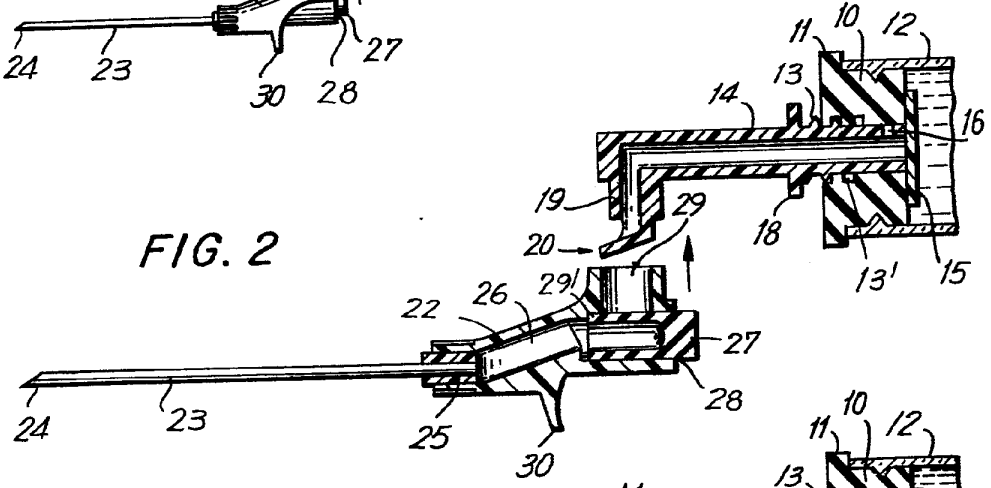


FIG. 3

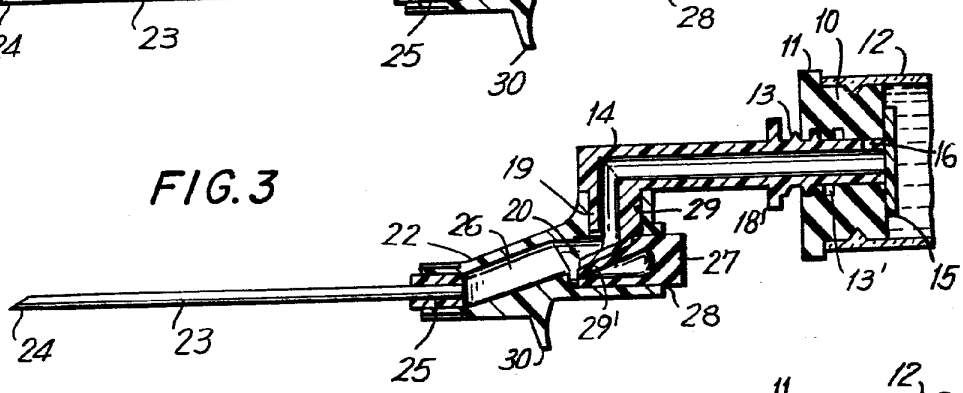


FIG. 4

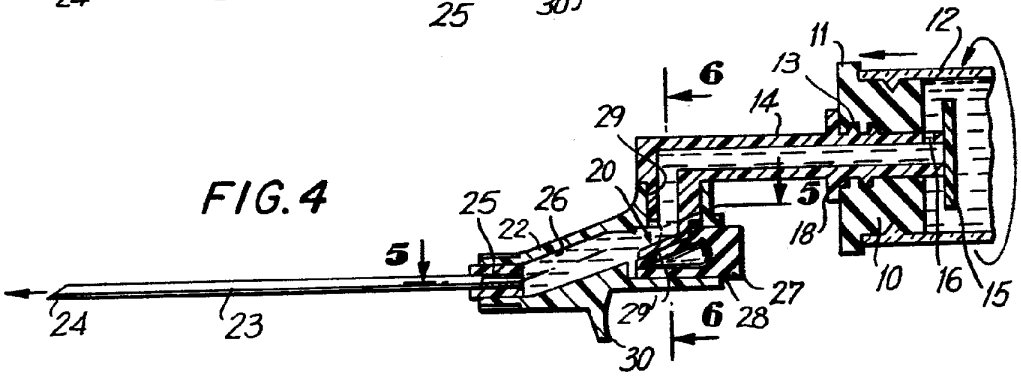


FIG. 5

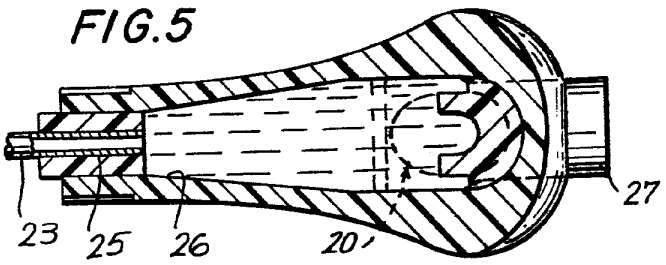
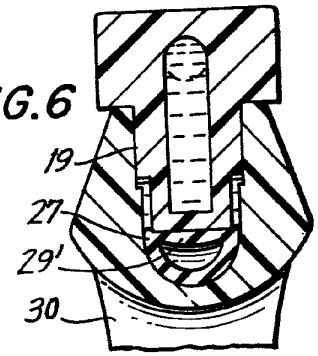


FIG. 6



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FIG. 7

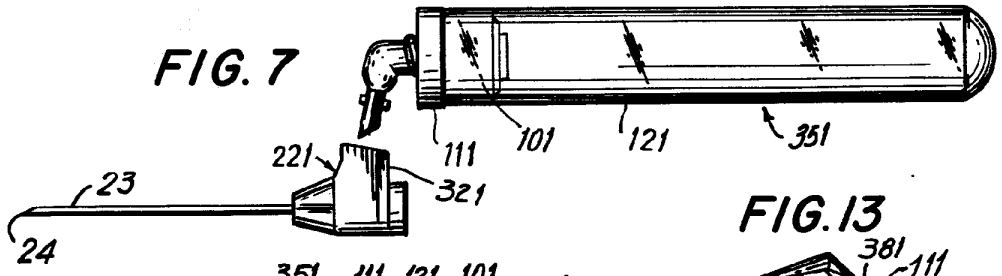


FIG. 13

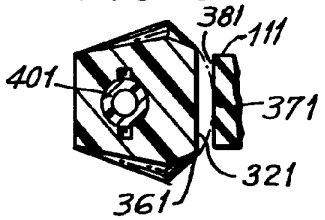


FIG. 8

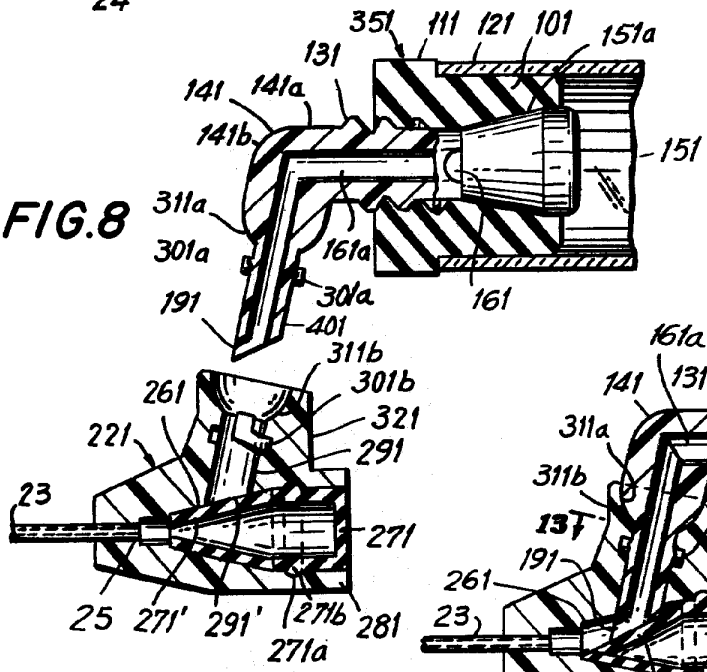


FIG. 9

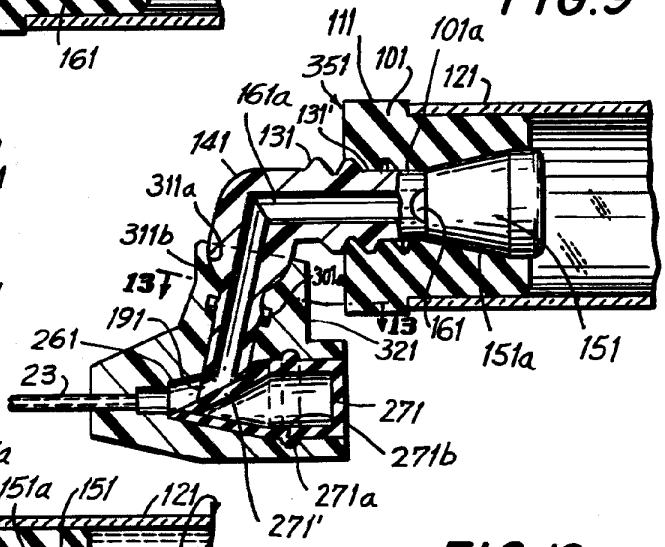


FIG. 10

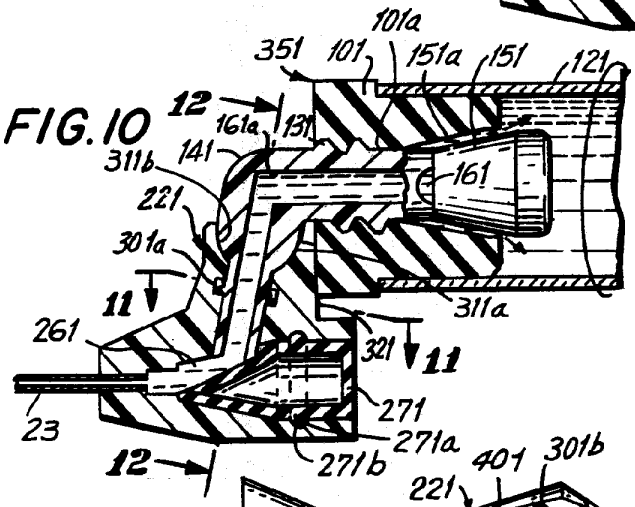


FIG. 12

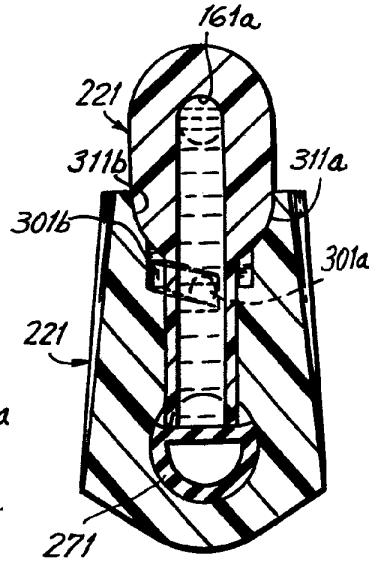
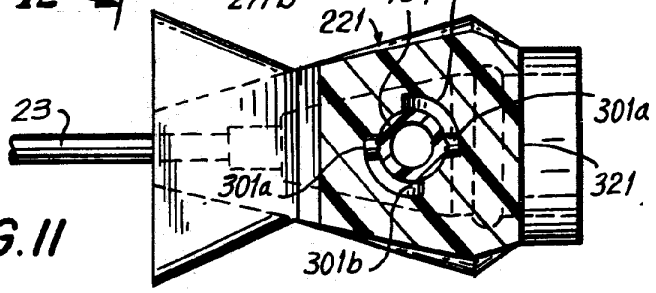


FIG. 11



NCCLS simplifies the order of draw: a brief history.

Print

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The order in which tubes should be filled seems to mutate daily into increasingly creative incarnations. In fact, it mutated right out of existence last year when one workshop presenter astonished her attendees by stating, "There is no order of draw." Adding to the confusion are Internet phlebotomy sites, training manuals, certification study guides, and textbooks that perpetuate many variations.

The proper order in which blood-collection tubes should be filled is designed to prevent the carryover of additives from one tube to the next. Such carryover alters the composition of the next tube and can lead to erroneous results--with the potential to mislead physicians and invite catastrophic errors in patient management. For the record, the order of draw has been established by NCCLS--the National Committee for Clinical Laboratory Standards, which develops voluntary standards--through its consensus process with industry, government, and laboratory professionals and is published by NCCLS in document H3, Procedure for the Collection of Blood Specimens for Diagnostic Testing by Venipuncture.

The order was revised and simplified this past December to one that works for both glass and plastic tubes, regardless of whether the specimen is drawn by using a tube holder and needle assembly or syringe. To understand the necessity for the order of draw and to clarify the widespread confusion on the matter, let us examine the history on how the order came about and how it has evolved through the years.

Historical perspective

The order has its origins in the literature as early as 1977, when evidence that additive carryover occurs was first published in the American Society of Clinical Pathologists' (ASCPs') Summary Report. (1) Authors Nilda Sun and Rita Knauf at the St. Barnabas Medical Center in Livingston, NJ, reported their observation of an asymptomatic patient who had a potassium level of 25.4 mEq/L (normal 3.5-5.3 mEq/L) obtained from a nonhemolyzed specimen. Upon investigation, the authors discovered that the phlebotomist filled the lavender-stopper tube containing potassium EDTA immediately prior to filling the tube from which the elevated potassium was obtained.

The first recommendation on establishing a formal order of draw for blood collection was published in a letter to the editor of Clinical Chemistry by Roger Calam, PhD, and Marsha Cooper of St. John Hospital in Detroit, MI, in 1982. (2) Although tube manufacturer Becton Dickinson (BD) had been recommending as early as 1976 that all additive tubes be drawn after nonadditive tubes, with citrate tubes being

the first additive tube filled, Calam and Cooper postulated that a more detailed order was necessary for additive tubes. They reported five cases in which they observed spuriously abnormal potassium and calcium levels, all of which resulted when a lavender-stopper tube containing potassium EDTA was filled immediately prior to the gel tube intended for chemistry tests. When specimens were re-collected, potassium and calcium fell within normal limits. Based on these observations and those of Sun and Knoff, Calam and Cooper concluded that not only should additive tubes be drawn after nonadditive tubes, as BD had been suggesting, but that heparin, EDTA, and potassium-oxalate/sodium-fluoride tubes (gray stoppers) should have a specific "order of draw."

The reasoning for their proposed order was based on the fact that if EDTA could carryover into nonadditive tubes, it could also carryover into tubes containing other additives. Such proof suggested that the additive of any tube could also carryover into a subsequent tube, threatening the accuracy of results.

The authors proposed that heparin tubes be drawn before the EDTA tube, and EDTA tube should precede oxalate/fluoride tubes. Since oxalate/fluoride is disruptive to cell membranes, placing it subsequent to the EDTA tube prevents problems with cell morphology that might otherwise occur. Also, with the gray top drawn after the green top, neither potassium oxalate nor sodium fluoride in the gray-top tubes would contaminate sodium or potassium testing.

The order proposed by Calam and Cooper for filling additive tubes (following nonadditive tubes) was adopted by the NCCLS in 1984 in document H3-A2 as: (1) sodium-citrate tube; (2) heparin tube; (3) EDTA tube; and (4) oxalate/fluoride tube. (3)

Gel separator tubes and clot activators

The introduction of serum gel tubes (1976) and plasma gel tubes (1987) provided a convenience to specimen-processing personnel who had been required to remove the stoppers of nongel tubes after centrifugation and physically remove the serum or plasma for testing or storage. The gel tubes provided a physical barrier between the serum or plasma following centrifugation, preventing the changes that occur when serum or plasma is allowed to remain in contact with the cells for prolonged periods of time prior to testing. Serum separator tubes contain a clot activator (glass or silica particles) to facilitate clotting. Although clot activators may shorten the time it takes for the specimen to clot, manufacturers stress that such tubes facilitate complete clotting, not rapid clotting, yielding serum that is less likely to contain fibrin strands that can interfere in testing.

Historically, tubes with anticoagulants (e.g., EDTA) or preservatives (e.g., sodium fluoride) were referred to as "additive tubes." In 1998, it was proposed that separator tubes containing gels and either a clotting activator or an anticoagulant also be considered as additive tubes. (4) The NCCLS incorporated these tubes into the order of draw in its 1998 revision (H3-A4). (5) The order evolved with the gel tubes (serum and plasma separators) following the citrate tube (blue stopper):

1. blood-culture tubes,
2. nonadditive tube,
3. additive tubes (in the following order):
a. sodium-citrate tube,
b. gel separator tube,
c. heparin tube,
d. EDTA tube, and
e. oxalate/fluoride tube.

Since possible carryover of the clot activator could conceivably alter results, a gel tube with a clot activator had to be drawn after the blue top. Although not spelled out, the serum gel tube should be drawn before the plasma gel tube, as the latter often contains lithium heparin, which could affect the accuracy of a patient's lithium test in the serum tube.

If required, a plastic red-stopper tube (plastic tubes contain a clot activator) can precede a heparin (green top) or EDTA (lavender top) tube without concern for carryover. The logic is that any carryover of the clot activator into tubes other than blue tops is irrelevant, since carryover should be neutralized by the excess anticoagulant. In contrast, carryover of a clot activator into a sodium citrate tube (blue top) could interfere with clotting factors, leading to inaccurate results.

Some facilities maintain the necessity for a different order for syringe transfer because not all syringe draws go quickly and, therefore, the potential exists for clotting to occur in the syringe prior to blood transfer to successive tubes. (6,7) To prevent clotting within the syringe, an order is implemented that fills all additive tubes first and then the nonadditive tubes. NCCLS consensus concluded, however, that the potential for carryover from the needle of the syringe had the potential to be a more significant problem than any clotting that might take place in the syringe during a properly performed venipuncture. Therefore, the 1998 NCCLS revision also recommended that the same order of draw be followed when transferring blood specimens from a syringe to multiple blood-collection tubes.

Plastic tubes

Motivated by increasing concern over broken-glass exposures, high biohazardous waste-disposal costs, and Occupational Safety and Health Agency (OSHA) guidelines mandating substitution, many laboratories began switching from glass collection tubes to plastic (see "Richard Fairfax of OSHA Talks About the Bloodborne Pathogens Standard" February 2003 MLO, p. 32.) This industry-wide transition from glass to plastic necessitated a modification to the order of draw. Plastic serum tubes are now positioned the same as gel separator tubes, which contain a clot activator. The revised order,* published in December 2003, is now as follows:

1. blood-culture tubes,
2. sodium-citrate tube (e.g., blue-stopper),
3. serum tubes with or without clot activator, with or without gel separator (e.g., red-, gold-, speckled-stopper),
4. heparin tubes with or without gel (e.g., green-stopper),
5. EDTA tubes (e.g., lavender-stopper), and
6. glycolytic inhibitor (e.g., gray-stopper). (8)

In the revised standard, NCCLS recognizes that some facilities may still be using glass serum tubes without a clot activator to serve as a waste tube before collecting special coagulation assays. Although the revised order functions well regardless of the presence of a clot activator in the facility's serum tube, a provision within H3-A5 affords the option of keeping the nonadditive serum tube before the citrate tube in the following passage: "The order of draw has been revised to reflect the increased use of plastic blood-collection tubes. Plastic serum tubes containing a clot activator may cause interference in coagulation testing. Glass nonadditive serum tubes may be drawn before the coagulation tube."

The NCCLS order of draw has gone through several revisions dictated by technology, publication, and common sense. The latest revision should make it easier for educators and trainers to teach the order of draw and prevent additive carryover, which can affect patient results.

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RELATED ARTICLE: Alternatives to current order of draw

Some facilities have conducted internal studies that support a variation to NCCLS' order of draw. When reliable documentation supports an alternative order, the facility's protocol should take precedence. The Mayo Clinic in Rochester, MN, developed its own when it found that calcium levels drawn early in the order of draw can be significantly different than those drawn later in the order. Since immediate tourniquet removal is not always feasible (nor appropriate for ionized calcium collection), phlebotomists there follow an order of draw designed to protect against potentially erroneous calcium results, which includes a separate order of draw for syringes. In addition, tubes for trace-metal analysis are always first in order of draw at Mayo, since such specimens have been found to be contaminated by penetration of the sheathed back-end of the needle into any nontrace metal tube stoppers. Mayo's current order of draw is:

1. trace-metal collection tube (nonadditive)
2. gel separator tube (glass and plastic)
3. nongel serum tube (glass and plastic)
4. citrate tube
5. heparin tube
6. EDTA tube

7. oxalate/fluoride tube
8. ACD tube

Mayo also advocates a previous NCCLS order of dispensing from a syringe, i.e., tubes containing anticoagulants are dispensed first in order to minimize microclot formation in the syringe.

By Dennis J. Ernst, MT(ASCP), and Roger Calam, PhD, DABCC

Dennis J. Ernst, MT(ASCP), is director of the Center for Phlebotomy Education, editor of Phlebotomy Today, and an MLO editorial advisory board member. Roger Calam, PhD, is associate director of Clinical Chemistry at St. John Hospital and Medical Center, Detroit, MI. Both participated in the revision of the NCCLS venipuncture standard.

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REVIEW

Detecting Bacterial Contamination in Platelet Products

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SUMMARY

Bacterial contamination of platelets is an important cause of transfusion-associated morbidity and mortality. It is currently the most frequent infectious complication of transfusion therapy, with between 1 in 1,000 and 1 in 3,000 platelet units being bacterially contaminated at time of transfusion. Several factors have contributed to the persistence of this problem including lack of sensitive detection methods, lack of recognition of the frequency of the problem, inadequate recognition of septic reactions by clinicians treating patients receiving platelet transfusions, differences in transfusion reactions between bacterial species and bacterial inocula transfused, and differing methodologies and time of testing for detection of bacteria in platelet units. There are also important correlations between the receipt of bacterially contaminated platelet units and the development of transfusion reactions and bacteremia. In the last few years the recognition of the importance of platelet bacterial contamination prompted the College of American Pathologists (CAP) and the American Association of Blood Banks (AABB) to set new standards requiring the screening of platelets for bacterial contamination. In the wake of these standards, an increasing number of approaches have been and are being developed to deal with this problem. The clinical sensitivity, specificity and predictive value of these detection methods vary considerably and need to be defined for routine laboratory practice. In this review, we focus on the practical aspects and feasibility of implementing FDA-cleared detection methods for identifying bacterially contaminated platelet units. We also present details of a number of methods under development for at-issue use. (Clin. Lab. 2006;52:443-456)

BACKGROUND

Platelets are currently administered as single donor plasmapheresis (SDP) and whole-blood derived, random donor platelet (RDP) units, with the latter typically being administered in pools of 4-6 units. Bacterial contamination of these platelet products is an ongoing problem associated with significant transfusion-associated morbidity and mortality.[1-10] Currently, platelet-transfusion-associated sepsis is the most frequent infectious complication of transfusion therapy, with between 1 in 1,000 and 1 in 3,000 platelet units being bacterially contaminated at time of transfusion.[1, 8, 11] Transfusion of contaminated units is estimated to cause life-threatening sepsis in between 10% and 40% of recipients receiving a bacterially contaminated platelet unit. Based on passive-reporting studies from the United States, the United Kingdom and France, the risk of death from a platelet transfusion due to bacterial contamination is between 1 in 7,500 and 1 in 100,000 transfusions.[8] These risks are up to two orders of magnitude higher than the incidence of transfusion-associated viral transmission.[1, 6, 7] Platelet units are more susceptible to contamination than other blood products because of the requirement to store platelets at room temperature to preserve platelet function.[12] At 22-24 °C, a small bacterial inoculum can grow into very high numbers within a short time period and therefore, older ("at-risk") units are most likely to be contaminated with a large number of organisms and to cause a septic reaction in the recipient.[11, 13, 14] In recognition that older platelets are at risk for significant bacterial contamination, the storage period of platelets was shortened by the United States Food and Drug Administration (US-FDA) from seven to five days in 1986 in response to an increased number of reports of transfusion-related sepsis in older platelet units.[9, 15] Only in

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Table 1: Bacteria associated with 60 cases of fatalities resulting from transfusion of platelet products as reported to the US-FDA, 1995-2004.[17]

Bacterial species	No. of cases
Gram-positive organisms (n = 22)	
Staphylococcus epidermidis	11
Staphylococcus aureus	4
Streptococcus group G	2
Clostridium perfringens (anaerobe)	1
Enterococcus spp	1
Streptococcus group B	1
Streptococcus group F/Eikenella	1
Gram + rods (unidentified)	1
Gram-negative organisms (n = 38)	
Klebsiella pneumoniae	10
Escherichia coli	9
Serratia marcescens	5
Enterobacter aerogenes	2
Enterobacter cloacae	2
Pseudomonas aeruginosa	2
Salmonella spp	2
Bacillus spp	1
Enterobacter agglomerans	1
Klebsiella oxytoca	1
Morganella/Providencia	1
Pasteurella multocida	1
Gram-negative rods (unidentified)	1

2005, with the advent of licensed storage containers for single donor apheresis platelets combined with aerobic and anaerobic culture testing under an US-FDA-approved post-market surveillance protocol, did it become permissible once again to store platelets (SDP only) for up to seven days following collection.[16]

The predominant organisms implicated in platelet bacterial contamination are the skin flora, including staphylococci (*Staphylococcus aureus* and coagulase-negative staphylococci), *Corynebacterium* species, and *Propionibacterium* species. Other contaminants include streptococci, Gram-negative bacilli and *Bacillus* species. Although Gram-positive organisms cause the majority of septic reactions, Gram-negative organisms are implicated in the majority of fatalities.[1, 3, 6] Among the Gram-negative organisms reported to contaminate platelet units are *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* species, *Enterobacter* species, *Morganella morganii*, and *Serratia* species.[9, 17] Indeed, *Klebsiella pneumoniae* was responsible for the majority of platelet transfusion-associated deaths related to Gram-negative organisms reported to the US-FDA from 1995 to 2004 (Table 1).[17] Although some of these organisms have a preference for anaerobic conditions, all are able to grow in aerobic conditions, with the exception of *Propionibacterium* spp., which grows only under anaerobic conditions. A single case of contamination of a platelet unit with *Clostridium perfringens*, also a strict anaerobe, has been reported.[17]

PREVALENCE OF BACTERIAL CONTAMINATION OF PLATELETS

The reported prevalence of bacterial contamination of platelets is highly variable and, in many cases, is difficult to assess due to differences in surveillance and testing methodologies and in case definitions. However, it is generally accepted that approximately 1 in 1,000 to 1 in 3,000 platelet units are contaminated with bacteria.[1, 8] Based on 1999 data, over 4 million platelet units are transfused per year in the USA, in the form of 1 million SDP units and 3 million RDP units, the latter administered in 0.5 to 0.75 million pools of 4-6 units.[10, 18] On this basis, it is likely that 1,300 to 4,000 platelet units and 500 to 1,500 platelet transfusions per year are bacterially contaminated. Projected fatalities from these transfusions, based on extrapolation from surveillance and other studies, vary from 15 to over 200 per year. Our nearly 15-year experience with bacterial contami-

nation surveillance in a university hospital using passive (transfusion-reaction triggered) and active (culture at issue) surveillance demonstrated that, while active surveillance detected 38 instances of bacterial contamination (1:2,090 RDP units and 1:2,213 SDP units), only one instance of contamination was detected by passive surveillance (0:48,067 SDP units and 1:168,216 RDP units).[11] The failure of passive surveillance to detect instances of bacterial contamination is attributed to the widespread lack of recognition of septic versus nonseptic reactions, and failure to associate signs of bacterial sepsis with the transfusion of a platelet unit. Additionally, transfusion of platelet units contaminated with bacterial species of low virulence such as coagulase-negative staphylococci frequently does not elicit signs and symptoms of a transfusion reaction.

Thus, there remain important outstanding questions relating to the clinical significance of detecting, defining and quantitating bacterial contamination in platelet units. Although the search for the perfect method is elusive, in the last few years a variety of different methodologies have been developed and evaluated for detection of bacteria in platelet units. Currently, three commercial methods have been cleared by the US-FDA for screening of platelets for bacterial contamination, BacT/ALERT (bioMerieux, Inc, Durham, NC), Pall eBDS (Medsep Corporation, Covina, CA), and Scansystem (Hemosystem, Marseilles, France). Based on the published information from centers that have used one or more of these systems for screening single donor platelet products,[19-23] these methods are sensitive and specific, but the culture-based systems have not detected all contaminated units in the clinical setting.[10, 24] Therefore, patients are still at risk for being transfused with bacterially contaminated platelet units due to false negative results. In addition to these US-FDA-cleared methods, there are several additional methods in various stages of development. It is our goal to present the feasibility and logistics of the application of various methods – both cleared and under development – for bacterial detection testing in platelet units and to describe their advantages and disadvantages.

CORRELATION OF TRANSFUSION OF BACTERIALLY CONTAMINATED PLATELET UNITS, BACTERIAL LOAD AND TRANSFUSION REACTIONS

The critical factor for the clinical use of any detection method is defining the number of bacteria, expressed as colony-forming units per mL (CFU/mL) that will result in a clinically significant transfusion reaction. Transfusion reactions may occur with as few as 10^2 to 10^3 CFU/mL, even with organisms of low virulence such as *S. epidermidis*.[1, 11, 25]

Transfusion of a contaminated platelet unit is often not recognized or directly associated with subsequent sepsis. Over a 3-year period, 1998 through 2000, from suspected cases reported to the CDC during the BaCon study, a voluntary reporting study with very restricted criteria for case definition, the rate of transfusion-transmitted bacteremia (in events/million) was estimated to be 9.98 for SDP and 10.64 for pooled RDP units. The rates of fatal reactions were 1.94 and 2.22 respectively.[6] Overall, the BaCon study estimated a fatality rate of 1 in 500,000 units for both SDP and RDP units.[6]

In France, over a 2-year period, of 16 cases of bacterial contamination associated with platelet transfusion 9 (56%) resulted in severe sepsis or shock. Estimates of the incidence of life-threatening reactions were 9.4 per million (1:106,000) units for RDP units and 17.7 per million (1:56,500) for SDP units.[26] A more recent report from the French Haemovigilance System identified seven confirmed cases of transfusion-transmitted bacterial contamination. Of these two were related to SDP and two to RDP pools, while the other cases were related to transfusion of red blood cells.[27] In the United Kingdom during six years of voluntary participation of blood services, the SHOT (Serious Hazards of Transfusion) study identified 26 episodes of bacterial contamination out of 40 transfusion-transmitted infection incidents reported. Twenty-two of these episodes were related to the transfusion of platelets, accounting for 5 of 6 deaths.[28]

A major problem in determining the magnitude of the problem of platelet bacterial contamination is the lack of recognition and reporting of cases, due in large measure to the failure to associate chills, rigors and fever – signs and symptoms common in patients receiving platelet transfusion therapy – with the possibility of transfusion of a bacterially contaminated platelet unit.[11, 25] Based on the reported prevalence of transfusion reactions and the detection rate of contaminated platelet units, however, it is estimated that a severe episode of transfusion-associated bacterial sepsis occurs in connection with about 17% of contaminated units transfused.[1] More serious clinical events, such as shock and death occurring in immunocompromised platelet transfusion recipients, are likewise often not linked to transfusion of a bacterially contaminated platelet unit.[11]

The data obtained by our group during more than 14 years of surveillance for bacterial contamination of platelets showed, for the first time, the correlation between the organism load in bacterially contaminated units, transfusion reactions and positive blood cultures.[11] From this study, it was clear that bacteremia did not correlate with transfusion reactions, with bacteremia not being documented in the three patients with fatal outcomes, while two patients showing no signs of a transfusion reaction were bacteremic. Absence of bacteremia was likely related to patients receiving antimicrobial agents and delays in obtaining blood cultures following transfusion. Correlation of organism load with occurrence of transfusion reactions showed that a system with a sensitivity of 10^5 CFU/ml would detect 10/11 (91%) serious reactions and 15/19 (79%) of all reactions, while one with a sensitivity of 10^4 CFU/ml would detect all 11

serious reactions and 16/19 (84%) of all reactions.[11, 29] Additionally, our study showed that rates of bacterial contamination, transfusion of contaminated units, transfusion reactions and bacteremia for RDP pool transfusions were significantly higher than those for SDP unit transfusions. These differences, however, were associated with the use of pools of 5 RDP units per transfusion as these rates were not statistically different based on the number of individual platelet units transfused. Our study also demonstrated the superiority of active surveillance over passive surveillance in detecting platelet bacterial contamination, with 38 of the 39 instances of platelet bacterial contamination being detected only by active surveillance. While our experience also highlights the finding that the vast majority of transfusion reactions with signs and symptoms consistent with sepsis are not due to transfusion of bacterially contaminated platelet units, paradoxically it demonstrates that the majority of patients who received bacterially contaminated platelet units and developed signs and symptoms of sepsis were not recognized or reported to the Blood Bank or Transfusion Service for further evaluation.

In 2004, the Infectious Diseases Society of America conducted a survey to assess clinician experience with transfusion-associated bacterial infections among infectious diseases specialists who are members of the Emerging Infections Network in the United States.[10] Among the 399 members that responded, 48 (12%) recalled consulting on 85 reactions to blood transfusions potentially caused by bacterial contamination, with 10 of these cases being fatal. A total of 143 (36%) respondents were aware that bacterial contamination of platelets is now the most common infectious risk of transfusion therapy while only 78 (20%) were aware of the new AABB standard for testing platelets for bacterial contamination. It is clear from this survey that efforts should be made to communicate with clinicians not only the new requirements from AABB and CAP, but also to recognize and request the appropriate testing to confirm the diagnosis of sepsis related to transfusion of potentially bacterially contaminated platelet units.[10]

STRATEGIES TO REDUCE OR PREVENT CONTAMINATION OF BLOOD PRODUCTS

In March of 2004, the AABB, an accrediting organization for Advancing Transfusion and Cellular Therapies Worldwide, added a new standard that requires members of this organization to implement measures to detect and limit bacterial contamination in all platelet components.[30] In an effort to assist blood banks and transfusion services, the AABB, in a supplemental guideline, suggested various strategies for reducing transfusion of bacterially contaminated platelet units and described several methods for detecting bacterial contamination,[31] which will be described in more detail below. In addition to the AABB, in 2002 the CAP added a requirement for laboratories to have a system in place to detect the presence of bacteria in platelet components.[32, 33] Thus, in order to be in compliance with the CAP Laboratory Accreditation Program, blood banks and transfusion medicine services need to have a system to detect the presence of bacteria in platelet components.

While bacterial detection methods garner most of the attention, additional strategies have been developed to reduce the risk of transfusion of bacterially contaminated platelets. These strategies include bacterial contamination avoidance methods, and bacterial growth inhibition or inactivation methods.[15] In order to accomplish the goal of eliminating bacterial contamination of platelets, these strategies likely will need to be used in combination with a detection method. Ideally, the responsibility for limiting bacterial contamination is shared between the collection center, which needs to insure suitable donor selection, proper aseptic collection technique and absence of measurable bacteria by using a sensitive detection method shortly after product collection, and by the transfusion service, which should ideally use a rapid test for detecting bacterial contamination at the time the platelet unit is issued for transfusion.

Bacterial Contamination Avoidance Methods

Platelet units are most commonly contaminated at the time of collection when bacteria from the skin or from bacteremia in the donor gain entry into the collection set during the phlebotomy process. Exhaustive donor screening and deferral if a history or symptoms of possible bacteremia is elicited has reduced contamination of blood products. Additional measures to minimize the entrance of bacteria into the blood collection system include improved disinfection of the skin, and diversion or removal of the first 20-30 mL of blood collected.[34, 35] Overall, rates of bacterial contamination of SDP and RDP units have been similar, but the rate of transfusion of contaminated products is proportionately higher in RDP pools than in SDP units.[11, 25, 36]

Bacterial Growth Inhibition and Inactivation Methods

While bacteria may gain entry into a platelet unit during collection, the number of bacteria entering the collection system is usually very small and it is only during room temperature platelet storage that the organisms may grow into large numbers. This problem can potentially be prevented by using a substance that inactivates bacteria or that inhibits bacterial growth during storage. The use of substances that inhibit or inactivate organisms present within a platelet bag should be implemented by the collection center. In order for this strategy to be feasible and practical, these substances should not cause substantial damage to platelet function, and the process should be automated and linked to the collection instrument. These

KUR-MAG-DE005174

Page 3747 of 5977

inhibitory substances need to be added in a particular concentration, and the instrument should be able to calculate and dispense the pathogen inhibitory reagent in a closed system and according to the volume collected. Although the cost is substantial, and safety concerns about the additive solutions remain, the potential application of inactivation methods seems to be a promising approach to avoiding bacterial contamination of blood products.[37] Two inhibitory substances are being evaluated for use in platelets: amotosalen S59, which is being developed as the Intercept PLT System (Cerus, Concord, CA), and riboflavin, which is being developed by Navigant (Lakewood, CO). When activated by light, amotosalen S59 binds to the nucleic acid of pathogens and prevents replication.[38, 39] A pilot study assessing the use of 7-day-old buffy-coat platelets treated photochemically with amotosalen S59 to transfuse patients with thrombocytopenia showed that treated platelets produced acceptable efficacy and safety compared to 7-day-old untreated platelets.[40] The Intercept PLT System obtained regulatory approval in 2002 in Europe to treat platelets for transfusion, and regulatory approval is being pursued in the United States. The other pathogen inhibitory system under development for platelets is a photochemical decontamination process utilizing riboflavin, and preliminary reports are encouraging.[41, 42]

Bacterial Detection Methods

At present, the focus in identifying and preventing bacterial contamination of platelet components by the collection centers as well as the transfusion services is on detection methods. The ideal detection method should be sensitive and specific, have a rapid turn-around time, require a small sample volume for testing and be inexpensive.

For SDP platelets, the CAP and AABB recommend the use of one of the commercial systems that have been cleared by the US-FDA for in-process quality control testing of platelet units. For RDP units, where application of testing with an US-FDA-cleared method may be impractical unless applied to pooled units, a variety of less sensitive testing methods are permissible. These include detection of decreased pH, detection of decreased glucose concentration, microscopic examination of dried smears stained with acridine orange or Gram stain, plate culture, and broth culture. These methods should be validated by the user.

As discussed above, the methods that have been cleared for bacterial contamination testing of platelet products by the US-FDA are two culture-based instruments, the BacT/ALERT and PALL eBDS. More recently, the US-FDA has also cleared the Scansystem, a scanning cytometry method that uses an automated microscopic analysis of particles stained with a fluorescent stain. Both culture-based methods (BactT/ALERT and eBDS) may potentially delay the use of platelets and shift the inventory to the use of older platelets because they require a 24-h holding period prior to sampling and a generally 24-h incubation period after sampling.

Description of US-FDA Cleared Bacterial Detection Methods for Quality Control Testing of SDP units

BacT/ALERT

A sample of platelet rich plasma from a leukocyte-reduced SDP unit is inoculated into aerobic (BPA) and anaerobic (BPN) culture bottles containing broth media and then placed into an instrument that automatically monitors the production of CO_2 as a result of growth of bacteria. This and similar systems have been used for many years for the routine culture of blood for clinical purposes. The manufacturer strongly recommends using one aerobic and one anaerobic bottle, each inoculated with 4 ml of the platelet product. For optimal bacterial detection, the manufacturer recommends that the platelet specimen should be taken at least 24 hours after collection to allow for natural proliferation in the platelet product. During this time bacteria, if present at the time of collection, would have an opportunity, in most instances, to reach a level adequate for sampling and subsequent growth in the culture system. Although procurement of the aliquot from the platelet unit is achieved with the use of a sterile docking device, the subsequent inoculation of the sample into the culture bottle involves an open system using a needle and syringe. Therefore, strict adherence to the manufacturer's instructions for antisepsis of the septum of the blood culture bottle and inoculation instructions are critical factors to prevent the occurrence of false positive results due to contamination during inoculation of the platelet unit itself. Distinguishing false positive culture results from true contamination is often confounded by the fact that the same bacterial species are commonly detected in both circumstances. According to the manufacturer's directions, the inoculated culture bottles are held for the shelf-life of the platelet unit unless a signal indicating bacterial growth is generated before this time period has elapsed.

Once the system identifies a bottle as being "positive", indicating that the CO_2 content is above the baseline, an aliquot is removed for Gram stain and subculture to agar media. Most collection centers send positive bottles and a sample from the original unit to a microbiology laboratory for further testing. Absolute proof that a true positive result is correct requires that the same organism be isolated from original platelet unit and positive culture bottle. If the culture from the original platelet unit is negative, it is likely that the positive culture bottle is a false positive.

In the USA, the BacT/ALERT culture bottles are accompanied by product inserts indicating that BacT/ALERT System (3D and 240) and culture bottles may be used for quality control testing of platelets and that the laboratory should follow its own quality control pro-

cedures for this use.[43] The product inserts also state that the BacT/ALERT System, including the culture bottles, should not be used in determining suitability for release of platelets for transfusion and that users considering such release testing should first consult the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) for the appropriate clinical studies. A report of "negative" should not be interpreted as meaning that the original product is sterile. The negative status could be due to underinoculation of the bottle, no organisms present in the inoculum, the number of organisms were too small for detection, or a culture bottle/medium that does not support the growth of the organism.[43]

eBDS

This method is a novel culture-based system, which assesses the reduction of the O_2 content in the head space of a sample pouch containing an enriched medium, compared to ambient O_2, as a marker for bacterial growth.[23] This method involves docking an eBDS sample pouch onto the tubing of a platelet bag, transfer of an aliquot of 2-3 mL of the platelet product into the sample pouch, which is then separated from the platelet unit using a heat sealer. The eBDS pouch is then incubated at 35 °C for 24 hrs. Pouches are then removed from the incubator, kept at room temperature for at least 2 minutes and the probe of the oxygen analyzer inserted into the sample port of the pouch. The oxygen analyzer automatically reads the oxygen concentration in the sample pouch. The instrument then gives a reading with a positive or negative interpretation for bacterial contamination.

Scansystem

This method detects bacteria using a laser-based, solid-phase scanning cytometry detection method. This method is a highly sensitive bacterial screening system, and can detect very low levels of bacteria after concentration from a larger volume by filtration.[60] The Scansystem solid-phase cytometry analyzer includes four modules: (i) a scan module, in which the black membrane is placed; (ii) an argon laser module (488 nm excitation light), which is connected directly to the scan module to scan the black membrane; (iii) an epifluorescence microscope with a suitable light source and filters, which has an automated motor-driven stage, for visual discrimination by the operator of fluorescent particles detected by the laser scan as bacteria or nonbacterial particles; and (iv) a computer with proprietary software to monitor the other modules.

The Scansystem is used by drawing a 3 ml sample of platelets into the syringe of a Scansystem Platelet kit through the sample injection port. The kit is then agitated in a platelet incubator at 22 °C for forty minutes in order to achieve platelet aggregation. The contents of the syringe are then expressed through a filter, which retains the aggregated platelets and allows passage of bacteria into the second portion of the kit. The kit is then incubated at room temperature for twenty minutes to allow labeling of any bacteria present with the fluorescent stain. A black membrane in a holder attached to a vacuum pump is then attached to the bottom port, and the contents of the pouch are then filtered through the black membrane. Any bacteria present will be deposited on the surface of this membrane. The membrane is then removed from the holder and placed into the Scansystem scan module for detection of fluorescent particles by laser scanning. The final step is visual determination, using the epifluorescence microscope, of the identity of fluorescent particles as bacteria or as other particles.

Other Detection methods

Although traditional culture and culture-based methods are far more sensitive than staining and measurement of pH or glucose, the latter methods have the advantage of having a rapid turn-around time and therefore the testing can be done at or near the time of releasing the platelet unit, while final culture results may not be available until after transfusion. For this reason, and because these non-culture based methods are among the suggested methods in the current AABB and CAP guidelines for testing of RDP units, many transfusions services and blood banks have adopted them for routine testing; and, as is discussed below, despite poor sensitivity for detection of bacterially contaminated platelet units, their use may reduce the fatalities associated with transfusion of bacterially contaminated platelet units.

Staining Methods

Among the staining methods recommended by AABB and CAP are the Gram stain and the acridine orange stain.

Gram stain procedure: A smear is prepared using a sterile pipette or syringe to transfer 1 or 2 drops from a platelet unit to a clean glass slide. The drop is spread into an even film and allowed to either air dry or heat dry on a slide warmer. Smears can also be prepared using a cytospin slide centrifuge to concentrate the sample. Cytospin preparations deposit the concentrated sample within a limited area for viewing.[44] The Gram stain procedure includes sequential staining steps with crystal violet, alcohol decolorization, and counterstaining with safranin or neutral red. Bacteria stain either Gram-positive (deep violet) or Gram-negative (red) on the basis of differences in their cell wall composition. Gram-positive bacteria have a thick peptidoglycan layer and they are unaffected by the decolorization step and retain the initial stain, appearing deep violet. Gram-negative bacteria have a thin peptidoglycan layer attached to an outer membrane containing lipids. This membrane is damaged by the decolorizer, allowing the initial stain to leak out and be replaced by the red counterstain. The smear is examined microscopically using a light microscope with a 100X oil objective. The sensitivity of the

KUR-MAG-DE005176

Page 3749 of 5977

Gram stain is 10^5 CFU/mL, or 10^4 CFU/mL if the specimen has been prepared with a cytocentrifuge.[44] Use of the Gram stain has been successful in interdicting platelet units heavily contaminated with bacteria prior to transfusion.[5]

Acridine orange stain procedure: Acridine orange is a fluorochromatic dye that binds to nucleic acids of bacteria and other cells. Under UV light, bacteria stain bright orange, whereas human cells and background debris stain pale green to yellow, although nuclei of activated leukocytes may also stain orange or red. The smear is prepared as for a Gram stain and stained with acridine orange (0.1 g/L in 0.5M acetate buffer) for 2 min. The smear is read on a suitable fluorescent microscope with a 40X dry or 100X oil objective. The sensitivity of the acridine orange stain is approximately 10^4 CFU/mL.[45]

Interpretation of Gram and acridine orange stains involve consideration of staining characteristics and cell size, shape, and arrangement. Sample preparation, reagents, and staining procedures may influence these characteristics. Therefore, use of quality control slides and competency training of the personnel reading the stains is essential. It is advisable that these staining methods be done in a clinical microbiology laboratory. In institutions where a microbiology laboratory is not available, the Gram stain can be performed by blood bank or transfusion service personnel that have been adequately trained to perform and interpret Gram stains. In addition, these laboratories should be participating in a Gram stain proficiency testing program.

pH and glucose analysis: Testing can be done separately using a handheld device or pH paper, or in combination on a multi-reagent dipstick. Although, handheld pH meters provide a more accurate result than do dipsticks, both methods are easy and rapid to perform and, for that reason, they have been adopted for many blood banks and transfusion services for testing RDP units.[46-49]

The sensitivity of pH and glucose testing, using one or both methods, is approximately10^6 to 10^7 CFU/mL. Because of this limited sensitivity, the AABB recommends that facilities use these methods on individual units rather than pooled units. A recent study showed that as platelets age, the rate of pH failures increases, and only 4 of 405 random platelet units that failed pH were culture positive.[49] A lower rate of pH failure has been demonstrated in random units that have undergone prestorage leukoreduction compared to non-leukoreduced, random platelets.[50]

IMPLEMENTATION OF DETECTION METHODOLOGY

A summary of the AABB fall 2004 survey of members on practices related to the new guidelines on detection and prevention of bacterial contamination in platelet units was presented at the US-FDA Blood Products Advisory Committee Meeting in January of 2005.[51] The survey results showed that the majority (88%) of blood centers were using a culture method – usually BacT/ALERT- to screen for bacterial contamination of SDP units. Most centers (85%) using BacT/ALERT did only aerobic cultures and held the cultures for 5 to 7days. Four out of the 34 blood centers surveyed used glucose or pH by dipstick or meters. A few transfusion services cultured platelets by plate culture or performed Gram stains. Among hospital blood banks, most cultured platelets if their supplier did not, or if the platelets were collected in-house. Half of the blood banks performing cultures used anaerobic and aerobic cultures, while the remainder used only aerobic culture.[51]

It is clear from the results of the survey that many transfusion services are using less sensitive techniques – glucose, pH or Gram stain as compared to methods cleared by the US-FDA - for quality control of platelets, particularly RDP units. The advantage of using these methods is that they are easy to implement in any hospital blood bank or transfusion service and they can be performed at or near the time of issue. However, there have been reports of false negatives with fatal consequences with these methods,[10] and investigators have strongly advised against the use of surrogate markers of bacterial metabolism, such as pH and glucose concentration, for detecting bacterial contamination of platelets due to the analytic insensitivity of these methods.[52]

Some of the practical aspects relating to implementation of the US-FDA-cleared detection methods are discussed below. In addition, the BacT/ALERT and the eBDS systems have also been evaluated for screening of individual and of pooled RDP units, and have been found to be reliable for monitoring bacterial contamination in these products.[53, 54] Table 2 summarizes the published contamination rates found by routine testing in a clinical setting using different detection methods. The rates of bacterial contamination varied considerably between and within methods, with methods such as plate culture, eBDS and BacT/ALERT generally reflecting realistic true positivity rates (0.02-0.05% for SDP and RDP units, and 0.1-0.25% for RDP pools), while Gram stain, pH determination and glucose determination resulted in low true positive rates while in the case of pH and glucose determination, very high false positive rates were also found. In many instances especially when the BacT/ALERT method was positive, the platelet product had already been transfused and was no longer available for retesting, and these cases are regarded as unconfirmed positives.

Table 2: Results of various methods used for routine testing of platelet products to detect bacterial contamination. Realistic true positive rates based on 1:1,000 to 1:3,000 units being contaminated are 0.03-0.1% for SDP and RDP units, and 0.17-0.5 for RDP pools of 5 units. Data was obtained or derived from the references indicated.

Method	Platelet product (total tested)	Overall positive rate (%)	True positive rate (%)	False positive rate (%)	Unconfirmed positive rate* (%)	False negative rate (%)	Reference #
Gram stain at issue	RDP pools of 5 units (N=7716) SDP (N=8761)	0.12 0	0.078 0	0.039 0	0 0	0.16 0.046	11
pH at issue	Individual RDP (N=37067)	1.09	0.01	1.08	0	NR	49
	Individual RDP (N=6590) SDP (N=671)	1.97 1.93	0 0	1.97 1.93	0 0	0.03 0.30	11
pH + glucose at issue	Individual RDP (N=3093)	0.96	0.06	0.9	0	0 (N=203)	47
BacT/ALERT at 12-24 h	SDP (N=350658)	0.06	0.02	0.03	0.01	0.0008	55
	RDP pools and SDP (N=4000)	1.2	0.13	0.9	0.02	NR	57
	Individual RDP units (N=10141) RDP pools of 5 units (N=2063)	1.4 3.4	0.02 1.9	0.75 1.5	0.64 0	NR NR	54
	RDP pools (N=28104)	0.72	0.65	0.06	0	NR	24
	RDP pools of 4 units and SDP (N=36896)	0.24	0.03	0.04	0.12	0.18 (N=1061)	20
eBDS at 24 h	Individual RDP units (N=12062) RDP pools of 5-6 units(N=2201)	0.04 3.6	0.02 0.04	0.008 3.5	0.008 0	NR NR	53
Plate culture at issue	RDP pools of 5 units (N=12,961) SDP (N=15,493)	0.26 0.077	0.24 0.045	0.023 0.032	0 0	0.0077 0	11

SDP: Single donor platelets; RDP: Random donor platelets; NR: Not reported
* Unconfirmed positives are those where the platelet product had been used at the time the bacterial detection system became positive

Implementation of BacT/ALERT: Laboratory and clinical studies have demonstrated the efficacy of this system in identifying many instances of bacterial contamination of platelets.[19-22] The American Red Cross implemented routine quality control testing for bacterial contamination in SDP products with BacT/Alert in all 36 regional blood centers in March 2004.[55] Platelet samples (4 ml) were obtained at least 24 h after collection and cultured in BacT/ALERT aerobic bottle only until the end of the product shelf life or until a positive reaction occurred.[55] Products were released for use if negative after incubation for at least 12 h, and, if not used, removed from supply when culture became positive. Reports and investigations of potential septic reactions to SDP platelets were also reviewed. In the first 10 months of bacterial testing, 226 of 350,658 collections tested initially positive. Sixty-eight (30%) were confirmed as true positives. Of the 354 apheresis platelet products derived from all 226 initial test-positive cases, 38 (10.7%) had been transfused by the time of the initial positive result, although none of these were confirmed positive. During this period, three septic episodes probably related to transfusion of bacterially contaminated platelets, which had negative screening, were documented, with *S. lugdunensis* implicated in one and other coagulase-negative staphylococci in the other two instances. In Norway, from May 1999 to May 2004, RDP pools were monitored for bacterial growth using BacT/ALERT during an average period of 6.5 days. The investigators found that from 88 platelet pools that were initially positive, only 12 (13.6%) were confirmed as true positives.[20] The main limitations related to culturing, either using traditional culture or using an automated system, is the time required to obtain results. In order to increase the sensitivity of culture, sample for testing should be taken 24 hours after collection, inoculated into culture media and incubated for at least five days before reporting it as negative. Although most of the bacterial organisms implicated in bacterial contamination of platelets are detected after 24 hours of incuba-

KUR-MAG-DE005178

Page 3751 of 5977

tion (48 hours after collection), slow growing organisms cannot be detected for several days. As documented in the survey described above, in most instances, because of the logistics of sample handling, BacT/ALERT testing is performed at the collection center rather than the transfusion service. Documentation of training of the personnel performing the testing is required by accrediting organizations. While inter-laboratory proficiency testing is currently not required due to lack of available defined methodologies, it is anticipated that this will soon be required.[56]

The survey did not evaluate whether the blood centers were performing Gram stains or confirmation cultures from positive BacT/ALERT bottles on site or whether the bottles were sent to an external microbiology laboratory. Because it is known that false positive bacterial contamination results may occur with this system,[57] if the bottles are sent out for confirmation results could be delayed, which may lead to an increase in wastage of products and unnecessary treatment of patients who received these units.

Another limitation of culturing using an automated system is the specimen volume required for testing, usually 4 ml per bottle, which for a SDP unit represents only 1.5% of the unit volume if using aerobic bottles only, or 3% if using both aerobic and anaerobic bottles, but if testing is done on a single RDP unit, the volume required for testing could represent 10% to 40% of the unit volume. This limitation makes routine culturing of individual random units impractical.

Implementation of Pall eBDS: The features of this culture-based US-FDA cleared test are similar to those of the BacT/ALERT. This system also requires that a large sample (3 ml) be obtained at least 24 hours after collection and requires an incubation period of 24 hours. Published laboratory studies have shown that the Pall eBDS system is able to detect 1 to 15 CFU/ml of aerobic bacteria in a contaminated unit.[58] The initial version of this system (BDS) gave some invalid or negative readings with organisms that rapidly consume O_2 during their metabolism, particularly *Klebsiella pneumoniae*, but the newer enhanced version (eBDS) has overcome this problem.[15, 58, 59]

There are several potential advantages of the eBDS system compared to automated blood culture systems: (1) it is easier to utilize in a laboratory environment not generally familiar with bacterial testing instrumentation; (2) the sampling and inoculation occurs in a closed system, reducing the opportunity for false positive culture results; and, (3) unlike the BacT/ALERT system in which continuous monitoring of the culture bottles is performed throughout the shelf-life of the platelet unit, the eBDS system is read at a single, discreet time point, eliminating the possibility that a positive result will be generated after the platelet unit has been transfused. It is believed that many of the positive results generated after the platelet unit has been transfused are either false positives or are not clinically significant, while adding a significant burden of work. A potential disadvantage of the eBDS compared to the BacT/ALERT is that only aerobic organisms are detected. And with a smaller sample volume than the BacT/ALERT, it is possibly slightly less sensitive. With both systems, since sampling is done relatively early in the storage period when the bacteria have had limited time for growth, it is possible that bacterial contamination will be missed entirely. While the number of such "breakthrough" cases is uncertain they have occurred, and some have been clinically significant.[29]

Implementation of the Scansystem: Our group and other investigators have evaluated this system and found that this method is able to detect most typical bacterial platelet contaminants in leukocyte-reduced SDP units 30 h after contamination, with a sensitivity equal to that of BactT/ALERT.[60, 61] The Scansystem can detect both live and dead bacteria, so that the presence of bacterial species such as *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, which are frequently inhibited or killed in the presence of human plasma,[62, 63] may still be detected, provided some bacterial growth occurred.

Advantages of the Scansystem method are that platelets, from 30 to 72 h after collection, can rapidly be tested for the presence of bacteria, with a total test time of approximately ninety minutes.[60, 64] Thus the Scansystem allows testing of platelets closer to time of use, and allows platelet units to be used as early as 32 h after collection, compared to typically 48 h for the BactT/ALERT and eBDS methods. Moreover, the Scansystem method is able to detect both live and dead bacteria, which may prevent transfusion of endotoxin-containing products. Disadvantages of the Scansystem are the labor-intensive nature of the system, the need to verify visually the presence or absence of bacteria for each positive test, and the need to test platelet units within 72 hours of collection as platelet aggregation – a requisite of the testing methodology as noted above – is less efficient after 3 days of storage.

Implementation of non US-FDA cleared culture methods: Traditional culture using plated or broth media as well as commercially available automated blood culture systems other than BacT/ALERT can be used for platelet bacterial contamination testing but requires strict validation to ensure that the performance of the technique is as expected.[11, 65, 66] The validation plan should be developed by each institution or laboratory before routine testing can be in place. AABB Association Bulletins, published to supplement the required AABB Standard, provide guidance on acceptable validation methods.[31, 67] Published studies have documented these systems to reliably detect bacterial contamination of platelets.[65, 66] In many cases, the burden of the internal validation pro-

KUR-MAG-DE005179

Page 3752 of 5977

cess is placed on the microbiology laboratory[68] and the cost of testing is passed on to the hospital. The legal risks of using a non-US-FDA-cleared detection system for quality control of platelets for which US-FDA cleared tests are available also need to be considered.

It is important to note that in emergency situations, as promulgated by the FDA any standard procedure may be bypassed if the clinical need is paramount. (see 21 Code of Federal Regulations 606.121(h) and www.fda.gov/ora/inspect_ref/igs/blood.html)

CHANGES IN REGULATIONS FOR PLATELET STORAGE

As discussed above, in 1984 the US-FDA extended the platelet storage from five to seven days based on the functional quality of the platelets. However, in response to an increasing number of reports of bacterial contamination episodes, the US-FDA reduced the storage time back to five days in 1986. Nevertheless, to comply with the new AABB and CAP recommendation for screening platelet products for bacterial contamination, the average time between collection and issuing the product has been increased and most SDP products are released three days after collection, making a difficult task for blood centers to satisfy the need for platelet products. In 2005, the US-FDA approved platelet bags made by Gambro BCT and Baxter for 7-day storage of SDP platelets provided that a US-FDA-cleared detection method is used,[15] and the US-FDA-approved protocol, the PASSPORT Study (www.passportstudy.com) is followed. The extended storage time would improve detection and confirmation of positive results before units have been used, and could limit the wastage of units.

SDP VERSUS RDP UNITS

Although several reports have demonstrated a reduced incidence of transfusion-associated platelet bacterial contamination with the use of SDP platelets compared with pooled RDP units,[11, 25, 36] the difficulty of maintaining a SDP platelet inventory has forced transfusion services to continue using pooled RDP units. However, if RPD units are screened for bacterial contamination with a sensitive method at the time of issue, the risk of transfusing a bacterially contaminated unit should be similar to that of SDP units. The obstacle in reaching that goal is that the US-FDA-approved methods for detection of bacterial contamination have been approved for quality control of SDP and, in some cases, RDP units, but not until recently (see below) for RDP pools, making approved systems prohibitively expensive to use on each RDP unit used to prepare a pool. Most hospital blood banks are therefore using methods such as pH or glucose determination, which have low sensitivity, but are rapid and easy to perform at the time of issue. The main reason that transfusion services and blood banks need to do the testing of RDP units is because the pooling of the units is done just before releasing the product for transfusion. This problem could be overcome by the allowance of early pooling along with screening for bacterial contamination with one of the methods already cleared by the US-FDA for SDP units.

Investigators have assessed the effectiveness of storing RDP platelets as a pool compared to SDP platelets and found that there is no detrimental effect of pooling RDP platelets as relates to platelet quality for products stored for up to 7 days.[69, 70] In February 2006, the US-FDA approved a platelet storage bag, the Pall Acrodose PL system, for the pooling of 4 to 6 ABO identical, leukocyte-reduced, RDP units shortly after collection and subsequent storage for up to 5 days after blood collection when coupled with a device cleared by US-FDA for detection of bacterial contamination in pooled, leukoreduced RDP units.[71]

Although some investigators have stated that the sensitivity of culture testing of pools may be insufficient to detect all contaminated products, and that manipulation of pools can also increase false positive results,[54] others have found pool testing to be reliable.[72-74] In addition, the use of both aerobic and anaerobic BacT/ALERT bottles may enhance the detection of contaminated units. This finding seems to be related to the volume of sample cultured rather than the isolation of strict anaerobic organisms.[74]

DETECTION METHODS UNDER DEVELOPMENT

Several detection methods suitable for use at the time of issue of platelet products are currently being developed, and include the following:

Detection of bacterial 16S ribosomal RNA with oligonucleotide probes. A chemiluminescence-linked universal bacterial rRNA probe for the detection of bacterial contamination in 0.4 mL aliquots of platelet concentrates detected the majority of samples containing 10^4 CFU/mL of *Bacillus cereus, P. aeruginosa, S. aureus* and *S. epidermidis*, and all samples with 2.1×10^5 CFU/mL or greater of these species.[75] Further development of this method is currently not being pursued.

Detection of conserved regions of bacterial 23S rRNA and a heat shock protein by real-time, reverse transcriptase PCR assay. Two real-time reverse transcriptase PCR (RT-PCR) assays performed in a LightCycler instrument were developed and compared regarding specificity and sensitivity by the use of different templates to detect the majority of the clinically important bacterial species in platelets.[76] Primers and probes specific for the conserved regions of the eubacterial 23S rRNA

KUR-MAG-DE005180

Page 3753 of 5977

gene or the *groEL* gene (encoding the 60-kDa heat shock protein Hsp60) were designed. With r*Tth* DNA polymerase in a one-enzyme system, 500 CFU/mL of *Escherichia coli* or *Staphylococcus epidermidis* were detected. With a two-enzyme system consisting of Moloney murine leukemia virus RT and *Taq* DNA polymerase, 16 CFU/mL were detected. With *groEL* mRNA as the target of RT-PCR under optimized conditions, 125 CFU/mL of *E. coli* were detected. False-positive results caused by reagent contamination or a cross-reaction with human nucleic acids were found with the 23S rRNA, but not with the *groEL* gene detection systems.

BacSTAT Antibody-based lateral flow device for detection of bacteria. This system, being developed by GenPrime Inc., Spokane, WA, (www.genprime.com) is a broad-spectrum, antibody-based lateral flow device for detection of bacteria in SDP or RDP units, and uses a unique lateral-flow scanning system and a reader with pass/fail software.[77] The antibody targets used in this system are unique surface antigens. Specimen processing is simple, and total test time is less than 20 minutes. The expected sensitivity of this method is 10^3 to 10^4 CFU/mL.

Rapid Bioluminescent Bacterial Detection System using Luciferase. This method, which detects bacterial ATP by generation of light in the presence of bioluminescent luciferase firefly extract, is being developed by SUBC Inc., Rochester, Minnesota.[78] The method consists of removing platelets and cellular debris from 2-3 mL platelet concentrate samples, isolation and immobilization of any bacteria present in an isolation chamber, rinsing the isolation chamber with buffer, adding a lysing solution in combination with localized heat to rapidly lyse bacterial membranes and release bacterial ATP, adding bioluminescent firefly extract, and detecting generated light with a photon counter. The burst of light is then converted into a bacterial inoculum in CFU/mL. The sensitivity of this method is claimed to be 10^2 to 10^3 CFU/mL. A fully automated, microprocessor-driven instrument with an internal reagent cartridge, GloBac, has been developed for this application, and processing time is 4 min per specimen.

Bacterial lipotechoic acid and lipopolysaccharide detection by lateral flow immunoprecipitation. This test is being developed as the Verax Biomedical Platelet PGD Test by Verax Biomedical Inc., Worcester, MA (www.veraxbiomedical.com).[79] This system consists of test kits with a double-sided, lateral flow test cartridge and a central specimen well. Testing is performed by adding 8 drops of a platelet lysis reagent to 0.5 mL of a platelet sample, and centrifuging for 5 min to sediment any bacteria present. The supernatant is decanted off and 8 drops of a resuspension agent and 4 drops of a bacterial lysis reagent are then added, and the fluid is then added to the central well of the lateral flow test cartridge. The test cartridge contains antibodies to bacterial lipotechoic acid on one side and lipopolysaccharide on the other side to detect Gram-positive and –negative bacteria, respectively. A positive test is shown by the development of a pink precipitation line on one side. The system is designed for use with leukoreduced or non-leukoreduced RDPs, pooled RDPs and SDPs, with testing taking 30 min, with 2 to 3 minutes attended labor per test. The sensitivity of this method is claimed to be 10^3 to 10^4 CFU/mL.

Bacteriological Biosensor using engineered spores as fluorogenic nanodetectors. This system, being developed by BCR Diagnostics, Jamestown, Rhode Island (www.bcrbiotech.com), is able to detect and count low bacterial levels quantitatively in less than 20 minutes with a linear detection response over a range of one to 10,000 bacteria per sample.[80] The instrumentation cost is low and the system is suitable for automated high-throughput operations. A 0.5 mL platelet sample is processed to separate bacteria, and the resulting suspension is mixed with engineered bacterial spores. The mixture is then combined with a germinogenic substrate and then filtered through a filter mounted on a biochip – the filter contains 80,000 micro-colanders, which are 20 μm in diameter and contain engineered biosensor bacterial spores. The presence of a bacterial aminopeptidase, present in all bacteria, in the platelet specimen triggers the biosensors on the spores, resulting in production of fluorescent light, which is detected by a camera. The expected sensitivity of this method is 10^3 CFU/mL.

Bacterial peptidoglycan chromogenic immunoassay. This method is being developed as BacTx by Immunetics, Inc., Boston, MA (www.immunetics.com) and consists of a test kit containing all needed reagents and a chromogenic reader.[81] The system has a turnaround time of less than one hour, a 1 mL sample volume, and premeasured vial reagent dispensers. The system detects bacterial peptidoglycan in Gram-positive and Gram-negative bacteria when a peptidoglycan binding protein triggers enzymatic conversion of a chromogenic substrate to a visible product with measurable absorbance. A 1 mL platelet sample is centrifuged for 10 min, the sediment incubated for 30 min with reagents, and absorbance is read on a reader. Assay sensitivity is claimed to be 10^3 to 10^4 CFU/mL.

CONCLUSIONS

Bacterial contamination of platelet units is the most prevalent infectious risk of blood products in the United States. In the last 3 years, a unified effort from professional and regulatory agencies has been committed to limiting bacterial contamination of platelet products. Strategies beginning with donor selection, collection guidelines, use of detection methods after collection and at time of issue have been developed in order to deal with this problem. Because of the multi-factorial etio-

logy of bacterial contamination and the heterogeneous growth and metabolic characteristics of the organisms involved, different strategies should be used in combination. Now that FDA-cleared methods and guidelines are available to meet the requirement that all platelet units be tested for bacterial contamination, it is hoped that data will continue to be collected and new strategies will be developed to reduce the occurrence and the fatalities associated with bacterial contamination of platelets. Several promising methods for at-issue testing are being developed and will hopefully obtain regulatory approval soon.

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Page 3757 of 5977

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wrap up close

(57) [Summary]
[Object] To discover a novel FVII-activating protease and its application.
SOLUTION: a) is inhibited by the presence of aprotinin, b) its activity is increased by calcium i ons and/or heparin or heparin analogues, and c) in SDS-PAGE, the molecular weight is reduce d in subsequent staining under non-reducing conditions. A protease that activates blood coag ulation factor VII, which exhibits one or more bands in the range of 50-75 kDa and, under red uced conditions, one or more bands in the molecular weight range of 10-35 kDa, as well as its The proenzyme is obtained from plasma or prothrombin complex (PPSB) concentrates by prior anion exchange chromatography followed by affinity chromatography using heparin or heparin analogues or dextran sulfate.

The present invention provides a test system for the qualitative and quantitative detection of said protease or its proenzyme, as well as a test system for its diagnostic application and said protease activating an amount of blood coagulation factor VII suitable for the lysis of fibrin-co ntaining thrombi. and/or pharmaceutical preparations containing the proenzyme thereof.
[Selection figure] None

The scope of the claims open —

Claims:

1.

a) inhibited by the presence of aprotinin,

b) its activity is increased by calcium ions and/or heparin or heparin sulfate,

c) subsequent non-reducing conditions in SDS-PAGE. shows one or more bands in the molec ular weight range of 50-75 kDa by staining with , and in reducing conditions one band in the molecular weight range of 40-55 kDa and one or more bands in the molecular weight range of 10-35 kDa. and

d) the band obtained in the reducing state in the molecular weight range 40-55 kDa in SDS-PAGE has the amino acid sequence: LLESLDP and the band obtained in the molecular weight r ange 10-35 kDa has the amino acid sequence: IYGGFKSTAGK. and/or

for the qualitative and quantitative detection of the proenzyme of said protease, the band ob tained in reducing conditions in SDS-PAGE has a molecular weight in the range of 60-65 kDa and contains the amino acid sequences: LLESLDP and IYGGFKSTAGK. In the test system, its p rotease activity is characterized by:

a) its activity to inactivate blood coagulation factor VIII/VIIIa or factor V/Va or b

) its activity to reduce blood clotting time in a comprehensive blood coagulation test or

c) its activity to activate the plasminogen activator or

d) its activity to activate FVII

.

2. The test system of claim 1

, wherein the activity of lowering blood clotting time comprises:

A test system measured by a) non-activated partial thromboplastin time (NAPTT) or

b) prothrombin time (PT) or

c) plasma recalcification time or

d) activated partial thromboplastin time (APTT) . 3. In the test system according to claims 1 and 2, the activity of activating and/or enhancing plasminogen activator comprises: a) single- chain urokinase PA (scuPA, single-chain urokinase plasminogen activator);) or b) a test system measuring by activation of single-chain tPA (sctPA, single-chain tissue plasminogen activator). 4. A test system according to any one of claims 1 to 3, which contains calcium ions in an amount of 0.001 mM or more. 5. a) inhibited by the presence of aprotinin, b) its activity increased by calcium ions and/or heparin or heparin sulfate, c) in SDS-PAGE with a molecular weight of 50 by subsequent staining under non-reducing conditions. showing one or more bands in the range of ~75 kDa, one band in the molecular weight range of 40-55 kDa and one or more bands in the molecular weight range of 10-35 kDa in the reduced state, and

and/or

Bands obtained in SDS-PAGE under reduced conditions are molecules in the range of 60-65 kDa

A mixture of the proenzyme of said protease containing the amino acid sequences: LLESLDP and IYGGFKSTAGK and a suitable proenzyme activator is used to test for prothrombin time-displaced tissue factor/thromboplastin.

6.

a) inhibited by the presence of aprotinin,

b) its activity is increased by calcium ions and/or heparin or heparin sulfate,

c) molecular weight 50 by subsequent staining in non-reducing conditions in SDS-PAGE. 1 or 2 or more bands in the range of ~75 kDa, in the reduced state 1 band in the molecular weight range of 40-55 kDa and 1 or 2 or more bands in the molecular weight range of 10-35 kDa, an

d d

) The band obtained in the range of molecular weight 40-55 kDa under reducing conditions i n SDS-PAGE has the amino acid sequence: LLESLDP, the band obtained in the range of molec ular weight 10-35 kDa has the amino acid sequence: IYGGFKSTAGK, and/or

SDS- The bands obtained under reduced conditions in PAGE have molecular weights in the ra nge of 60-65 kDa and contain the amino acid sequences: LLESLDP and IYGGFKSTAGK. Assay system used for sex testing and quantification of single-chain plasminogen activator forms.

7.

In the test system according to claims 1 to 6, the plasminogen activator enhancing activity i s

a) measured using a chromogen test or

b) A test system measuring the formation of plasmin itself or the lysis of fibrin clots brought about by plasmin in a coupling reaction in the presence of plasminogen.

detailed description open —

Description: FIELD OF THE INVENTION

The

present

invention relates to a protease for the activation of blood coagulation factor VII, methods for isolating, detecting and inactivating it and pharmaceutical preparations comprising this protea se. . BACKGROUND

OF THE INVENTION The blood coagulation system consists of two different cascade-like path ways that activate blood coagulation factors present in plasma. Depending on the induction m echanism, the intrinsic or extrinsic pathway is preferentially used to initiate blood coagulation. [0003] When tissues are injured, thromboplastin (tissue factor, TF and phospholipids) is exp osed by the affected cells as starters of the extrinsic coagulation pathway. Membrane-localize d thromboplastin can bind both blood coagulation factor VII (FVII) and circulating, activated F VII (FVIIa). In the presence of calcium ions and lipids, this TF-FVIIa complex leads to binding of FX, which is converted to its activated form (FXa) by limited proteolysis. FXa then activates prothrombin to form thrombin, leading to the formation of fibrin, which ultimately causes wou nd closure. [0004] Further activation of thromboplastin-binding FVII occurs initially by autoc atalytic reactions, but especially after initiation of the coagulation cascade it is supported by F Xa and thrombin, leading to a marked enhancement of the reaction cascade among others. [0 005]

Administration of FVIIa or FVIIa-containing concentrates has been indicated for certain clinic al conditions. For example, in patients with hemophilia A who develop antibodies to FVIII as a result of administration of FVIII.
used the so-called FVIII alternative pathway activity (FEIBA) of FVIIa. Based on presently kno wn findings, FVIIa is well tolerated in this relationship, it does not produce thrombotic tendenc ies, and is sufficient to ensure that a limited but adequate degree of clotting occurs. Are suita ble. Recombinant FVIIa is already used therapeutically and prophylactically. FVII isolated from plasma can also be used after activation. Proteases such as thrombin can be used for this acti vation, however, these proteases themselves are capable of strongly activating blood clots an d may pose a thrombotic risk. For this reason, subsequent removal or inactivation of thrombin is necessary, resulting in losses. As a result of the thrombotic risk associated therewith, the us e of FXa or FIIa (thrombin) is often contraindicated and indicated only in emergencies, eg in c onnection with significant loss of blood and uncontrolled bleeding.
SUMMARY OF THE INVENTION
[
0006]
FVIIa is found in very low concentrations in the plasma of healthy individuals. Little is known so far about the formation and origin of FVIIa circulating in the blood. Traces of thromboplasti n expressed or released with cell destruction may play a role in this association. Factor XIIa, f or example, is known to cause activation of FVII under certain conditions, but the physiologica l relevance of this response has not yet been clarified.
[0007]
Surprisingly, a FVII-activating protease, distinct from all previously known proteases, has no w been discovered associated with the fractionation of human plasma and certain prothrombin complex concentrates. A study of this protease showed that it exhibited a particularly high am idolytic activity towards the peptide substrate S2288 (HD-isoleucyl-L-prolyl-L-arginine-pNA) fr om Chromogenix AB, Sweden. A special property of this protease is that its amidolytic activity is effectively inhibited by aprotinin. Other inhibitors such as the antithrombin III/heparin com plex are also suitable for its inhibition. On the other hand, its activity is increased by heparin and heparin-related substances such as heparin sulfate or dextran sulfate and calcium ions. Fi nally, it was found that this protease is capable of converting FVII to FVIIa in a time- and conc entration-dependent manner. This reaction is also inhibited by aprotinin. SUMMARY
OF THE INVENTION Accordingly , part of the subject matter of the present invention is that

a) aprotinin is inhibited by the presence and b) its activity is elevated by calcium ions and/or heparin or heparin-related substances. and c) in SDS-PAGE, subsequent staining in non-reducing conditions shows one or more bands in the molecular weight range of 50-75 kDa, and in reducing conditions one band in the molecular weight range of 40-55 kDa and molecular weight It is a protease that activates blood coagulation factor VII , exhibiting one or more bands ranging from 10 to 35 kDa . BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows protease concentration and inactivation of FVIII when protease and FVIII are incubated for a certain period of time.

FIG. 2 shows the inactivation of FVIII when the protease concentration is constant and FVIII is incubated for various times.

FIG. 3 shows the inactivation of FVIII when protease and FVIII are incubated with varying calcium concentrations in the mixture.

[Mode for carrying out the invention]

In the following specification, the activated form of the protease is called "protease" and the non-activated form is called "proenzyme".

[0011]

This protease was further investigated and after concentration or isolation underwent a rapid loss of activity, which was observed in a solution containing 20 mM tris, 0.15 M NaCl, pH 7.5. Addition of albumin at a concentration of 0.1% also failed to prevent the activity of this protease from dropping to 50% after 1 hour at room temperature. On the other hand, very good stabilization of this protease was observed in solutions buffered to pH 6.5 with 50 mM sodium citrate. No or very little loss of activity was observed when the solution was adjusted to pH 4-7.2, preferably pH 5.0-7.0, even without the addition of specific stabilizers to the protease solution. However, it is expedient to add stabilizers to the solution, suitable stabilizers being, in addition to citrate, especially glutamate, amino acids such as arginine, glycine or lysine, calcium ions and sugars such as glucose, arabinose or An amount of 1 to 200 mmol/L, preferably 5 to 100 mmol/L of mannose can be mentioned. Effective stabilization is also achieved by the addition of glycols such as ethylene glycol or glycerol 5-80% by weight, preferably 10-60% by weight is used. In that case, the pH value of the stabilized solution should be between 4 and 9.

[0012]

The novel proteases, and also their proenzymes, are obtained by recombinant DNA methods or, for example, by production in the milk of suitable transgenic animals, in particular by fracti onation of plasma or prothrombin complex (PPSB) concentrates. can be done. The starting ma terial is then first subjected to anion exchange chromatography, followed by affinity chromato graphy of the eluate. Heparin or heparin-related substances immobilized on a matrix, such as heparin sulfate or dextran sulfate, are particularly suitable for affinity chromatography. Using such chromatographic methods, the novel proteases and/or proenzymes are selectively bound and can then be eluted again using known methods. The use of spacers can be recommended for coupling ligands to mattrex. A heparin-lysine matrix has been found to be particularly suit able for the isolation of novel proteases.

[0013]

In SDS-PAGE followed by staining, the proteases isolated by this method show one to severa l closely spaced bands in the molecular weight range of 55-75 kDa under non-reducing conditi ons. After reduction, one to several bands were observed in the molecular weight range of 15-35 kDa and one band was observed at 40-55 kDa. One additional band at 60-65 kDa was sho wn to constitute 5-10% of the total protein after scanning and quantitative evaluation, and th at non-activated proenzyme was also present. This result was supported by a suitable study u sing a monoclonal antibody directed against this protease. It was therefore concluded that the proenzyme of this protease could also be prepared, sterilized and used according to the meth od of the invention. Part of the subject matter of the present invention is therefore the proenz ymes of proteases that activate blood coagulation factor VII. The proportion of proenzyme is i ndicated by the 60-65 kDa band. Examples of suitable physiological activators of proenzymes correspond to amino acid sequences constituting the activation region of proenzymes, thrombi n, kallikrein or FVIIa, depending on their substrate specificity. Some of the properties of the novel protease mentioned above, namely the fact that it can be isolated from plasma or plasm a-derived prothrombin complex (PPSB) concentrates, inhibition of its amidolytic activity by ap rotinin and reduction and non-

reduction

The migration behavior described above in SDS-PAGE under both reducing conditions has bee n demonstrated by Hunfeld et al. 1999, 78: A42)

It recalls a protease isolated from a PPSB concentrate that has not been defined in detail. In t hat case, preparation was primarily accomplished using an aprotinin matrix. The activity has b een described as a thrombin-like activity as a result of the amidolytic cleavage of certain pepti de substrates. Hunfeld et al. found no effect on global coagulation parameters such as prothro mbin time, quick or platelet aggregation.

[0015]

N-terminal sequencing of the protease described by Hunfeld et al. shows that its cDNA is con sistent with that of the protein reported by Choi-Miura et al. (J. Biochem. 119:1157-1165, 19 96). In its primary structure, the corresponding protein exhibits homology with an enzyme na

med hepatocyte growth factor activating enzyme (HGFA). Two bands isolated from SDS-PAG E under reducing conditions were subjected to N-terminal sequencing and the following identit ies were established

. Molecular weight range of bands Amino acid sequence Reporter 10-35 kDa IYGGFK STAGK Present invention 30 kDa IYGGFKSTAG Hunfeld et al. 17 kDa IYGGFKSTAGK H Choi-Miura et al. 40-55 kDa LLESLDP Present invention

50 kDa SLDP Hunfeld et al.

57 kDa SLLESLDPWTPD Choi-Miura et al.

Nevertheless, at present it is still not possible to presume that these proteins are identical. In any event, none of the previously studied proteins described above have been reported to hav e FVIIa or other factor activating properties (see below).

[0017]

Based on its above-mentioned properties, the novel protease can be used diagnostically and therapeutically.

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. Test Systems Using the Novel Proteases

The novel proteases can be used diagnostically in test reagents. Thus the presence of factor VII can be determined qualitatively and quantitatively in blood coagulation tests by adding no vel proteases.

Conversely

, the test system developed for measuring FVII activation can also be used for the detection and quantification of proteases. For this, the protease-containing solution is mixed with the FV II-containing solution and the FVIIa produced is quantified after an appropriate incubation tim e. This is for example Staclot(R) It can be performed using the FVIIa-rTF test (Stago/Boehring er Mannheim). Using the preferred procedure, this test is not limited to the concentration of F VII supplied. If the amount of protease in the form of a ratio of total protein is known, the rati o is: -

in a pure protease preparation, by the Kjeldahl method or other protein assays well known t o those skilled in the art, or

- can be determined using, for example, specific antibody-based antigen tests and suitable i mmunochemical assay methods such as ELISA, and then the specific activity of the protease p

reparation can be determined in a corresponding manner.

Surprisingly

, with further characterization of proteases, new properties have been discovered that allow additional measurements. Incubation of the proteases with blood coagulation factors VIII/VIII a and V/Va followed by quantification reveals that the blood coagulation factors are inactivate d in a manner independent of protease concentration and length of incubation. made rice field.

Another part of the subject matter of the present invention is therefore a novel test system for the qualitative and quantitative detection of proteases that activate blood coagulation fac tor VII, in which proteases are blood It can be quantified by its activity to inactivate coagulati on factor VIII/VIIIa or V/Va. This test system involves incubating a solution containing a prote ase with Factor VIII/VIIIa or Factor V/Va and determining the amount of residual Factor VIII/V IIIa or the amount of residual Factor V/Va by a conventional activity test. It is based on meas uring and then determining from this the amount of protease by comparison with a standard c urve. In carrying out this test, the incubation of the protease activity is inhibited by the additi on of limited amounts of aprotinin for a predetermined period of time, which has the advantag e that these concentrations do not affect the subsequent measurements of the test system. T he residual activity of the blood clotting factor is then determined by test methods well known to those skilled in the art. For this, the so-called Coamatic factor VIII test (Chromogenix AB), which mainly contains factors IX and X and quantifies the amount of FXa obtained by conversi on of a chromogenic substrate in the presence of a thrombin inhibitor, is used In terms of en abling (see description in [0007]), especially test systems have proven their worth. On the ot her hand, this amount is proportional to the amount of FVII or FVIIa. Determining the residua l FVIII activity then makes it possible to derive the concentration of protease present.

[0022]

Degradation of FVIII/FVIIIa or FV/FVa factors by proteolytic action can be clearly demonstrat ed by SDS-PAGE. Depending on how long the protease was incubated with, for example, the F VIII concentrate, the bands typical of FVIII disappear, while other new bands develop or the i ntensity of weaker bands increases. Thus, protease activity can also be correlated by quantifyi ng the attenuation or enhancement of a band, and thus can be quantitatively measured using, for example, protease preparations. Band intensities in SDS-PAGE electropherograms, or chan ges in band intensities by other electrophoretic methods, can be quantified using, for exampl e, a scanner and appropriate programs well known to those skilled in the art. Additionally, anti bodies to the blood clotting factors described above can be used in Western blots and can be employed for evaluation in the methods described above. Antibodies that specifically detect at tenuated bands or specifically developed bands are particularly suitable. In this connection, th ese antibodies can also be used to establish other immunochemical tests, such as ELISA.

[0023]

The proteolytic inactivation described for FVIII/FVIIIa is also observed when the protease is i ncubated with Factor V/Va, which exhibits some degree of structural homology with FVIII. De gradation can be monitored in a suitable activity test system and SDS-PAGE/Western blotting.

[0024]

Despite the inactivation of FV and FVIII, the addition of proteases to blood, platelet-rich plas ma or plasma at this time shortens the blood clotting time, i. It was found to exhibit gulent ac tivity. These test systems are understood to be, for example, non-activated partial thrombopla stin time (NAPTT), prothrombin time (PT) and recalcification time. These shortenings of time, measured for example in so-called coagulometers, by thrombus elastographs or otherwise in c hromogenic tests, correlate with the concentration of the procoagulant substance, so that the concentration of that substance in the sample is , can be inferred inversely using the calibratio n curve for blood clotting time. Concentrations of "FVII activators" can also be determined usi ng selected comprehensive coagulation tests.

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FVII activator" also includes single-chain urokinase (scuPA, single-chain urokinase plasminog en activator), and single-chain tPA (sctPA, single-chain tissue

It has also been surprisingly found that it can provide an effective activator of plasminogen ac tivator), ie act as a plasminogen activator activator (PAA). The activity of activated PA can be measured, for example, using a chromogen. This property can therefore be used for the detec tion and quantification of "FVII activators". Activation of plasminogen activators can also be d etermined in coupling reactions in the presence of plasminogen, either by formation of plasmi n itself or by lysis of fibrin clots brought about by plasmin.

In summary

, therefore, it can be said that the protease can be incubated with a solution containing FVIII or FVIIIa and then the residual amount of FVIII/FVIIIa can be both detected and quantified by a suitable activity test. . Fv or Fva can be incubated with protease in the same manner and th e amount of Fv/Fva remaining can then be quantified. An unknown protease concentration ca n be quantitatively determined by comparing the increase in the amount of protease included in the test to a standard curve. Various comprehensive blood coagulation tests are likewise sui table for quantification, and protease concentrations are read from calibration curves based o n reduction of clotting times. The PAA activity of proteases can also be used for quantitation p urposes. A feature of these tests is that $CaCl_2$ is added to high concentrations of calcium, preferably >0.001 mM, particularly preferably >0.005 mM, suitable for FV and FVIII inactivation and PAA activity

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It is particularly well exhibited when present in the form of As noted above, FV/FVIII inactivat ion is not enhanced by heparin or Only non-significant enhancement is observed. In contrast, PAA activity is stimulated in the presence of any substance, namely calcium and/or heparin or heparin-like substances. The protease-induced reaction can be performed in the presence of

a protease inhibitor, particularly heparin or a heparin-like substance (preferably in the presenc e of heparin) antithrombin III, C1-esterase inhibitor, α 2 -antiplasmin, inter-α-trypsin inhibitor or known inhibitors

. can be very efficiently attenuated or prevented by incubation with a low molecular weight pr otease inhibitor such as guanidinocaproic acid-p-ethoxycarbonylphenyl ester available under t he tradename FOY® . These substances can thus be used to stop the reaction, for example to accurately determine the incubation time or to further increase the specificity of the test. Red uction of free calcium ions in the mixture, for example with chelating agents, can also be used for this purpose. 2 . Stabilized preparations of Factors V and VIII

From the above observations regarding the proteolytic activity of novel proteases against blo od coagulation factors V and VIII, the problem of inhibiting the protease activity or attenuatin g its activity is due to the loss of production and the formation of fragments which are presum ably fragments of interfering proteins. occur to avoid All this is all the more important since F V and FVIII are usually prepared from cryoprecipitates obtained from plasma in the presence of calcium ions, the latter being required for maintenance of protein conformation. Another p art of the subject-matter of the present invention thus includes proteolytically formed Factor V and VIII fragments as a result of the fact that the proteases that activate blood coagulation Fa ctor VII are inhibited

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is a stabilized preparation of free FV or FVIII. Further investigation revealed that the inactivati on of factors V and VIII by the proteases was particularly

It has been shown to occur efficiently in the presence of calcium ions at concentrations of 0.5 mM or higher, suggesting that the coagulation factor V or factor VIII preparations for inhibitio n of proteases that activate blood coagulation factor VII. Adjusting the concentration of calciu m ions to less than 1.0 mM, preferably less than 0.5 mM can effectively stabilize the Factor V and Factor VIII preparations. Although the factor V and factor VIII inactivating action of the pr otease is significantly reduced at these concentrations, the amount of calcium ions is still suffi cient to stabilize the conformation of the FV and FVIII molecules. The amount of calcium ions mentioned above should not be excessive not only in the final product, but also in the cryopre cipitate itself and in subsequent purification steps. Due to the aforementioned affinity of the protease or proenzyme for heparin and heparin-like substances, the protease/proenzyme can be isolated from FVIII- or FV-containing solutions by incubation with immobilized heparin or o ther immunological or affinity adsorbents

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can be removed. Polyclonal or monoclonal antibodies, respectively antibody fragments, useful for the preparation of immunoadsorbents can be readily obtained by techniques known in the

art using all or part of the protease or proenzyme as the antigen.

However ,

in order to prevent proteolytic degradation of FV or FVIII, natural or synthetic protease inhibitors may optionally be used in addition to lowering the amount of calcium ions. Aprotinin, α2-Proteins such as antiplasmin, C1-esterase inhibitor or intertrypsin inhibitor can also be used as inhibitors. Low molecular weight substances known to those skilled in the art as synthetic serine protease inhibitors can also be used in this context. Inhibitors such as antithrombin III, whose inhibitory potency is increased by heparin or heparinoids, can be added as well. Thus, although heparin by itself can increase the amidolytic activity of proteases on small chromogens, it was surprisingly found that it does not support the inactivation of FV/FVIII.

3

. Pharmaceuticals Comprising the Novel Proteases

The novel proteases and/or proenzymes can be used therapeutically.

They can be used alone or with substances that increase the activity of proteases, such as heparin or heparin-related substances, such as heparin sulfate, and/or calcium ions. In addition, factor VII can be added to this drug as well. The use of such agents that utilize their FVIII alternative pathway activity (FEIBA) is, for example, well tolerated due to the presence of, for example, antibodies against FVIII and/or FIX and/or FXI and/or contact phase proteins such as FXII. is present, or other types of missing conditions are present. In this context, FVII can be activated either in vitro, in plasma, in concentrated fractions, or by action on purified FVII. The novel blood clotting agents can also be used ex vivo for prevention of systemic bleeding or to stop bleeding.

[0034]

On the other hand, the observed inhibition of novel proteases by aprotinin or the inhibitors mentioned above can be used to develop drugs comprising protease inhibitors with reduced ability to clot blood. In addition to this, the novel proteases can also be used to identify physiological and non-physiological factors such as synthetic peptides that impair blood coagulation through their protease inhibitory action. Particularly efficiently transformed chromogenic substrates, such as the peptide sequence of S2288 (see above for details), can be used as a structural basis for this. If these preparations do not contain proteolytic activity, the addition of suitable inhibitors to the clot preparations may also be necessary during their preparation.

[0035]

As the protease was further characterized, properties were discovered that open up additional potential uses as so-called "Factor VII activator" proteases. single-stranded plasmid Incubation of a nogen activator, e.g., pro-urokinase (single-chain urokinase, sucPA, single-chain urokinase plasminogen activator) or sctPA (single-chain tissue plasminogen activator) results in the activation of these positive 'factor VII activators'. Resulting in activation of the minogen activator (PA). In this connection, the proteolysis of single-chain PA is limited, resulting in the formation of double-chain proteases, which are particularly suitable for plasminogen activa

tion. The plasmin produced is the effector of fibrinolysis, the physiological system involved in the dissolution of thrombi. PA, such as pro-urokinase or tPA, is an endogenous protein that is released on demand and, as is known, activated by plasmin or kallikrein (scuPA). The mechanism by which scuPA is activated in health has not yet been fully elucidated. The plasminogen activator is for therapeutic use as an isolated or recombinantly prepared protein in pharmaceutical preparations associated with thrombotic diseases or complications such as femoral vein thrombosis, myocardial infarction or stroke

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can be done.

[0037]

The nature of the now discovered "Factor VII activator" allows the latter to be used for in vivo or ex vivo activation of plasminogen activators such as urokinase or sctPA. This activity also applies to the use of this protease, particularly in combination with single- or double-chain plasminogen activators or anticoagulants, as well for the prevention or treatment of thromboembolic disease. This potential use is consistent with the fact that proteases can also act in a procoagulant fashion. The question of which of the two responses takes precedence is presumably resolved by the availability of physiological substances. According to current knowledge, factor VII is moderately activated in plasma and is constantly maintained at a certain concentration so that sudden vascular injury can be dealt with immediately. On the other hand, tissue plasminogen activator as well as urokinase plasminogen activator are present in only nanogram quantities in 1 ml of plasma. Its concentration is elevated by secretion or synthesis of plasminogen activators only when fibrin deposition or thrombi occur, which are then activated locally, especially when they bind to thrombi, and then Activating plasminogen to exert their thrombolytic action. When single-chain PAs are present, their activation exceeds that of FVII, especially in a locally restricted manner, thereby allowing regulation to physiological conditions. Therefore, this protease also modulates hemostasis, thereby potentially applying to replacement by proteases and/or proenzymes in cases of congenital or acquired defect conditions.

[0038]

Another part of the subject matter of the present invention is therefore a pharmaceutical preparation consisting of an amount of blood coagulation factor VII-activating protease and/or its proenzyme form sufficient to lyse fibrin-containing thrombi. The formulation can also contain a single chain plasminogen activator (PA) and/or an anticoagulant. If a proenzyme is present, it may also be advantageous to use a suitable activating agent within or together with the pharmaceutical formulations described above.

[0039]

Since it has been found that the plasminogen activator potentiating action of the "FVII activator" is enhanced in particular by calcium and/or heparin and heparin-like substances such as dextran sulfate, soluble calcium salts and/or heparin Alternatively, pharmaceutical preparations containing heparin-like substances can be advantageously used for lysing fibrin-containing thr

ombi according to the present invention. In this context, the protease/proenzyme, alone or in combination with a single- or double-chain plasminogen activator, optionally exerts a specific affinity for the protease, thereby increasing plasma half-life. It can be used as an extended ca rrier material or as a mediator to the surface together with a material that increases its activit y.

[0040]

Pharmaceutical preparations consisting of blood coagulation factor VII-activating protease ca n be used for the treatment of diseases caused by fibrin-containing thrombi due to their specif ic fibrinolytic action. The fibrinolytic process is also involved in the wound healing process. In t his connection, the proteases and/or proenzymes can be administered intravenously or topical ly, subcutaneously, intradermally or intramuscularly or topically in the case of injuries or woun ds or bound to a suitable carrier matrix. . Both proteases/proenzymes isolated from body fluid s such as blood or plasma and recombinantly or transgenically prepared proteases/proenzyme s can be used in this context. The protease/proenzyme is also suitable as a component of so-c alled fibrin glues, which must not contain substances that inhibit the protease/proenzyme, suc h as aprotinin. In this case, the clot-shortening action of proteases is utilized. The above pro teases/proenzymes can be used for congenital or acquired hemostatic defects, (generalized) b leeding episodes, various thrombosis-related complications

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When used to treat bleeding, it is advantageous to add the protease/proenzyme together with FVIII and, if desired, further clotting factors.

4

. Method for Sterilizing FVII-Activating Protease

Being a protein isolated from human plasma, the novel protease and/or its proenzyme can o nly be used as a pharmaceutical preparation if it has been previously subjected to virus-inacti vating treatment. can do. The sterilization process is recognized as the most important proces s, especially for virus inactivation. However, the proteins to be processed require adequate sta bility to heating at about 60° C. for up to 10 hours. Optimal stabilizers must be determined se parately for each protein and their concentrations optimized.

In the case of novel proteases and/or their proenzymes, the conditions for stabilizing protein s in non-sterilized solutions have already been described above. A slightly acidic pH has prove n to be particularly advantageous in this case. However, novel proteases and/or their proenzy mes typically lose 50% or more of their original activity upon sterilization under these conditio ns. The sterilization of the pharmaceutical formulations comprising the novel proteases and/ or their proenzymes is carried out by subjecting the preparation to a

) pH range 3.5-8.0, preferably pH range 4.0-6.8; and/or c) one added sugar or combinatio n of different sugars at a total concentration of 0.01 mol/L or more, preferably 0.05 mol/L or more . 05 g/ml or more, preferably 0.2 g/ml or more; and/or d) one or more substances cap able of forming a complex with added calcium ions such as citric acid, oxalic acid, ethylenedia

minetetraacetic acid, etc. Preparing in the presence ensures optimum stabilization results. A dditives such as albumin, Haemaccel® ′ heparin and heparinoids, glycerol , glycols and polyet hylene glycols can be used separately or mixed together. After sterilization is complete, sugar s, amino acids and other additives added as stabilizers can be reduced or completely removed from the preparation using methods well known to those skilled in the art. The results of the s terilization process are shown in Examples 12 and 13. [Example]

Example 1

Activation of FVII by the proteases prepared was demonstrated using the Staclot® FVIIa-rTF test system (Stago/Boehringer Mannheim) . This detection system has the specific property th at preformed activated FVII (FVIIa) can only be used to inhibit the extrinsic coagulation pathw ay.

It is based on (recombinant) soluble tissue factor (rTF). This allows the actual content of FVII a to be accurately determined, as opposed to using intact tissue factor.

Activation experiments were

performed using isolated FVII (Enzyme Research Labs). This FVII itself contains traces of FVI Ia since it was isolated from human plasma. The concentration was adjusted to 0.05 IU/ml of FVII by dilution with buffer. FVII was incubated with test substances for 10 minutes at room t emperature and then tested for true FVIIa content. FVIIa content was quantified using a stan dard curve constructed in parallel.

In preliminary

experiments, not described here, aprotinin completely inhibited the activity of the prepared protease at the concentrations used, but had no direct effect on FVIIa and showed no direct ef fect on the FVIIa-rTF test system. It was confirmed that there was no significant effect on

The results listed below relate in each case to triplicate measurements. That is, the following experiments were set up as follows.

1

. FVII:

Non-activated FVII was used as a control assay. It already contains traces of FVIIa (see abov

e) in the order of 10 mIU/ml of FVIIa.

2

. FVII+Aprotinin:

In this assay, FVII was incubated in the presence of aprotinin and the FVIIa-rTF assay was u sed to demonstrate that FVIIa itself was not inhibited nor was the test affected by the aprotini n used. This was confirmed (by comparison with Assay 1).

[0050]

3. Protease + FVII (incubation) then addition of aprotinin:

Result: FVIIa 18 mIU/ml

In this case the protease was given time to activate FVIIa. Aprotinin was added only to wash out the protease, after 10 minutes of incubation. The resulting FVIIa was quantified by the FV IIa-rTF assay. Thus, subtracting the basal value of FVIIa (assay 1), 8 mIU/ml of FVIIa was for med by the activity of the protease under the conditions chosen.

4

. Protease + aprotinin then addition of FVII:

Results: FVIIa 11 mIU/ml

In this assay the protease was inhibited with aprotinin prior to contact with FVII. Neither sub sequent incubation with FVII nor subsequent quantification of FVIIa resulted in a significant in crease in FVIIa content (the range of variation in the assay, ie 11 and 10 mIU/ml in assay 1, i s not considered significant).

5

. Protease:

Results: FVIIa 0 mIU/ml

This assay demonstrated that the protease itself had no effect on the FVIIa-rTF test system at the concentrations chosen.

In summary, from the above

- the described proteases activate FVII;

- the activation of FVII by proteases occurs "directly", i.e. independently of the presence of r TF;

- FVII activation is inhibited by aprotinin; aprotinin itself has no significant effect on the test system;

is concluded. Example 2 This example illustrates how FVII is activated in a reaction that is in dependent of the concentration of protease and the time the protease is incubated with FVII . The test system and reagents were selected to correspond to those described in Example 1. In the first series of experiments, the initially introduced FVII was preincubated (5 min at roo m temperature) with protease-containing solutions at various dilutions (1:5, 1:10 and 1:20), f ollowed by aprotinin (a protease inhibiting) and subsequently tested for their FVIIa content in the FVIIa-rTF assay. Again, a parallel assay in which the protease was inhibited by aprotinin b efore contacting with FVII served as a control. Results are given as activation factors. ie x ti

mes the value measured in the control assay described above. Assay: protease + FVII, incub ation, + aprotinin Control: protease + aprotinin, incubation + FVII

[Table 1]

プロテアーゼ溶液の希釈度	活性化係数	
	アッセイ	対 照
1：5	2.6	1.0
1：10	2.0	1.0
1：20	1.6	1.0

From this it is concluded that FVII is activated by proteases in a protease concentration-depe ndent manner. It was also demonstrated that FVII was activated by proteases in a manner t hat was independent of the length of incubation when the co-reactant concentration was kept constant

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When equal volumes of a solution containing 0.2 IU/ml FVII and a 1:10-diluted protease solut ion were incubated together, aprotinin was added (to stop activation) after a corresponding pe riod of incubation, followed by: of FVIIa content was obtained.

[Table 2]

インキュベーションの長さ	活性化係数
0 分	1.0
2.5 分	1.3
5.0 分	2.0
10.0 分	2.8
40.0 分	＞3.8

From this it is concluded that FVII is activated in a time-dependent manner by proteases. Ex ample 3 This example will be used to demonstrate that protease activation of FVII is enhanc

ed by the presence of calcium ions and heparin

. 25 µl of protease-containing solution was added to 50 µl of

- buffer (control)
- 15 mM $CaCl_2$
- heparin 50 USP units/ml
- Pathromtin (lipid mixture, aliquot dissolved according to manufacturer's instructions) for 5 minutes at room temperature, then 150 µl of tris/NaCl buffer (pH 8). .2) and 25 µl of chromogenic substrate S2288 (3 mM), followed by measurement of absorbance over time at 405 nm (37° C.). Activation factors (x-fold) relative to buffer controls are shown in the table below. [Table 3]

アッセイ	活性化係数（緩衝液対照に対する倍数x）
緩衝液対照	1.0
＋$CaCl_2$	3.6
＋ヘパリン	2.6
＋脂質	0.9
＋$CaCl_2$＋ヘパリン	4.3
＋$CaCl_2$＋脂質	3.3
＋ヘパリン＋脂質	2.7
＋$CaCl_2$＋ヘパリン＋脂質	3.7

Under the conditions used in this example, a significant increase in protease activity can be observed in the presence of calcium ions and/or heparin. Example 4 In each case a solution containing 10, 1 or 0.1 µg/ml of protease was mixed with 25 µl of FVII (2 IU/ml) followed by 25 µl of CaCl 2 (25 mM) and

25 µl of Pathromtin® (Dade Behring GmbH) was added. After incubation for 0, 3, 10 and 20 minutes at 37° C., the reaction was stopped by adding 400 µl of aprotinin (500 KIU/mg). A sample to which aprotinin was added first was used as a control. Each sample was diluted in tris buffer/BSA. In each case 50 µl of this solution were mixed with 50 µl of the factor reagent [mainly consisting of FIXa, FX and thrombin inhibitors, modified according to the Cosmatic® $^{F}_{VIII}$ test, Chromogenix AB] and incubated at 37° C. for 10 minutes. 50 µl of substrate (eg S2765, Na-Cbo-D-Arg-Gly-Arg-pNA) was added, followed by the addition of 50 µl of acetic acid (5

0%) to stop the reaction after a defined time of incubation, OD 405 nm was then measured. A s tandard curve of FVIII was used to determine the concentrations in the samples. Results :

In the first assay, the protease incubation time with FVIII (2 IU/ml) was kept constant (10 m in), but the protease concentration was varied (0.1, 1 and 10 µg/ml). The reaction was stoppe d and the residual concentration of active FVIII was determined. Increasing protease concentr ations resulted in a corresponding inactivation of FVIII (Fig. 1).

The protease content of samples can be quantified using a suitable standard curve.

In the second assay, the concentration of protease was held constant (10 µg/ml), FVIII (2 I U/ml) and incubation time were varied. A significant decrease in the residual concentration of active FVIII was observed with increasing incubation time (Fig. 2).

Example 5 The effect of "FVII activator

" on factor V activity was examined.

25 µl of protease-containing solution (0-100 µg/ml) was incubated with 50 µl of FV (5 IU/ml) and 25 µl of $CaCl_2$ (0-20 min), then 400 µl of buffer containing 100 KIU/ml aprotinin was add ed. .

In both cases, 100 µl of each incubation assay was then incubated with 100 µl of FV-deficien t plasma for 1 minute at 37° C., then 200 µl of Thromborel S® were added, mixed and clottin g time was measured using a Schnitger & Gross coagulometer . was measured. Residual activity of FV was determined.

result:

[Table 4]

プロテアーゼ濃度 (µg/ml)	FVの残留活性 プロテアーゼとFVのインキュベート時間(分) 0	10	20
10	93	91	100
30	100	93	28
100	100	29	13

This example demonstrates that FV was inactivated by proteases over time. Example 6 The effect of "FVII activators" on blood clotting

times in a so-called global test was investigated using a Schnitger & Gross coagulometer. All the difference values given correspond to a shortened blood clotting time by this amount. NAPTT (non-activated partial thromboplastin time) protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml. 100 μl of each of these solutions were incubated with 100 μl of citrated plasma (from standard plasma pools or individual donors) and 100 μl of Pathromtin® for 2 minutes at 37° C., then 100 μl of 25 mM $CaCl_2$ were added, followed by blood. Clotting time was measured. Differences between these measurements and the corresponding blood clotting times obtained using buffer instead of protease were determined.

[Table 5]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(213秒)	0	13	20	42	43
1	0	20	33	42	41
2	0	27	31	45	47
3	0	13	14	23	29
4	0	18	37	51	50
5	0	25	49	54	46

Addition of the FVII activator resulted in a concentration-dependent shortening of NAPTT. Plasma Calcium Reprecipitation Time Protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml

. 100 μl of each of these solutions were incubated with 100 μl of citrated plasma (either from standard plasma pools or from individual donors) at 37° C. for 1 minute, then 100 μl of 25 mM $CaCl_2$ were added and clotting times were measured . Differences between these measurements and the corresponding blood clotting times obtained using buffer instead of protease were determined.

[Table 6]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(283秒)	0	17.2	15.1	30.5	50.4
1	0	29.8	51.7	60.3	90.1
2	0	25.2	51.7	69.5	101.3
3	0	28.0	—	39.0	74.6
4	0	27.3	42.7	55.6	91.8
5	0	44.3	69.1	101.2	134.2

PT (prothrombin time)

protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml . 100 μl of each of these solutions are incubated with 100 μl of citrated plasma (either from standard pla sma pools or from individual donors) at 37° C. for 1 minute, then 200 μl of Thromborel S® (D ade Behring GmbH) are added, followed by blood clotting . time was measured.

Differences between these measurements and the corresponding clotting times obtained usi ng buffer instead of protease were determined.

[Table 7]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(13.6秒)	0	1.0	1.7	1.5	2.4
1	0	0.7	1.3	2.4	2.7
2	0	0.3	0.4	1.7	3.1
3	0	0.4	0.7	1.5	1.8
4	0	0.1	0.7	1.8	3.1
5	0	0.3	0.5	1.2	2.8

Example 7 The

plasminogen activator activating action of "FVII activator" was examined using single-chain urokinase (scuPA) and single-chain tPA (sctPA).

Assay:

0.1 ml PA solution (20 μg/ml scuPA or 100 μg/ml sctPA)

+ 0.1 ml test buffer or

100 U/ml heparin in test buffer or

20 mM $CaCl_2$

in test buffer + 0.5 ml test buffer + 0.1 ml test buffer

1 ml protease/sample (increasing concentrations; 2-10 μg/ml scuPA

or 50-200 μg/ml sctPA)

incubation at 37° C.

+ 0.1 ml aprotinin at 100 KIU/ml in test buffer

2 min incubation at 37° C.

+ 0.1 ml For the substrate S-2444 (3 mM)

control, aprotinin is first introduced instead of plasminogen activator (PA) prior to the first in cubation, and so on through each case. On the other hand, PA was not added thereafter until i t was added instead of aprotinin.

The difference in measurements (Δ) $\Delta OD_{405\ nm}$ was measured optically. The control values obtained were subtracted from the sample/protease values and in this way the PA activity pro duced by the PAA activity was measured (mIU/min).

Results

:

Activation of scuPA (20 μg/ml scuPA, 2-10 μg/ml "FVII activator")

[Table 8]

A．刺激物質：なし

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	25	60	117
5	79	179	165
10	186	449	517

B．刺激物質：ヘパリン

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	190	332	425
5	330	455	458
10	417	462	460

C．刺激物質：$CaCl_2$

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	255	370	401
5	338	424	438
10	416	445	448

The table illustrates the fact that scuPA is activated in a manner that depends on the concentration of the "FVII activator" and the length of incubation. At the same time, both heparin and calcium showed a stimulatory effect on the activation of PA induced by proteases. Activation of scuPA (100 µg/ml sctPA, 50-200 µg/ml "FVII activator") The turnover rate of activated tPA is only increased by a factor of 3-4 compared to the tPA proenzyme
. (In the case of uPA it increases by a factor of 1000-1500), so high concentrations of the two co-reactants had to be chosen in order to obtain an analyzable measurement signal.

[Table 9]

A.

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） ＦＶＩＩアクティベーター(200μｇ／ｍｌ)
1	１０．２
2	１６．８
5	３８．８
１０	６０．２
２０	７３．３

B. 「ＦＶＩＩアクティベーター」の濃度依存性(インキュベーション、時間：20分、37℃）、刺激物質：ヘパリン（100IU/ml）

ＦＶＩＩアクティベーター（μｇ／ｍｌ）	ＰＡ活性(ΔmIU／分)
５０	３３．６
１００	５１．０
２００	７１．９

C. 刺激物質（インキュベーション、時間：20分、37℃）

刺激物質	ＰＡ活性(ΔmIU／分)
なし	5．9
$CaCl_2$	２５．３
ヘパリン	６３．８

The table demonstrates that sctPA was also activated in a protease concentration- and incubation time-dependent manner. Both heparin and calcium ions showed a stimulatory effect on the ability of the 'FVII activator' to activate PA. Example 8 Two FVIII-containing solutions , one essentially free of von Willebrand Factor and the other containing vWF, were incubated in the presence of the protease described above and calcium. Residual FVIII activity was measured by a chromogen test after a predetermined time and correlated with a protease-free control assay. For this, 25 µl of a solution containing 0.1 IU/ml of FVIII were treated with an equ

al volume of protease solution (μg/ml) and the whole was mixed with 25 μl of CaCl 2 (25 mM) . After incubation at 37° C. for 0, 5, 10 and 20 minutes, it was treated in each case with 400 μl of a solution containing 200 KIU/ml aprotinin in order to terminate the proteolytic activity o f the protease. Preliminary experiments have shown that this concentration of aprotinin has n o significant interfering effect on the FVIII activity test (assays 1+3) described below. In Assa y 2, the protease was incubated with aprotinin prior to contact with FVIII and then manipulate d as described above.

In each case 50 μl of the stopped sample (or after further dilution) were then treated with s o-called factor reagents, consisting mainly of FIX, FX and thrombin inhibitors, and incubated a t 37° C. for 10 minutes . Addition of 50 μl of chromogenic substrate which is cleaved by activa ted FX was followed by incubation for 5 minutes before adding 50 μl of acetic acid (50%) to st op the reaction and ΔOD 405 nm was measured . FVIII activity (mIU) was determined using a s tandard curve prepared from FVIII concentrates and constructed using the dilution series inclu ded in the test.

FVIII activity is

expressed as a percentage of the control to which no protease was added.

result:

[Table 10]

	FVIII活性(%)			
	インキュベーション時間(分)			
アッセイ	0	5	10	20
1. FVIII	97	27	11	<1
2. FVIII／アプロチニン	98	97	97	96
3. FVIII／vWF	98	16	14	1

In the presence of CaCl 2 (6.25 mM in this case), FVIII was inactivated by proteases in a len gth-of-incubation-dependent manner. vWF did not protect FVIII from inactivation by protease s. Inhibition of the protease with aprotinin prior to contact with FVIII prevented inactivation of the former.

Example

9

In this series of experiments, Example 1/Assay 1 was performed, but in this case the calcium concentration in the mixture of protease and FVIII was varied. For this, $CaCl_2$ was added from a calcium stock solution to the final concentrations shown in FIG.

Results:

Approximately 50% FVIII remains under these conditions when the calcium concentration in the assay is reduced to less than 1 mM. Below 0.5 mM calcium the residual percentage is greater than 60% (Fig. 1). Example 10 The effect of "FVII activators" on blood clotting times in a so-called global

test was investigated by thrombus elastography. Changes in shear elasticity or strength of associated clots were recorded continuously using a Hilgard TEG meter (from Hellige). The so-called r and k values, the time from the onset of blood arrest and from the onset of clotting reaction respectively, for citrated plasma the time of recalcification to the TEG curve extends up to 1 mm, the r value The time from the end point to the curve extended to 20 mm (clotting time). [0074]

For this, 150 µl aliquots of blood or plasma from 5 donors were in each case incubated at 37° C. for 2 minutes in the measurement cuvette, then 50 µl of sample (protease) were added and mixed. 100 µl of 25 mM $CaCl_2$ was added to initiate the reaction. The final concentration of "FVII activator" in the assay was 15 µg/ml. Reduction in r time was measured for assays containing buffer instead of sample.

result:

[Table 11]

血液番号	サンプル	r時間(分)	k時間(分)	r＋k時間(分)
1	プロテアーゼ	5.2	3.4	8.6
1	緩衝液	7.8	5.6	13.4
2	プロテアーゼ	5.2	5.1	10.3
2	緩衝液	6.8	7.1	13.9
3	プロテアーゼ	4.0	5.2	9.2
3	緩衝液	6.5	6.3	12.8
4	プロテアーゼ	4.5	4.8	9.3
4	緩衝液	4.8	6.0	10.8
5	プロテアーゼ	4.2	3.8	8.0
5	緩衝液	7.0	5.8	12.8

血漿番号	サンプル	r時間(分)
1	プロテアーゼ	9.0
1	緩衝液	11.3
2	プロテアーゼ	9.2
2	緩衝液	12.5
3	プロテアーゼ	9.5
3	緩衝液	9.6
4	プロテアーゼ	8.2
4	緩衝液	12.1
5	プロテアーゼ	9.7
5	緩衝液	14.1

This

example demonstrates that in almost all cases the addition of protease causes a marked reduction in blood clotting time. In the example shown here the fibrinolytic effect of the "FVII activator" was hidden in the background. The reason for this is that in "normal subjects" the concentration of plasminogen activator in plasma is in the nanogram range and has no effect on in vitro coagulation tests. Example 11 Protease FVIII alternative

pathway activity was demonstrated by the following experimental assays. That is, thrombus elastography was used as a measurement technique. The r time was evaluated (see Example 10). Whole blood samples were incubated with monoclonal antibodies known to inhibit FVIII a ctivity (antibodies against FVIII) in order to stimulate the presence of natural FVIII inhibitors. Samples were compared to a whole blood sample control (buffer instead of Mab). FE of protea se

IB activity was tested by adding protease (17 μg/ml final concentration) to Mab-inhibited whol e blood samples. Additionally, protease was added to the samples to determine the effect of t he protease itself on rtime.

Results

:

[Table 12]

	r時間
全血対照	8.0
全血＋ｍＡｂ	11.0
全血＋ｍＡｂ＋プロテアーゼ	8.0
全血＋プロテアーゼ	3.5

The rtime prolongation caused by the anti-FVIII mAb was again normalized by the presence of the protease, demonstrating the FEIB activity of the protease. As already demonstrated ab ove, the protease itself shortened the blood clotting time. Example 12 To a solution containin g 50 μg/ml FVII-activating protease was added the following substances to the corresponding final concentrations

. 25 mM sodium citrate 25 mM HEPES 100 mM arginine 0.75 g/ml sucrose This solution was divided into portions and in each case aliquots were adjusted to various pH values from 5.0 to 8.6 and then heated to 60° C. for 10 hours. bottom. The activity of the heated protea se solution was determined by the chromogenic assay, recording deamidation of the chromog enic substrate S2288 (HD-Ile-Pro-Arg-pHA x 2HCl, Chromogenix AB, Sweden) over time. The activity was expressed as a percentage of aliquots measured in parallel without heating. Resul ts :

[Table 13]

アッセイ	活性(%)
出発原料	100
pH5.0	76
pH5.5	65
pH6.1	81
pH6.5	50
pH7.1	43
pH7.5	46
pH8.1	46
pH8.6	32

This series of experiments showed that stabilization, especially in the acidic pH range, markedly inactivated proteases.
decreased sharply. The slight "breakthrough" at pH 5.5 can be explained by the fact that the isoelectric point of the protease lies in this range. Sodium citrate prevents the >50% loss of activity that occurs in the preferred pH range. Example 13 The assay at pH 6.1 (Example 1) showed the best stabilization of the protease
. Therefore, various activities were tested and evaluated at pH 6.0 as described in Example 1.
The following final concentrations were set and the protease concentration was 50 μg/ml. 50 mM sodium citrate/50 mM NaCl, pH 6.0 0.75 g/ml sucrose 100 mM glycine 100 mM arginine Results:

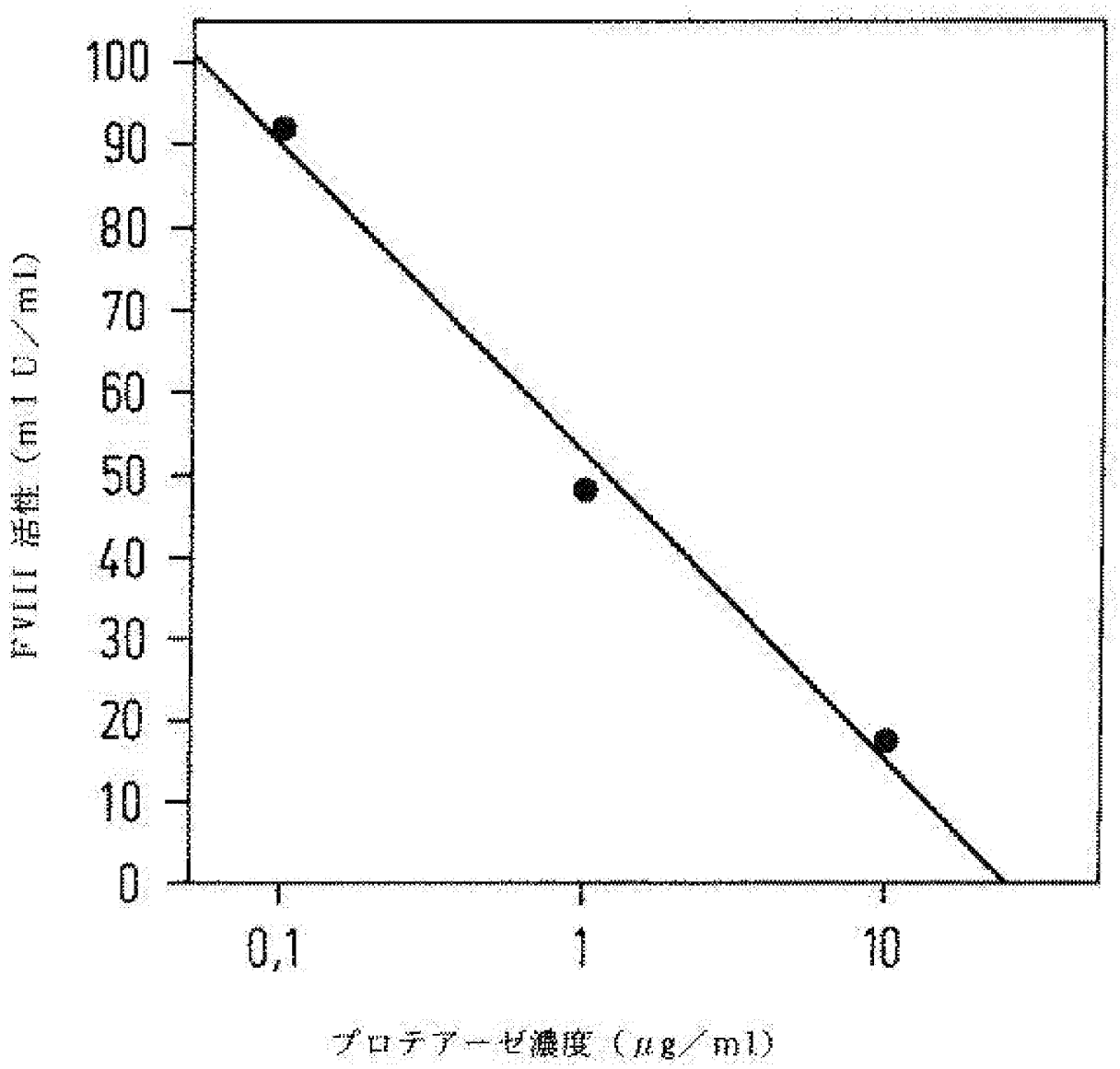
[Table 14]

アッセイ	活性(%)
出発原料	100
クエン酸ナトリウム／NaCl	54
クエン酸ナトリウム／NaCl／スクロース	85
クエン酸ナトリウム／NaCl／スクロース／グリシン	92
クエン酸ナトリウム／NaCl／スクロース／アルギニン	97

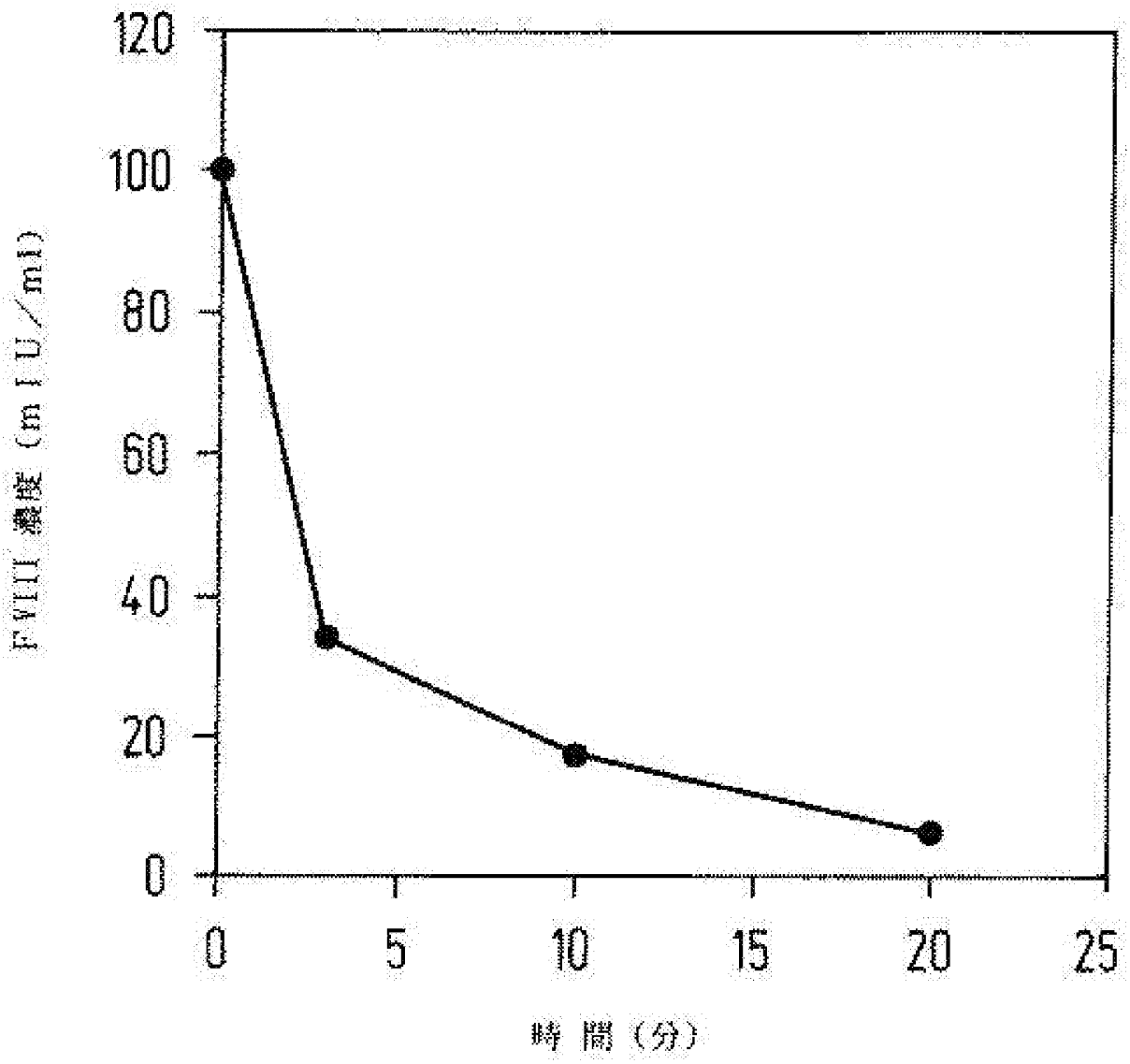
Addition of sucrose and one amino acid in each case demonstrated a significant stabilization of the protease.

drawing open —

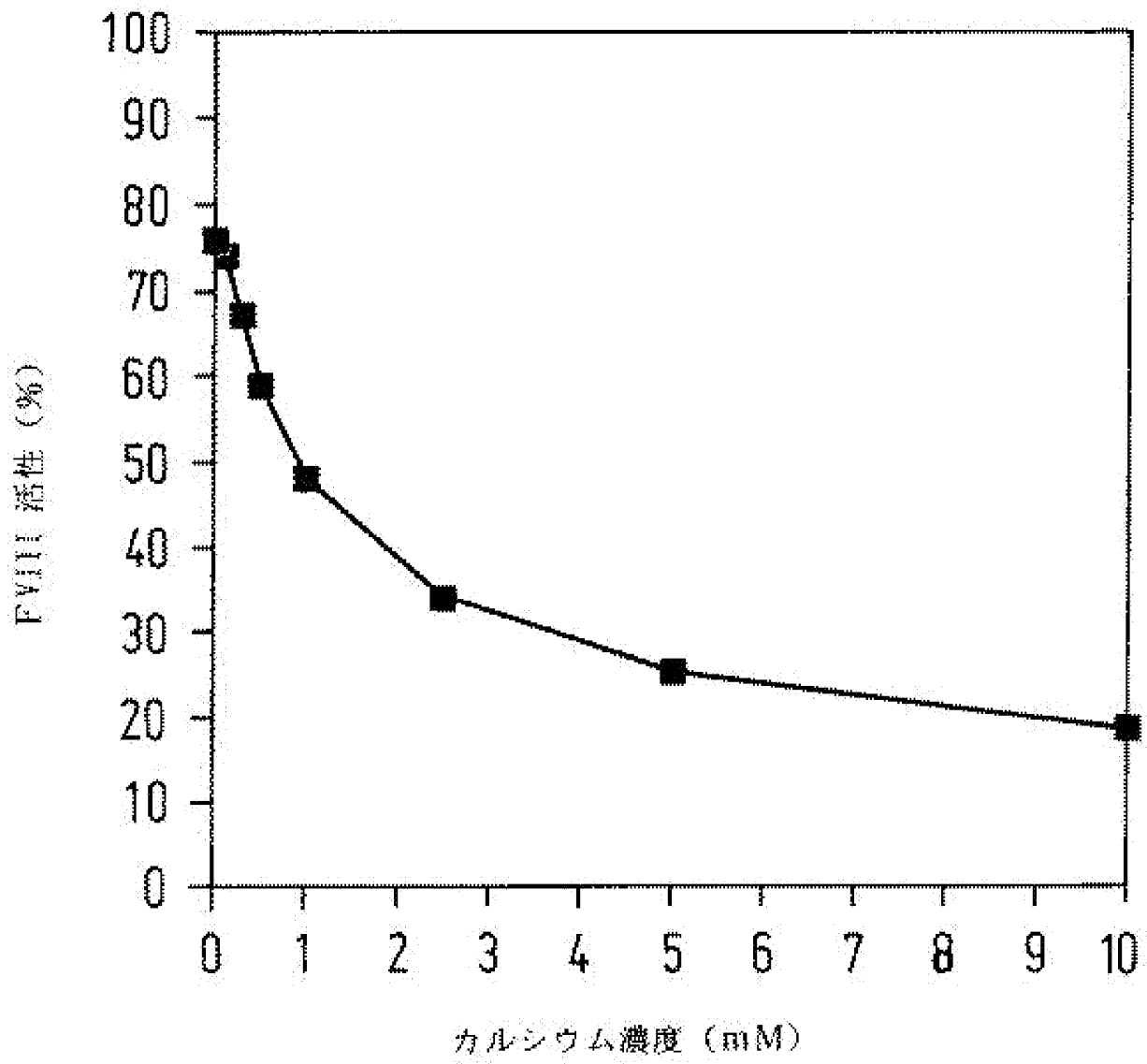
[Fig. 1]



[Figure 2]



[Figure 3]



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1 2 3

Magnify and Rotate

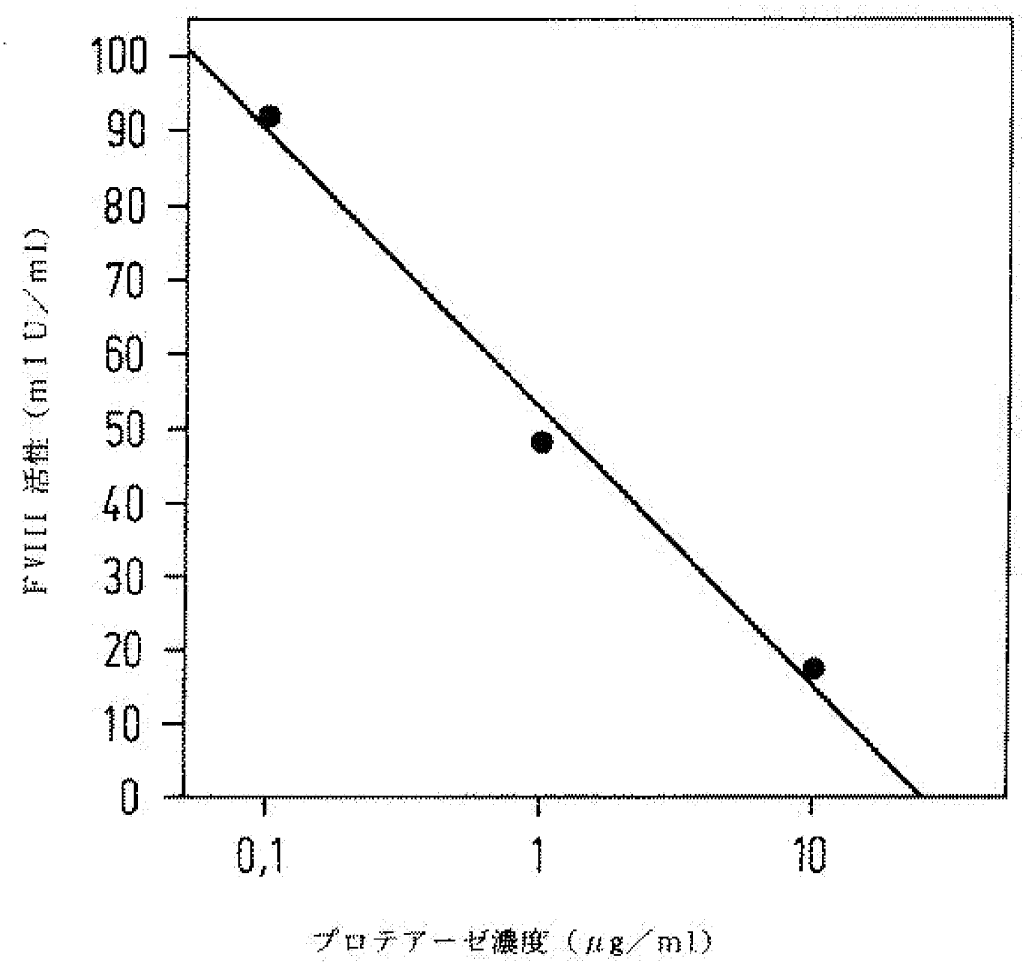


Figure 1

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(54)【発明の名称】血液凝固第ＶＩＩ因子を活性化するプロテアーゼ

(57)【要約】
【課題】　新規なFVII活性化プロテアーゼの発見とその応用。
【解決手段】　ａ）アプロチニンの存在によって阻害され、ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン類縁物質によってその活性が上昇し、またｃ）ＳＤＳ－ＰＡＧＥにおいて、以後の非還元状態での染色では分子量　５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量１０～３５ｋＤａの範囲の１個もしくは２個以上のバンドを示す、血液凝固第VII因子を活性化するプロテアーゼならびにそのプロ酵素は、血漿またはプロトロンビン複合体（ＰＰＳＢ）濃縮物から予め陰イオン交換クロマトグラフィーに付したのち、ヘパリンもしくはヘパリン類縁物質またはデキストラン硫酸を用いる親和性クロマトグラフィーによって得られる。
本発明は、上記プロテアーゼまたはそのプロ酵素の定性的および定量的検出、ならびにその診断的応用のための試験システムおよびフィブリン含有血栓の溶解に適当な量の血液凝固第VII因子を活性化する上記プロテアーゼおよび／またはそのプロ酵素を含有する医薬製剤が含まれる。
【選択図】　なし

【特許請求の範囲】
【請求項1】
ａ）アプロチニンの存在によって阻害され、
ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、
ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲に１個または２個以上のバンドを示し、そして
ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または
ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素の定性的および定量的検出のための試験システムにおいて、そのプロテアーゼ活性は、
ａ）血液凝固第VIII／VIIIａ因子もしくは第V／Ｖａ因子を不活性化するその活性または
ｂ）包括的血液凝固試験における血液凝固時間を低下させるその活性または
ｃ）プラスミノーゲンアクティベーターを活性化するその活性または
ｄ）FVIIを活性化するその活性
によって測定する試験システム。
【請求項2】
請求項１に記載の試験システムにおいて、血液凝固時間を低下させる活性は、
ａ）非活性化部分トロンボプラスチン時間（ＮＡＰＴＴ）または
ｂ）プロトロンビン時間（ＰＴ）または
ｃ）血漿カルシウム再沈着時間または
ｄ）活性化部分トロンボプラスチン時間（ＡＰＴＴ）
によって測定する試験システム。
【請求項3】
請求項１および２に記載の試験システムにおいて、プラスミノーゲンアクティベーターを活性化および／または増強する活性は、
ａ）一本鎖ウロキナーゼＰＡ（scuＰＡ、一本鎖ウロキナーゼプラスミノーゲンアクティベーター）または
ｂ）一本鎖 ｔＰＡ（sctＰＡ、一本鎖組織プラスミノーゲンアクティベーター）の活性化により測定する試験システム。
【請求項4】
請求項１～３に記載の試験システムにおいてカルシウムイオン０．００１ｍM以上の量を含む試験システム。
【請求項5】
ａ）アプロチニンの存在によって阻害され、
ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、
ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲の１個または２個以上のバンドを示し、そして
ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または

ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素と適当なプロ酵素アクティベーターの混合物をプロトロンビン時間置換組織因子／トロンボプラスチンの試験に使用するアッセイシステム。

【請求項6】

ａ）アプロチニンの存在によって阻害され、

ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、

ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲の１個または２個以上のバンドを示し、そして

ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または

ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素と適当なプロ酵素アクティベーターの混合物を、プラスミノーゲンアクティベーターの機能性の試験ならびに一本鎖プラスミノーゲンアクティベーター型の定量に使用するアッセイシステム。

【請求項7】

請求項１～６に記載の試験システムにおいて、プラスミノーゲンアクティベーターを増強する活性は、

ａ）色素原試験を用いて測定するかまたは

ｂ）プラスミノーゲンの存在下におけるカップリング反応でプラスミン自体の形成もしくはプラスミンによってもたらされるフィブリン凝血の溶解で測定する試験システム。

【発明の詳細な説明】

【技術分野】

【0001】

本発明は血液凝固第VII因子の活性化のためのプロテアーゼ、それを単離、検出および不活性化する方法ならびにこのプロテアーゼからなる医薬製剤に関する。

【背景技術】

【0002】

血液凝固系は、血漿中に存在する血液凝固因子を活性化する２つの異なるカスケード様経路から構成される。その誘導機構によって、内因系または外因系経路が血液凝固の開始に優先的に使用される。

【0003】

組織が傷害された場合、トロンボプラスチン（組織因子、ＴＦとリン脂質）が外因性凝血経路のスターターとして冒された細胞により暴露される。膜局在性のトロンボプラスチンは、血液凝固第VII因子（ＦVII）および循環する、活性化ＦVII（ＦVIIａ）の両者を結合することができる。カルシウムイオンおよび脂質の存在下に、このＴＦ－ＦVIIａ複合体はＦＸの結合を招き、これは限定された蛋白分解によってその活性化型（ＦＸａ）に変換される。続いてＦＸａはプロトロンビンを活性化してトロンビンを形成させることにより、フィブリンの形成を招来し、それによって最終的に創傷の閉鎖が起こる。

【0004】

トロンボプラスチン結合ＦVIIの更なる活性化は最初は自触反応によって起こるが、特に、凝血カスケードの開始後には、それはＦＸａおよびトロンビンによって支持され、特に反応カスケードの著しい強化を招くことになる。

【0005】

ＦVIIａまたはＦVIIａ含有濃縮物の投与はある種の臨床状態に適用されている。たとえば、血友病Ａに冒されＦVIII投与の結果としてＦVIIIに対する抗体が発生している患者で

は、ＦＶＩＩａのいわゆるＦＶＩＩＩ副経路活性（ＦＥＩＢＡ）が用いられる。現時点で分かっている所見によれば、ＦＶＩＩａはこの関係で十分な耐容性を有し、それは血栓傾向を生じることはなく、限られているが適切な程度の凝血が起こることを保証するのに適している。組換えＦＶＩＩａは既に治療的におよび予防的に使用されている。血漿から単離されたＦＶＩＩはまた、活性化されてから用いることもできる。トロンビンのようなプロテアーゼをこの活性化に使用できるが、しかしながら、これらのプロテアーゼは、それら自体凝血を強力に活性化することが可能で、血栓の危険を招くことがある。この理由から、以後のトロンビンの除去または不活性化が必要であり、損失を生じることになる。それに伴う血栓の危険の結果として、多くの場合、ＦＸａもしくはＦＩＩａ（トロンビン）の使用は禁忌とされ、緊急時、たとえば血液の著しい喪失および止血不能の出血の関連でのみ適用される。

【図面の簡単な説明】

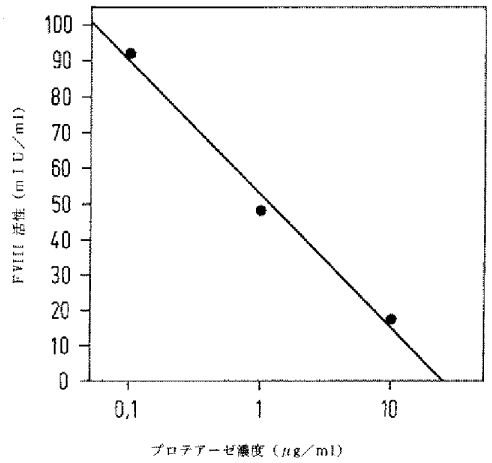
【0009】

【図1】プロテアーゼとＦＶＩＩＩを一定時間インキュベートした場合のプロテアーゼ濃度とＦＶＩＩＩの不活性化を示す。

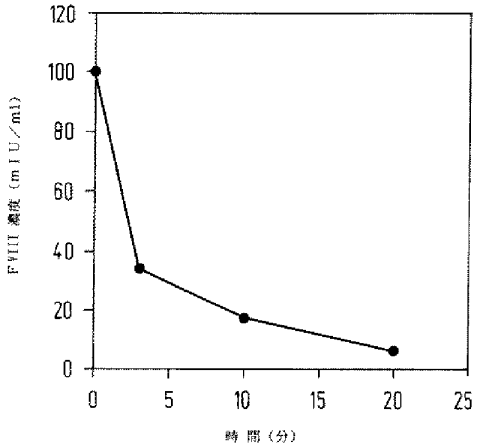
【図2】プロテアーゼ濃度を一定とし、ＦＶＩＩＩを様々な時間インキュベートした場合のＦＶＩＩＩの不活性化を示す。

【図3】プロテアーゼとＦＶＩＩＩを混合物中におけるカルシウム濃度を変動させインキュベートした場合のＦＶＩＩＩの不活性化を示す。

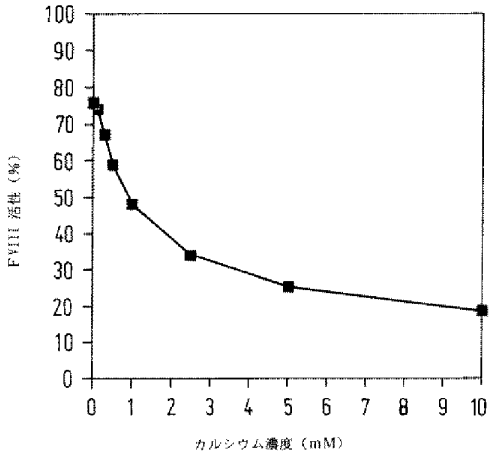
【図1】


100
90
80
70
60
50
40
30
20
10
0
FVIII 活性（mIU/ml）
0,1
1
10
プロテアーゼ濃度（μg/ml）

【図2】



【図3】


100
90
80
70
60
50
40
30
20
10
0
FVIII 活性（%）
0 1 2 3 4 5 6 7 8 9 10
カルシウム濃度（mM）

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Date
22.04.2024

Reference	Application No./Patent No.
KUR-008EP1	21818838.1 - 1122 / 4158303 PCT/US2021035294
Applicant/Proprietor	
Kurin, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the supplementary European search report (Art. 153(7) EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

Refund of the search fee
If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued shortly (R. 70(2) EPC).

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The examination is being carried out on the **following application documents**

Description, Pages

1-49 as published

Claims, Numbers

1-15 filed in electronic form on 01-09-2023

Drawings, Sheets

1/81-81/81 as published

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 5 December 2019 (2019-12-05)

D2 WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 21 March 2019 (2019-03-21)

1. The amendments filed with the letter dated 01-09-2023 introduce subject-matter which extend beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendments concerned are the following:

- removal of the features "**a displaceable plug between the inlet and the sample path that is displaced by the subsequent pressure differentials to allow the subsequent portions of the fluid to be conveyed through the sample path**" in claim 1.

Indeed these features appear to be described as essential throughout the original description and figures (see also claim 6 of the original application and Guidelines H-V. 3.1). Furthermore no alternatives for theses features are presented in the application as originally filed.

The applicant is invited to indicate where the basis for claim 1 can be found in the original application as filed.

Further amendments appear to be contrary to Article 123(2) EPC:

- features "**wherein the displaceable plug (3119) is hollowed out towards the sample path (3118) or hollowed out away from the sample path (3118)**" in claim 10

- features "**wherein the device (3100) is configured to allow a free flow of fluid from the inlet (3112) to the sample path (3118) when the displaceable plug (3119) moves into a receptacle**" in claim 15

No basis for these amendments could be found in the original application.

The applicant is invited to indicate where the basis for the dependent claims 10 and 15 as well as for the dependent claims 2-9 and 11-14 can be found in the original application as filed.

2. The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claim 1 is not new within the meaning of Article 54(1) and (2) EPC.

2.1 D1 discloses **a device** (see fig.11-14: 600;700) **comprising:**
an inlet (612);
an outlet (616);
a sample path (654;754) **connected between the inlet and the outlet;**
a chamber (614) **connected between the inlet and the outlet, the chamber having an air permeable fluid resistor** (615) **proximate the outlet** (see par.[0148]:"The flow controller 615 can be any suitable shape, size, and/or configuration and can be configured to selectively control, permit, allow, and/or transfer a flow of fluid therethrough. For example, as described above, the flow controller 615 can be a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid (e.g., bodily fluid)."), **the chamber being arranged to receive, when a pressure differential is applied between the inlet and the outlet, a first portion of a fluid sample to displace air therein through the air permeable fluid resistor and the outlet** (see par.[0158]:"Thus, when a negative pressure is generated within a portion of the device 700 (e.g., in response to coupling a fluid collection device to an outlet of the device 700), an initial volume of bodily fluid can flow into a sequestration chamber of the device 700 (e.g., a sequestration portion of the device 700, a sequestration flow path, a sequestration reservoir or container, etc.), as

described in detail above with reference to the device 600."), **with subsequent portions of the fluid sample conveyed by the sample path from the inlet to the outlet** (see par.[0160]:" Thus, a subsequent volume of bodily fluid that is substantially free of contaminants can flow through the device 700 and into the fluid collection device coupled thereto."); **and**
a displaceable plug (676;775) **which, when displaced, allows the subsequent portions of the fluid sample to be conveyed through the sample path.**

The subject-matter of claim 1 is therefore not new (Article 54(1) and (2) EPC).

2.2 Furthermore, the document D2 also disclose all the features of claim 1. For further details, see the relevant parts thereof as cited in the Search Report.

3. The dependent claims 2 to 15 seem not to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC in respect of novelty and/or inventive step, defining either features already known from any of D1-D2 or straightforward possibilities from which the person skilled in the art would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

4. The applicant **should bring the description into conformity** with the claims on file (Article 84 EPC). In particular should features that are present in the independent claim(s) not be referred to as options in the form of e.g. "in some instances", "in some embodiments", "in a preferred embodiment" and so forth, but be clearly identified as forming part of the invention. **This applies to the description as a whole**, not only to the introductory part. The "Summary of The Invention" should likewise be amended, i.e. recitation of superseded claims be removed or adapted to the wording of the new claims. Please also note that no method is claimed.

5. To meet the requirements of Rule 42(1)(b) EPC, the documents D1 and D2 should be identified in the description and the relevant background art disclosed therein should be briefly discussed, observing that references to the prior art introduced after filing must be purely factual.

6. In order to meet the requirements of Rule 43(1) EPC, the independent claim should be properly cast in the two-part form, with those features which in combination are part of the prior art being placed in the preamble (see Guidelines F-IV, 2.2). Arguments in support of inventive step should be presented in an accompanying letter.

If the applicant is of the opinion that a two-part form of claim would be inappropriate he is invited to provide reasons in his reply. In addition, the applicant should ensure that it is clear from the description which features of the subject-matter of the independent claim are known from the prior art (see Guidelines F-IV, 2.3.2).

7. The features of the claims should be provided with **reference signs placed in parentheses** to increase the intelligibility of the claims (Rule 43(7) EPC). This applies to both the preamble and characterising portion (see Guidelines F-IV, 4.19).

8. The vague and imprecise statements (e.g. "any modifications", "spirit of the invention") used in the description at paragraphs [0065],[0194],[0212] imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Article 84 EPC) when used to interpret them (see the Guidelines, F-IV, 4.4). These statements should therefore be amended to remove this inconsistency.

9. "Incorporation by reference" is not an option in the European procedure; the description thus requires amendments in this respect at paragraph [0001].

10. The unit inch expressed in paragraphs [0095],[0101],[0117],[0158] does not meet the requirements of Rule 49(10) EPC and should be replaced by the appropriate SI unit (see Guidelines F-II, Annex 2). The present expression should, however, be retained in parentheses after the replacement expression.

11. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage**, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).**

12. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should **clearly identify the amendments made**, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed on which these amendments are based (**see Guidelines H-IV**).

If the applicant considers it appropriate, these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

13. Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 123(2) EPC and the Guidelines H-V, 2.2 to 2.5).

14. Amendments should be made by filing replacement pages. Unnecessary recasting of the description should be avoided. An amended abstract is not required. The applicant should also take account of the requirements of Rule 50(1) EPC. According to Rule 50(1) in conjunction with Rule 49(8) EPC, amendments shall be typed or printed. Handwritten amendments may only be made in documents other than those replacing application documents (Rule 50(2) EPC); they may, for example, be used to fulfil the requirements of Rule 137(4) EPC (identifying amendments and indicating basis for them).

15. In order to expedite the procedure, the applicant is requested to deal with all of the raised objections and to **perform all necessary amendments along with the first response to this communication**.

Information on Search Strategy

The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number

EP 21 81 8838

TITLE: FLUID OPTIMIZATION AND CONTAMINANT CONTAINMENT DEVICE AND METHOD USING DISPLACEABLE PLUG

APPLICANT: Kurin, Inc.

IPC CLASSIFICATION: G01N1/10, G01N1/02, A61B5/15, A61B5/00, A61M39/00, A61M39/06, B01L3/00, G01N1/18, A61B5/154

EXAMINER: Coja, Michael

CONSULTED DATABASES: EPODOC, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B5/15003, A61B5/150213, A61B5/150221, A61B5/150251

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

EPO FORM P04A42

Europäisches Patentamt
European Patent Office
Office européen des brevets

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 21 81 8838

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 5 December 2019 (2019-12-05) * the whole document *	1-15	INV. G01N1/10 G01N1/02 A61B5/15 A61B5/00 A61M39/00 A61M39/06 B01L3/00 G01N1/18 A61B5/154
X	WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 21 March 2019 (2019-03-21) * paragraph [1070] - paragraph [1092]; figures 2-5 *	1-15	
A	US 2017/020427 A1 (ROGERS BOBBY E [US] ET AL) 26 January 2017 (2017-01-26) * the whole document *	1-15	
A	US 2018/353117 A1 (BULLINGTON GREGORY J [US] ET AL) 13 December 2018 (2018-12-13) * the whole document *	1-15	
A	US 2019/175087 A1 (BULLINGTON GREGORY J [US] ET AL) 13 June 2019 (2019-06-13) * the whole document *	1-15	TECHNICAL FIELDS SEARCHED (IPC) A61B
A	US 2008/145933 A1 (PATTON RICHARD G [US]) 19 June 2008 (2008-06-19) * the whole document *	1-15	

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
The Hague	10 April 2024	Coja, Michael

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

2

EPO FORM 1503 03.82 (P04C04)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 21 81 8838

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 21 81 8838

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China National Intellectual Property Administration

Room 503, 5.F, Building 8/Sinotrans Tower A, No. 5, Anding Road, Chaoyang District, Beijing 100029, PR China Beijing Pat SF Intellectual Property Agency Co Ltd	Issue date: April 28, 2024

Application No.: 202080000666.0 Issue serial No.: 2024042801618990

Applicant（s）: KURIN, INC.

Title of invention-creation: NON-VENTING BODILY FLUID SAMPLE OPTIMIZATION DEVICE AND SYSTEM

Second Office Action

1 ☒ The observations submitted by the applicant were received on February 5, 2024, on the basis of which the examiner has continued the substantive examination for the above-identified patent application.

☐ On the basis of the reexamination decision made by the reexamination board of the China National Intellectual Property Administration on _____, the examiner has continued the substantive examination for the above-identified patent application.

☐ _____

2 ☐ The amended document submitted by the applicant on _____ is not in conformity with the provisions of Rule 57.3 of the Implementing Regulations of the Patent Law, and the amended document has not been accepted.

3 Continuation of examination has been conducted based on the following documents:

☐Amended application document(s) attached to the above-identified observations.

☒Application document(s) at which the previous Office Action is directed, and the replacement sheet(s) of the amended application document(s) attached to the above-identified observations.

☐Application document(s) at which the previous Office Action is directed.

☐Application document(s) confirmed in the above-identified Reexamination Decision.

☐ _____

4 ☒ No new reference document is cited in this Office Action.

☐ The following reference document(s) has/have been cited in this notification. (its/their serial number(s) shall come after those previously cited and will be referred to in the following examination procedure):

Serial No.	Number or title of reference document(s)	Publication date (or filing date of conflict patent application)
2	US 2018297303A1	20181018

5 The conclusion of the examination:

In regard to the Description:

☐The subject matter of the application belongs to the objects mentioned in Article 5 of the Patent Law, for which no patent right shall be granted.

☐The description is not in conformity with the provisions of Article 26.3 of the Patent Law.

☐The amendment of the description is not in conformity with the provisions of Article 33 of the Patent Law.

☐The description is not in conformity with the provisions of Rule 20 of Implementing Regulations of the Patent Law.

☐_____

In regard to the Claims:

☐ Claims_____are not in conformity with the provisions of Article 2.2 of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Article 9.1 the Patent Law.

☐ Claims___do not possess the novelty under Article 22.2 of the Patent Law.

☒ Claims__1-13____do not possess the inventiveness under Article 22.3 of the Patent Law.

☐ Claims_____do not possess the practical applicability under Article 22.4 of the Patent Law.

☐ Claims_____ belong to the objects mentioned in Article 25 of the Patent Law, for which no patent right shall be granted.

☐ Claims_____are not in conformity with the provisions of Article 26.4 of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Article 31.1 of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Article 33 of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Rule 22 of the Implementing Regulations of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Rule 23 of the Implementing Regulations of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Rule 24 of the Implementing Regulations of the Patent Law.

☐ Claims_____are not in conformity with the provisions of Rule 25 of the Implementing Regulations of the Patent Law.

☐_____

☐ The application is not in conformity with the provisions of Article 26.5 of the Patent Law or with the provisions of Rule 29 of Implementing Regulations of the Patent Law.

☐ The application is not in conformity with the provisions of Article 19.1 of the Patent Law.

☐ The application is not in conformity with the provisions of Rule 11 of Implementing Regulations of the Patent Law.

☐ The division application is not in conformity with the provisions of Rule 49.1 of Implementing Regulations of the Patent Law.

The explanation of the conclusion is given in the text of the Office Action in details.

6 According to the above conclusion, the examiner deems that:

☐ The applicant shall amend the application documents as required by the text of Office Action.

☐ The applicant shall state the reason why the application can be accepted and amend the part that is indicated not to be in conformity with the provisions, otherwise the application will be rejected.

☒ The present application will be finally rejected if there is still indicated defect in the Observation and Text as filed

7 The applicant shall pay attention to the following items:

(1) In accordance with the provisions of Article 37 of the Patent Law, the applicant shall submit the observations within **2** months from the date of receiving this notification. If the applicant, without any justified reason, fails to reply within the time limit, the application shall be deemed to have been withdrawn.

(2) The amendments to the application made by the applicant shall be in conformity with the provisions of Article 33 of the Patent Law and shall not go beyond the disclosure scope of the initial description and claims. Meanwhile the amendments to the application made by the applicant shall be in conformity with the provisions of Rule 51.3 of the Implementing Regulations of the Patent Law and the applicant can amend the application according to this notification.

(3) Any observation and/or amended text shall be mailed or sent by hand to the Receiving Division of the Patent Office. Any document that is not mailed or sent by hand to the Receiving Division does not have legal effect.

(4) The applicant and/or his agent shall not go to the Patent Office to hold an interview with the examiner if no interview is arranged in advance.

8 The text of the notification embraces __7__ pages, along with the enclosures herein:

☐____Copy of the cited references is enclosed in pages of _____.

☐_____

Examiner: Examining Department:

Tel:

210403 With regard to the paper application, Mail to: 100088, 6 Xitucheng Road, Jimen Bridge, Haidian District, Beijing, China

2010.2 With regard to the electronic application, the relevant documents shall be filed in the form of electronic documents through the electronic system of patent application. The application documents filed by paper or other forms are deemed not to have been submitted unless there are particular provisions.

Text of the Second Office Action

Application number: 2020800006660

The Applicant submitted observations and amended application document on 5 February 2024. After reading said documents, the Examiner continues to examine the present case and further raises the following examination opinions.

I. Regarding amended claims

(*Translator's note: the comments on dependent claims 2-4, 6-9, 11-13 are substantively the same as those on claims 2-4, 7-9, 13, 16-18 raised in the First Office Action, and therefore we have refrained from translating the same so as to save the cost.*)

1. Claim 1 does not comply with the provision under Article 22.3[1] of the Patent Law.

Claim 1 seeks to protect a device for optimizing a fluid sample collected by a fluid collection device from a fluid source. Reference 1 (US2018/0271425A1) discloses a fluid sample optimization device, specifically, a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source (equivalent to: device for optimizing a fluid sample collected by a fluid collection device from a fluid source), and in particular discloses the following (see paragraphs [0141] to [0149] of the description, and FIGS. 23A-23B of the description):

A blood sequestration device 2300 in another implementation, having an inlet

[1] Article 22.3 Inventiveness means that, as compared with the prior art, the invention possesses prominent substantive features and represents a notable progress and that the utility model possesses substantive features and represents a progress.

port 2302 to connect with a patient needle (equivalent to: an inlet configured to connect with the fluid source), an outlet port 2304 to connect with a blood sample collection device (equivalent to: an outlet configured to connect with the fluid collection device), a sequestration chamber 2306, and a sampling channel 2308 (equivalent to: a sample path). Once the sequestration chamber 2306 (equivalent to: a chamber) is filled to an initial aliquot of potentially contaminated blood to be sequestered, the sequestration chamber 2306 is filled.

The sequestration chamber 2306 includes a hydrophobic plug 2312 at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302 (equivalent to: the chamber having a fluid resistor proximate the outlet).

A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there (equivalent to: the chamber being arranged to receive, when a pressure differential is applied between the inlet and the outlet, a first portion of the fluid sample from the fluid source). It could be clear that a first portion of the blood sample in Reference 1 potentially has contaminants.

A small amount of blood may make its way into the sampling channel 2308, which is initially closed off by valve 2308.

Upon release of the valve 2308, and under further force of the vacuum or other force (equivalent to: subsequent pressure differentials are applied), follow-on amounts of blood (equivalent to: the fluid sample) will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 (equivalent to: a sample path connected between the inlet and

the outlet) toward the outlet port 2304 and to the collection device (equivalent to: such that upon receipt of the first portion of the fluid sample in the chamber, subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet).

A small amount of blood may make its way into the sampling channel 2308 (equivalent to: sample path), which is initially closed off by valve 2308 (equivalent to: resistive plug) (equivalent to: the sample path further having a resistive plug).

The distinguishing technical features of the technical solution claimed by claim 1 over Reference 1 are: (1) the fluid resistor is air permeable, and "to displace air therein through the air permeable fluid resistor and the outlet"; (2) the resistive plug including a membrane that is pierceable, and a piercing member configured to pierce the membrane, wherein the device is configured such that, once the chamber fills with the first portion of the fluid sample, pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member.

With regard to the above distinguishing technical feature (1): as has been recorded in Reference 1, [a] vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. Therefore, in order to allow the blood to be drawn into sequestration chamber 2306 under the action of vacuum, it would not be difficult for those skilled in the art to envisage that the specific hydrophobic plug 2312 is air permeable and to ensilage displacing air therein through the air permeable fluid resistor and the outlet.

With regard to the above distinguishing technical feature (2): Reference 2 (US2018297303A1, 20181018) discloses a puncture repair liquid holding container, and in particular discloses (see the claims, the description, paragraphs [0024]-[0041], and Figs. 1-5): the tube is provided with a sealing film (equivalent to: membrane) that blocks inflow of the puncture repair liquid to the second flow channel, and a closed condition where the sealing film blocks (equivalent to: the resistive plug including a membrane that is pierceable) the second flow channel can be switched to an opened condition where the sealing film is broken by container internal pressure such that the second flow channel is opened; comprising a piercing mechanism for breaking the sealing film on an inner portion of the tube; the piercing mechanism 63 (equivalent to: a piercing member) does not contact the sealing film 61 during storage, but contacts the sealing film 61 when the container internal pressure is increased during puncture repair work and the sealing film 61 bulges toward an inner portion of the tube 60 (equivalent to: pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member), such that the sealing film 61 breaks (equivalent to: a piercing member configured to pierce the membrane, the resistive plug including a membrane that is pierceable and a piercing member). Accordingly, Reference 2 provides enabling the sealing film to stretch or bulge when the pressure increases, further causing the piercing mechanism to contact the sealing film, making the sealing film break and the second flow channel to open. This is the same as the function in the present application, and when confronted with the same technical problem, a person skilled in the art can envisage applying the same to Reference 1. When specifically applying said means to Reference 1, the person skilled in the art has ability to configure the device to exert pressure against the membrane causing the membrane to stretch and contact the piercing member once the chamber fills with the first portion of the fluid sample.

It would be obvious for those skilled in the art to obtain the technical solution claimed by claim 1 based on Reference 1 in combination with Reference 2 and conventional technical means in the art. Therefore, the technical solution claimed by claim 1 neither has any prominent substantive feature nor represents a notable progress, and thus does not possess inventiveness prescribed under Article 22.3 of the Patent Law.

3. Claim 5 does not comply with the provision under Article 22.3 of the Patent Law.

Claim 5 seeks to protect a device for optimizing a fluid sample collected by a fluid collection device from a fluid source. Reference 1 discloses a fluid sample optimization device, especially for optimizing a fluid sample collected by a fluid collection device from a fluid source (equivalent to: a device for optimizing a fluid sample collected by a fluid collection device from a fluid source), and in particular discloses the following (see paragraphs [0141] to [0149] of the description, and FIGS. 23A-23B of the description):

A blood sequestration device 2300 in another implementation, having an inlet port 2302 to connect with a patient needle (equivalent to: an inlet configured to connect with the fluid source), an outlet port 2304 to connect with a blood sample collection device (equivalent to: an outlet configured to connect with the fluid collection device), a sequestration chamber 2306, and a sampling channel 2308 (equivalent to: a sample path). Once the sequestration chamber 2306 (equivalent to: a chamber) is filled to an initial aliquot of potentially contaminated blood to be sequestered, the sequestration chamber 2306 is filled. As it is clear in combination with FIG. 23A of the description, the sequestration chamber 2306 is disposed between the inlet and the outlet (equivalent to: a chamber connected between the inlet and the outlet).

The sequestration chamber 2306 includes a hydrophobic plug 2312 (equivalent to: a fluid resistor) at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302 (equivalent to: a fluid resistor, the chamber further having a fluid resistor proximate the outlet).

A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood (equivalent to: a first portion of the fluid sample) will contact the hydrophobic plug 2312 (equivalent to: the fluid resistor) and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there (equivalent to: the chamber being arranged to receive the first portion of the fluid sample from the fluid source). It could be clear that a first portion of the blood sample in Reference 1 potentially has contaminants. Receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir could be determined with respect to Reference 1.

A small amount of blood may make its way into the sampling channel 2308 (equivalent to: a sample path), which is initially closed off by valve 2310 (equivalent to: a resistive plug) (equivalent to: the sample path further having a resistive plug that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path).

Upon release of the valve 2310, and under further force of the vacuum or other force, follow-on amounts of blood (equivalent to: the fluid sample) will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 (equivalent to: a sample path connected between the inlet and the outlet) toward the outlet port 2304 and to the collection device (equivalent to: such that upon receipt of the first portion of the fluid sample in the chamber, subsequent portions of the fluid sample can be forced

through the resistive plug and conveyed by the sample path from the inlet to the outlet).

The distinguishing technical features of the technical solution claimed by claim 5 over Reference 1 are: (1) the fluid resistor is air permeable to displace air therein through the air permeable fluid resistor and the outlet; (2) the resistive plug including a membrane that is pierceable, and a piercing member configured to pierce the membrane, wherein the device is configured such that, once the chamber fills with the first portion of the fluid sample, pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member.

With regard to the above distinguishing technical feature (1): as has been recorded in Reference 1, [a] vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. Therefore, in order to allow the blood to be drawn into sequestration chamber 2306 under the action of vacuum, it would not be difficult for those skilled in the art to envisage that the specific hydrophobic plug 2312 is air permeable and to ensilage displacing air therein through the air permeable fluid resistor and the outlet.

With regard to the above distinguishing technical feature (2): Reference 2 (US2018297303A1, 20181018) discloses puncture repair liquid holding container, and in particular discloses (see the claims, the description, paragraphs [0024]-[0041], and Figs. 1-5): the tube is provided with a sealing film (equivalent to: membrane) that blocks inflow of the puncture repair liquid to the second flow channel, and a closed condition where the sealing film blocks

(equivalent to: the resistive plug including a membrane that is pierceable) the second flow channel can be switched to an opened condition where the sealing film is broken by container internal pressure such that the second flow channel is opened; comprising a piercing mechanism for breaking the sealing film on an inner portion of the tube; the piercing mechanism 63 (equivalent to: a piercing member) does not contact the sealing film 61 during storage, but contacts the sealing film 61 when the container internal pressure is increased during puncture repair work and the sealing film 61 bulges toward an inner portion of the tube 60 (equivalent to: pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member), such that the sealing film 61 breaks (equivalent to: a piercing member configured to pierce the membrane, the resistive plug including a membrane that is pierceable and a piercing member). Accordingly, Reference 2 provides enabling the sealing film to stretch or bulge when the pressure increases, further causing the piercing mechanism to contact the sealing film, making the sealing film break and the second flow channel to open. This is the same as the function in the present application, and when confronted with the same technical problem, a person skilled in the art can envisage applying the same to Reference 1. When specifically applying said means to Reference 1, the person skilled in the art has ability to configure the device to exert pressure against the membrane causing the membrane to stretch and contact the piercing member once the chamber fills with the first portion of the fluid sample.

It would be obvious for those skilled in the art to obtain the technical solution claimed by claim 5 based on Reference 1 in combination with Reference 2 and conventional technical means in the art. Therefore, the technical solution claimed by claim 5 neither has any prominent substantive feature nor represents a notable progress, and thus does not possess inventiveness prescribed under Article 22.3 of the Patent Law.

5. Claim 10 does not comply with the provision under Article 22.3 of the Patent Law.

Claim 10 seeks to protect a fluid sample optimization device for optimizing a fluid sample. Reference 1 discloses a fluid sample optimization device, specifically an optimization device for optimizing a fluid sample (equivalent to: an optimization device for optimizing a fluid sample), and in particular discloses (see paragraphs [0141] to [0149] of the description, and FIGS. 23A-23B of the description):

[Y]et another implementation of a blood sequestration device 2300, having an inlet port 2302 to connect with a patient needle (equivalent to: an inlet), an outlet port 2304 to connect with a blood sample collection device (equivalent to: an outlet), a sequestration chamber 2306, and a sampling channel 2308 (equivalent to: a sample path). Once the sequestration chamber 2306 (equivalent to: a chamber) is filled to an initial aliquot of potentially contaminated blood to be sequestered, the sequestration chamber 2306 is filled. As it is clear in combination with FIG. 23A of the description, the sequestration chamber 2306 is disposed between the inlet and the outlet (equivalent to: a chamber connected between the inlet and the outlet). The sample path is disposed between the inlet and the outlet (equivalent to: a sample path connected between the inlet and the outlet).

The sequestration chamber 2306 includes a hydrophobic plug 2312 (equivalent to: a fluid resistor) at a distal end of the sequestration chamber 2306 that is farthest from the inlet port 2302 (equivalent to: a fluid resistor, the chamber having an air permeable fluid resistor proximate the outlet).

A vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into

the sequestration chamber 2306, where the initial aliquot of blood (equivalent to: a first portion of the fluid sample) will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there (equivalent to: the chamber being arranged to receive a first portion of the fluid sample). It could be clear that a first portion of the blood sample in Reference 1 potentially has contaminants. It can be determined to receive the first portion of the fluid sample in the chamber in Reference 1.

A small amount of blood may make its way into the sampling channel 2308 (equivalent to: a sample path), which is initially closed off by valve 2310.

Upon release of the valve 2310 (equivalent to: a resistive plug, the sample path further includes a resistive plug), and under further force of the vacuum or other force (equivalent to: subsequent pressure differentials are applied), follow-on amounts of blood (equivalent to: the fluid sample) will flow into inlet port 2302, bypass the sequestration chamber 2306, and flow into and through sampling channel 2308 toward the outlet port 2304 and to the collection device (equivalent to: upon receipt of the first portion of the fluid sample in the chamber, subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet). It can be determined by the person skilled in the art that Reference 1 discloses: a resistive plug that is configured to inhibit at least a part of the first portion of the fluid sample from entering the sample path during receipt of the first portion of the fluid sample in the chamber.

The distinguishing technical features of the technical solution claimed by claim 10 over Reference 1 are: (1) the fluid resistor is air permeable to displace air therein through the air permeable fluid resistor and the outlet; (2) the resistive plug including a membrane that is pierceable, and a piercing member configured to pierce the membrane, wherein the device is configured such that,

once the chamber fills with the first portion of the fluid sample, pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member.

With regard to the above distinguishing technical feature (1): as has been recorded in Reference 1, [a] vacuum or other drawing force applied from the outlet port 2304, such as from a Vacutainer or the like, draws in blood into the inlet port 2302 and directly into the sequestration chamber 2306, where the initial aliquot of blood will contact the hydrophobic plug 2312 and cause the initial aliquot of blood to back up into the sequestration chamber 2306 and be sequestered there. Therefore, in order to allow the blood to be drawn into sequestration chamber 2306 under the action of vacuum, it would not be difficult for those skilled in the art to envisage that the specific hydrophobic plug 2312 is air permeable and to ensilage displacing air therein through the air permeable fluid resistor and the outlet.

With regard to the above distinguishing technical feature (2): Reference 2 (US2018297303A1, 20181018) discloses puncture repair liquid holding container, and in particular discloses (see the claims, the description, paragraphs [0024]-[0041], and Figs. 1-5): the tube is provided with a sealing film (equivalent to: membrane) that blocks inflow of the puncture repair liquid to the second flow channel, and a closed condition where the sealing film blocks (equivalent to: the resistive plug including a membrane that is pierceable) the second flow channel can be switched to an opened condition where the sealing film is broken by container internal pressure such that the second flow channel is opened; comprising a piercing mechanism for breaking the sealing film on an inner portion of the tube; the piercing mechanism 63 (equivalent to: a piercing member) does not contact the sealing film 61 during storage, but contacts the sealing film 61 when the container internal pressure is increased during puncture repair work and the sealing film 61 bulges toward an inner portion of

the tube 60 (equivalent to: pressure is exerted against the membrane causing the membrane to stretch and contact the piercing member), such that the sealing film 61 breaks (equivalent to: a piercing member configured to pierce the membrane, the resistive plug including a membrane that is pierceable and a piercing member). Accordingly, Reference 2 provides enabling the sealing film to stretch or bulge when the pressure increases, further causing the piercing mechanism to contact the sealing film, making the sealing film break and the second flow channel to open. This is the same as the function in the present application, and when confronted with the same technical problem, a person skilled in the art can envisage applying the same to Reference 1. When specifically applying said means to Reference 1, the person skilled in the art has ability to configure the device to exert pressure against the membrane causing the membrane to stretch and contact the piercing member once the chamber fills with the first portion of the fluid sample.

It would be obvious for those skilled in the art to obtain the technical solution claimed by claim 10 based on Reference 1 in combination with Reference 2 and conventional technical means in the art. Therefore, the technical solution claimed by claim 10 neither has any prominent substantive feature nor represents a notable progress, and thus does not possess inventiveness prescribed under Article 22.3 of the Patent Law.

II. Regarding the observations submitted by the Applicant:

The Applicant primarily holds the following opinions.

Reference 1 does not disclose the piercing member configured to pierce the membrane.

The present invention detailedly depicts the above technical feature and

operation principle thereof by reference to Figs. 9A-9C. The pierceable membrane 702 is spaced apart from the piercing member 704, the membrane 702 can be an elastic sheet of material, such as a rubber or other elastomeric material. As shown in FIG. 9C, once the contaminant containment reservoir fills with fluid, an amount of pressure is exerted against the membrane 702 to stretch it further to contact the piercing member 704. Once contact is made between the membrane 702 and the piercing member 704, the membrane 702 is punctured or otherwise broken by the piercing member 704 to open a larger area for subsequent amounts or portions of fluid to flow into the sample path (paragraph [0086] (*Translator's note: corresponding to paragraph [0082] of the description of WO2020206047A1, from which the present application is derived*)). Accordingly, the device of claim 1 prevents accumulation of contaminant in the collected blood sample, thereby avoiding the false positive test result caused by contaminants in blood samples.

Taking the Applicant's observations into full consideration, the Examiner sets forth the following responses.

Although Reference 1 does not disclose a piercing member configured to pierce the membrane, Reference 2 (US2018297303A1, 20181018) discloses puncture repair liquid holding container, and in particular discloses (see the claims, the description, paragraphs [0024]-[0041], and Figs. 1-5): the tube is provided with a sealing film that blocks inflow of the puncture repair liquid to the second flow channel, and a closed condition where the sealing film blocks the second flow channel can be switched to an opened condition where the sealing film is broken by container internal pressure such that the second flow channel is opened; comprising a piercing mechanism for breaking the sealing film on an inner portion of the tube; the piercing mechanism 63 does not contact the sealing film 61 during storage, but contacts the sealing film 61 when the container internal pressure is increased during puncture repair work and the

sealing film 61 bulges toward an inner portion of the tube 60, such that the sealing film 61 breaks. Accordingly, Reference 2 provides enabling the sealing film to stretch or bulge when the pressure increases, further causing the piercing mechanism to contact the sealing film, making the sealing film break and the second flow channel to open. This is the same as the function in the present application, and when confronted with the same technical problem, a person skilled in the art can envisage applying the same to Reference 1.

For the above reasons, neither the independent claims nor the dependent claims of the present application possess inventiveness. Meanwhile, the description does not contain any other patentable substantive contents. Therefore, the present application does not have a prospect of grant even if the Applicant would recombine and/or further define the claims according to the contents disclosed in the description. The present application will be finally rejected if the Applicant cannot present sufficient reasons as to why the present application possesses inventiveness within the time limit for response specified in the present office action.

Examiner: Yuanyuan LI

Code: 30110854

国 家 知 识 产 权 局

100088

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卓霖(010-82800919) 许向彤(010-82800919)

发文日：

2024 年 04 月 28 日

申请号：202080000666.0 **发文序号：** 2024042801618990

申请人： 酷睿有限公司

发明创造名称： 非排气机体流体样品优化装置和系统

第 二 次 审 查 意 见 通 知 书

1.☒审查员已经收到申请人于 2024 年 02 月 05 日提交的意见陈述书，在此基础上审查员对上述专利申请继续进行实质审查。

☐根据国家知识产权局于_____年_____月_____日作出的复审决定，审查员对上述专利申请继续进行实质审查。

☐_____

2.☐经审查，申请人于_____提交的修改文件，不符合专利法实施细则第 57 条第 3 款的规定，不予接受。

3.继续审查是针对下列申请文件进行的：

☐上述意见陈述书中所附的经修改的申请文件。

☒前次审查意见通知书所针对的申请文件以及上述意见陈述书中所附的经修改的申请文件替换文件。

☐前次审查意见通知书所针对的申请文件。

☐上述复审决定所确定的申请文件。

☐_____

4.☐本通知书未引用新的对比文件。

☒本通知书引用下列对比文件(其编号续前，并在今后的审查过程中继续沿用)：

编号	文 件 号 或 名 称	公开日期（或抵触申请的申请日）
2	US 2018297303A1	20181018

5.审查的结论性意见：

关于说明书：

☐申请的内容属于专利法第 5 条规定的不授予专利权的范围。

☐说明书不符合专利法第 26 条第 3 款的规定。

☐说明书的修改不符合专利法第 33 条的规定。

☐说明书的撰写不符合专利法实施细则第 20 条的规定。

☐_____

关于权利要求书：

☐权利要求_____不符合专利法第 2 条第 2 款的规定。
☐权利要求_____不符合专利法第 9 条第 1 款的规定。
☐权利要求_____不具备专利法第 22 条第 2 款规定的新颖性。
☒权利要求 1-13 不具备专利法第 22 条第 3 款规定的创造性。
☐权利要求_____不具备专利法第 22 条第 4 款规定的实用性。
☐权利要求_____属于专利法第 25 条规定的不授予专利权的范围。
☐权利要求_____不符合专利法第 26 条第 4 款的规定。
☐权利要求_____不符合专利法第 31 条第 1 款的规定。
☐权利要求_____的修改不符合专利法第 33 条的规定。
☐权利要求_____不符合专利法实施细则第 22 条的规定。
☐权利要求_____不符合专利法实施细则第 23 条的规定。
☐权利要求_____不符合专利法实施细则第 24 条的规定。
☐权利要求_____不符合专利法实施细则第 25 条的规定。
☐_____

☐申请不符合专利法第 26 条第 5 款或者实施细则第 29 条的规定。
☐申请不符合专利法第 19 条第 1 款的规定。
☐申请不符合专利法实施细则第 11 条的规定。
☐分案申请不符合专利法实施细则第 49 条第 1 款的规定。
上述结论性意见的具体分析见本通知书的正文部分。

6.基于上述结论性意见，审查员认为：
☐申请人应当按照通知书正文部分提出的要求，对申请文件进行修改。
☐申请人应当在意见陈述书中论述其专利申请可以被授予专利权的理由，并对通知书正文部分中指出的不符合规定之处进行修改，否则将不能授予专利权。
☒专利申请中没有可以被授予专利权的实质性内容，如果申请人没有陈述理由或者陈述理由不充分，其申请将被驳回。
☐_____

7.申请人应注意下列事项：

（1）根据专利法第 37 条的规定，申请人应在收到本通知书之日起的 2 个月内陈述意见，如果申请人无正当理由逾期不答复，其申请被视为撤回。

（2）申请人对其申请的修改应当符合专利法第 33 条的规定，不得超出原说明书和权利要求书记载的范围，同时申请人对专利申请文件进行的修改应当符合专利法实施细则第 57 条第 3 款的规定，按照本通知书的要求进行修改。

（3）申请人的意见陈述书和/或修改文本应当邮寄或递交国家知识产权局专利局受理处，凡未邮寄或递交给受理处的文件不具备法律效力。

（4）未经预约，申请人和/或代理师不得前来国家知识产权局与审查员举行会晤。

8. 本通知书正文部分共有 7 页，并附有下列附件：
☐引用的对比文件的复印件共_____份_____页。
☐_____

审查员：李媛媛　　联系电话：0371-87791927　　审查部门：专利审查协作河南中心

第 二 次 审 查 意 见 通 知 书

申请号:2020800006660

申请人于 2024 年 2 月 5 日提交了意见陈述书和经过修改的申请文件，审查员在阅读了上述文件后，对本案继续进行审查，再次提出如下审查意见。

一、针对修改后的权利要求书

1. 权利要求 1 不符合专利法第 22 条第 3 款的规定

权利要求 1 请求一种用于优化由流体收集装置从流体源收集的流体样品的装置，对比文件 1(US2018/0271425A1)公开了一种流体样品优化装置，具体的用于优化由流体收集装置从流体源收集流体样品(相当于一种用于优化由流体收集装置从流体源收集的流体样品的装置)，并具体公开了(参见说明书第 0141-0149 段，说明书附图 23A-23B)：

血液隔离装置 2300 的又一实施方式，其具有与患者针连接的入口端口 2302(相当于被配置为与所述流体源连接的入口)、与血液样本收集装置连接的出口端口 2304(相当于被配置为与流体收集装置接触的出口)、隔离室 2306 和旁路的采样通道 2308(相当于样品路径)。一旦隔离室 2306(相当于腔室)被填充至待隔离的潜在污染血液的初始等分部分，则隔离室 2306 被填充。

隔离室 2306 包括在隔离室 2306 的距入口 2302 最远的远端处的疏水塞 2312(相当于腔室在所述出口附近具有流阻器)。

从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里(相当于当入口和出口之间施加压差时，所述腔室被布置为从所述流体源接收所述流体样品的第一部分)。可以明确对比文件 1 中血液的第一部分潜在地具有污染物。

少量血液可以进入采样通道 2308，采样通道 2308 最初被阀 2308 关闭。

当释放阀 2308 时，并且在进一步的真空力或其他力的作用下(相当于施加后续压差)，后续量的血液(相当于流体样品)将流入入口端口 2302，绕过隔离室 2306，并且流入并穿过采样通道 2308(相当于连接在所述入口和所述出口之间的样品路径)朝向出口端口 2304 并至收集装置(相当于使得当腔室接收到流体样品的第一部分时，所述流体样品的后续部分能够由所述样品路径从所述入口传送到所述出口)。

少量血液可以进入采样通道 2308(相当于样品路径)，采样通道 2308 最初被阀 2310(相当于阻力塞)关闭(相当于样品路径还具有阻力塞)。

权利要求 1 请求保护的技术方案与对比文件 1 相比，其区别技术特征为：(1)流阻器为透气的，通过所述透气的流阻器和所述出口置换其中的空气；(2)所述阻力塞包括可刺穿的膜和刺穿构件，该刺穿构件被配置为刺穿所述膜，其中，所述装置被配置为使得一旦所述腔室填充有所述流体样品的所 20 述第一部分，则在所

述膜上施加压力使得所述膜拉伸并接触所述刺穿构件。

针对上述区别技术特征(1)：对比文件 1 中已经记载了从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离空 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离空 2306 中并被隔离在那里流阻隔器；因此为了使得血液能在真空的作用下使得被吸入隔离空 2306，具体的疏水塞 2312 为透气的，通过透气的流阻器和所述出口置换其中的空气是本领域技术人员不难想到的。

针对上述区别技术特征(2)：对比文件 2（US2018297303A1，20181018）公开了一种刺破修补液盛装容器，并具体记载了(参见权利要求书，说明书第 0024-0041 段，说明书附图 1-5)管设置有阻挡所述穿孔修复液流入所述第二流动通道的密封膜(相当于膜)， 并且其中密封膜阻塞(相当于阻力塞包括可刺穿的膜)第二流动通道的闭合状态可以切换到其中密封膜被容器内部压力破坏使得第二流动通道打开的打开状态。包括刺穿机构，所述刺穿机构用于破坏所述管的内部部分上的所述密封膜。刺穿机构 63a(相当于刺穿构件)在储存期间也不接触密封膜 61，但是当在刺穿修复工作期间容器内部压力增加并且密封膜 61 朝向管 60 的内部凸出时，刺穿部分 63b 接触密封膜 61(相当于在膜上施加压力使得所述膜拉伸并接触所述刺穿构件)，使得密封膜 61 破裂(相当于该刺穿构件被配置为刺穿所述膜，阻力塞包括可刺穿的膜和刺穿构件)。因此，对比文件 2 给出了在压力增加时，可以使得密封膜拉伸或凸出，进而使得穿刺机构接触密封膜，进而使得密封膜破裂，第二流动通道打开。这与本申请的作用相同，在面对相同的技术问题时，本领域技术人员能够想到将其应用于对比文件 1 中。具体的应将该手段应用于对比文件 1 中时，装置被配置为使得一旦腔室填充有流体样品的第一部分，则在膜上施加压力使得膜拉伸并接触刺穿构件对于本领域技术人员来说是有能力做到的。

因此，在对比文件 1 的基础上结合对比文件 2 及本领域常规的技术手段，得出该权利要求的技术方案对本技术领域的技术人员来说是显而易见的，因此该权利要求所要求保护的技术方案不具有突出的实质性特点和显著的进步，该权利要求不具备专利法第二十二条第三款规定的创造性。

2. 权利要求 2-4 不符合专利法第 22 条第 3 款的规定

权利要求 2-4 对其引用的权利要求作了进一步限定。在对比文件 1 的基础上根据需要，设置外壳，该外壳容纳和/或限定所述入口、所述出口、所述样品路径和所述腔室中的一个或多个是本领域技术人员有能力选择的；

对比文件 1 中记载了隔离空 2306 包括在隔离空 2306 的距入口 2302 最远的远端处的疏水塞 2312，从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离空 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离空 2306 中并被隔离在那里(相当于透气的流阻器包括与所述流体样品的第一部分接触时密封的材料)；

在对比文件 1 的基础上，根据需要可以选择腔室包括曲折路径；

因此，当其引用的权利要求不具备创造性时，权利要求 2-4 不具有突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

3. 权利要求 5 不符合专利法第 22 条第 3 款的规定

权利要求 5 请求一种用于优化由流体收集装置从流体源收集的流体样品的装置，对比文件 1 公开了一种流体样品优化装置，具体的用于优化由流体收集装置从流体源收集流体样品(相当于一种用于优化由流体收集装置从流体源收集的流体样品的装置)，并具体公开了(参见说明书第 0141-0149 段，说明书附图 23A-23B)：

血液隔离装置 2300 的又一实施方式，其具有与患者针连接的入口端口 2302(相当于被配置为与所述流体源连接的入口)、与血液样本收集装置连接的出口端口 2304(相当于被配置为与流体收集装置接触的出口)、隔离室 2306 和旁路的采样通道 2308(相当于样品路径)。一旦隔离室 2306(相当于腔室)被填充至待隔离的潜在污染血液的初始等分部分，则隔离室 2306 被填充，结合说明书附图 23A 可以明确隔离室 2306 设置在入口和出口之间(相当于连接在所述入口和所述出口之间的腔室)。

隔离室 2306 包括在隔离室 2306 的距入口 2302 最远的远端处的疏水塞 2312(相当于流阻器，相当于腔室在所述出口附近还具有流阻器)。

从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样(相当于流体样品的第一部分)将接触疏水塞 2312（相当于流阻器）并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里(相当于腔室被布置为从所述流体源接收所述流体样品的第一部分)。可以明确对比文件 1 中血液的第一部分潜在地具有污染物。可以确定对比文件 1 中接收到流体样品的第一部分并将污染物容纳在所述污染物容纳储库中。

少量血液可以进入采样通道 2308(相当于样品路径)，采样通道 2308 最初被阀 2310(相当于阻力塞)关闭(相当于样品路径还具有阻力塞，该阻力塞被配置为抑制所述流体样品的第一部分的至少一部分和污染物进入所述样品路径中)。

当释放阀 2310 时，并且在进一步的真空力或其他力的作用下，后续量的血液(相当于流体样品)将流入入口端口 2302，绕过隔离室 2306，并且流入并穿过采样通道 2308(相当于连接在所述入口和所述出口之间的样品路径)朝向出口端口 2304 并至收集装置(相当于使得当在所述腔室中接收到所述流体样品的所述第一部分时，流体样品的后续部分能够被迫通过所述阻力塞，并由所述样品路径从所述入口传送到所述出口)。

权利要求 5 请求保护的技术方案与对比文件 1 相比，其区别技术特征为：(1)流阻器为透气的，以通过所述透气的流阻器和所述出口置换其中的空气；(2)所述阻力塞包括可刺穿的膜和刺穿构件，该刺穿构件被配置为刺穿所述膜，其中，所述装置被配置为使得一旦所述腔室填充有所述流体样品的所述第一部分，则在所述膜上施加压力使得所述膜拉伸并接触所述刺穿构。

针对上述区别技术特征(1)：对比文件 1 中已经记载了从出口端口 2304(例如从真空采血管等)施加的真空

或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里流阻隔器；因此为了使得血液能在真空的作用下使得被吸入隔离室 2306，具体的疏水塞 2312 为透气的，通过透气的流阻器和所述出口置换其中的空气是本领域技术人员不难想到的。

针对上述区别技术特征(2)：对比文件 2（US2018297303A1，20181018）公开了一种刺破修补液盛装容器，并具体记载了(参见权利要求书，说明书第 0024-0041 段，说明书附图 1-5)管设置有阻挡所述穿孔修复液流入所述第二流动通道的密封膜(相当于膜)， 并且其中密封膜阻塞(相当于阻力塞包括可刺穿的膜)第二流动通道的闭合状态可以切换到其中密封膜被容器内部压力破坏使得第二流动通道打开的打开状态。包括刺穿机构，所述刺穿机构用于破坏所述管的内部部分上的所述密封膜。刺穿机构 63a(相当于刺穿构件)在储存期间也不接触密封膜 61，但是当在刺穿修复工作期间容器内部压力增加并且密封膜 61 朝向管 60 的内部凸出时，刺穿部分 63b 接触密封膜 61(相当于在膜上施加压力使得所述膜拉伸并接触所述刺穿构件)，使得密封膜 61 破裂(相当于该刺穿构件被配置为刺穿所述膜，阻力塞包括可刺穿的膜和刺穿构件)。因此，对比文件 2 给出了在压力增加时，可以使得密封膜拉伸或凸出，进而使得穿刺机构接触密封膜，进而使得密封膜破裂，第二流动通道打开。这与本申请的作用相同，在面对相同的技术问题时，本领域技术人员能够想到将其应用于对比文件 1 中。具体的应将该手段应用于对比文件 1 中时，装置被配置为使得一旦腔室填充有流体样品的第一部分，则在膜上施加压力使得膜拉伸并接触刺穿构件对于本领域技术人员来说是有能力做到的。

在对比文件 1 的基础上结合对比文件 2 和本领域常规技术手段以获得该权利要求所要求保护的技术方案，对所属技术领域的技术人员来说是显而易见的，因此该权利要求所要求保护的技术方案不具备突出的实质性特点和显著的进步，因而不具第 22 条第 3 款规定的创造性。

4. 权利要求 6-9 不符合专利法第 22 条第 3 款的规定

权利要求 6-9 对其引用的权利要求作了进一步限定。在对比文件 1 的基础上根据需要，设置外壳，该外壳容纳和/或限定所述入口、所述出口、所述样品路径和所述腔室中的一个或多个是本领域技术人员有能力选择的；

对比文件 1 中记载了隔离室 2306 包括在隔离室 2306 的距入口 2302 最远的远端处的疏水塞 2312，从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里(相当于透气的流阻器包括与所述流体样品的第一部分接触时密封的材料)；

在对比文件 1 的基础上，根据需要可以选择污染物容纳储库包括曲折路径；

对比文件 1 中记载了当释放阀 2308 时，并且在进一步的真空力或其他力的作用下，后续量的血液将流入入口端口 2302，绕过隔离室 2306，并且流入并穿过采样通道 2308；

对比文件 1 中已经公开了采样通道 2308 最初被阀 2310(相当于阻力塞)关闭；在对比文件 1 的基础上，关于阻力塞的设置方式是根据需要可以选择的，具体的阻力塞包括具有可溶解材料的网，该可溶解材料在与流体样品的后续第一部分接触时溶解也是不难确定出的一种方式。

因此，当其引用的权利要求不具备创造性时，权利要求 6-9 不具有突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

5. 权利要求 10 不符合专利法第 22 条第 3 款的规定

权利要求 10 请求保护一种用于优化流体样品的流体样品优化装置，对比文件 1 公开了一种流体样品优化装置，具体的为一种优化流体样品的优化装置(相当于一种用于优化流体样品的优化装置)，并具体公开了(参见说明书第 0141-0149 段，说明书附图 23A-23B)：

血液隔离装置 2300 的又一实施方式，其具有与患者针连接的入口端口 2302(相当于入口)、与血液样本收集装置连接的出口端口 2304(相当于出口)、隔离室 2306 和旁路的采样通道 2308(相当于样品路径)。一旦隔离室 2306(相当于腔室)被填充至待隔离的潜在污染血液的初始等分部分，则隔离室 2306 被填充，结合说明书附图 23A 可以明确隔离室 2306 设置在入口和出口之间(相当于连接在所述入口和所述出口之间的腔室)；样品路径设置在入口和出口之间(相当于连接在所述入口和所述出口之间的样品路径)。

隔离室 2306 包括在隔离室 2306 的距入口 2302 最远的远端处的疏水塞 2312(相当于流阻器，腔室在所述出口附近具有透气的流阻器)。

从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样(相当于流体样品的第一部分)将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里(相当于腔室被布置为接收所述流体样品的第一部分)。可以明确对比文件 1 中血液的第一部分潜在地具有污染物。可以确定对比文件 1 中腔室中接收到流体样品的第一部分。

少量血液可以进入采样通道 2308(相当于样品路径)，采样通道 2308 最初被阀 2310 关闭。

当释放阀 2310 （相当于阻力塞，样品路径还包括阻力塞）时，并且在进一步的真空力或其他力的作用下(相当于施加后续压差)，后续量的血液(相当于流体样品)将流入入口端口 2302，绕过隔离室 2306，并且流入并穿过采样通道 2308 朝向出口端口 2304 并至收集装置(相当于当在所述腔室中接收到所述流体样品的所述第一部分时，所述流体样品的后续部分能够由所述样品路径从所述入口传送到所述出口)。本领域技术人员可以确定对比文件 1 中公开了所述阻力塞被配置为，当在所述腔室中接收了所述流体样品的第一部分时，抑制所述流体样品的所述第一部分的至少一部分进入所述样品路径。

权利要求 10 请求保护的技术方案与对比文件 1 相比，其区别技术特征为：(1)流阻器为透气的，以通过所述透气的流阻器和所述出口置换其中的空气：(2)所述阻力塞包括可刺破的膜；和刺穿构件，该刺穿构件被配置为刺穿所述膜，其中，所述装置被配置为使得一旦所述腔室填充有所述流体样品的所述第一部分，则在

所述膜上施加压力使得所述膜拉伸并接触所述刺穿构件。

针对上述区别技术特征(1)：对比文件 1 中已经记载了从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里流阻隔器；因此为了使得血液能在真空的作用下使得被吸入隔离室 2306，具体的疏水塞 2312 为透气的，通过透气的流阻器和所述出口置换其中的空气是本领域技术人员不难想到的。

针对上述区别技术特征(2)：对比文件 2（US2018297303A1，20181018）公开了一种刺破修补液盛装容器，并具体记载了(参见权利要求书，说明书第 0024-0041 段，说明书附图 1-5)管设置有阻挡所述穿孔修复液流入所述第二流动通道的密封膜(相当于膜)， 并且其中密封膜阻塞(相当于阻力塞包括可刺穿的膜)第二流动通道的闭合状态可以切换到其中密封膜被容器内部压力破坏使得第二流动通道打开的打开状态。包括刺穿机构，所述刺穿机构用于破坏所述管的内部部分上的所述密封膜。刺穿机构 63a(相当于刺穿构件)在储存期间也不接触密封膜 61，但是当在刺穿修复工作期间容器内部压力增加并且密封膜 61 朝向管 60 的内部凸出时，刺穿部分 63b 接触密封膜 61(相当于在膜上施加压力使得所述膜拉伸并接触所述刺穿构件)，使得密封膜 61 破裂(相当于该刺穿构件被配置为刺穿所述膜，阻力塞包括可刺穿的膜和刺穿构件)。因此，对比文件 2 给出了在压力增加时，可以使得密封膜拉伸或凸出，进而使得穿刺机构接触密封膜，进而使得密封膜破裂，第二流动通道打开。这与本申请的作用相同，在面对相同的技术问题时，本领域技术人员能够想到将其应用于对比文件 1 中。具体的应将该手段应用于对比文件 1 中时，装置被配置为使得一旦腔室填充有流体样品的第一部分，则在膜上施加压力使得膜拉伸并接触刺穿构件对于本领域技术人员来说是有能力做到的。

在对比文件 1 的基础上结合对比文件 2 和本领域常规技术手段以获得该权利要求所要求保护的技术方案，对所属技术领域的技术人员来说是显而易见的，因此该权利要求所要求保护的技术方案不具备突出的实质性特点和显著的进步，因而不具第 22 条第 3 款规定的创造性。

6. 权利要求 11-13 不符合专利法第 22 条第 3 款的规定

权利要求 11-13 对其引用的权利要求作了进一步限定。在对比文件 1 的基础上根据需要，设置外壳，该外壳容纳和/或限定所述入口、所述出口、所述样品路径和所述腔室中的一个或多个是本领域技术人员有能力选择的；

对比文件 1 中记载了隔离室 2306 包括在隔离室 2306 的距入口 2302 最远的远端处的疏水塞 2312，从出口端口 2304(例如从真空采血管等)施加的真空或其他牵引力将血液吸入入口端口 2302 并直接吸入隔离室 2306，其中血液的初始等分试样将接触疏水塞 2312 并导致血液的初始等分部分返回到隔离室 2306 中并被隔离在那里(相当于透气的流阻器包括与所述流体样品的第一部分接触时密封的材料)；

在对比文件 1 的基础上，根据需要可以选择腔室包括曲折路径；

因此，当其引用的权利要求不具备创造性时，权利要求 11-13 不具有突出的实质性特点和显著的进步，不符合专利法第 22 条第 3 款有关创造性的规定。

二、针对申请人的意见陈述书

申请人主要认为：

对比文件 1 没有公开刺穿构件，该刺穿构件被配置为刺穿所述膜。

本发明参照图 9A-9C 详细描述了上述技术特征及其运作原理。可刺穿的膜 702 与刺穿构件 704 间隔开，膜 702 可以是弹性材料片，例如橡胶或其他弹性材料。如图 9C 所示，一旦污染物容纳容器中充满了流体，便在膜片 702 上施加一定的压力以使其进一步拉伸，从而与刺穿构件 704 接触。一旦在膜片 702 与刺穿构件 704 之间形成接触，膜 702 被刺穿构件 704 刺穿或以其他方式破裂，以打开较大的区域，以便随后的一定量或部分的流体流入样品路径（[0086]段）。由此，权利要求 1 所述的装置避免了收集的血液样品中污染物的积累，从而避免了由血液样品中的污染物导致的假阳性的检查结果

审查员充分考虑了其意见陈述，答复如下：

虽然对比文件 1 没有公开穿刺构件，穿刺构件被配置为刺穿膜；然而，对比文件 2（US2018297303A1，20181018）公开了一种刺破修补液盛装容器，并具体记载了(参见权利要求书，说明书第 0024-0041 段，说明书附图 1-5)管设置有阻挡所述穿孔修复液流入所述第二流动通道的密封膜， 并且其中密封膜阻塞第二流动通道的闭合状态可以切换到其中密封膜被容器内部压力破坏使得第二流动通道打开的打开状态。包括刺穿机构，所述刺穿机构用于破坏所述管的内部部分上的所述密封膜。刺穿机构 63a 在储存期间也不接触密封膜 61，但是当在刺穿修复工作期间容器内部压力增加并且密封膜 61 朝向管 60 的内部凸出时，刺穿部分 63b 接触密封膜 61，使得密封膜 61 破裂。因此，对比文件 2 给出了在压力增加时，可以使得密封膜拉伸或凸出，进而使得穿刺机构接触密封膜，进而使得密封膜破裂，第二流动通道打开。这与本申请的作用相同，在面对相同的技术问题时，本领域技术人员能够想到将其应用于对比文件 1 中。

基于上述理由，本申请的独立权利要求以及从属权利要求都不具备创造性，同时说明书中也没有记载其他任何可以授予专利权的实质性内容，因而即使申请人对权利要求进行重新组合和/或根据说明书记载的内容作进一步的限定，本申请也不具备被授予专利权的前景。如果申请人不能在本通知书规定的答复期限内提出表明本申请具有创造性的充分理由，本申请将被驳回。

审查员姓名:李媛媛　　审查员代码:30110854

国 家 知 识 产 权 局

检 索 报 告

申请号：2020800006660	申请日：2020 年 04 月 01 日	首次检索
申请人：酷睿有限公司	最早的优先权日：2019 年 04 月 01 日	
权利要求项数：20	说明书段数：95	

审查员确定的 IPC 分类号：G01N1/10,G01N1/02,A61B5/15

检索记录信息：US2018271425A1: 参考国际检索报告以及美局通知书

EP3324845A1: 参考同族检索报告

US2014112841A1: 参考同族检索报告

WO2019232196A1: 参考同族检索报告

CN104107054A: CNTXT 语义检索,语义基准:2020800006660

CN104981203A: CNTXT 语义检索,语义基准:CN213588280U

CN1717280A: 425 CNTXT, (G01N1/IC) and (((阻隔 or 阻塞 or 流阻 or 阻力塞) and ((流体 or 血 or 样品) s 污染)) and (真空 or 压差 or 负压))

相 关 专 利 文 献

类型	国别以及代码[11] 给出的文献号	代码[43]或[45] 给出的日期	IPC 分类号	相关的段落 和/或图号	涉及的权 利要求
X	US2018271425A1	2018-09-27	A61B5/15	说明书第 0141-0149 段，说明书附图 23A-23B	1-20
A	EP3324845A1	2018-05-30	A61M39/06	全文	1-20
A	US2014112841A1	2014-04-24	B01L3/00	全文	1-20
L	WO2019232196A1	2019-12-05	A61B5/15	全文	1-20

A	CN104107054A	2014-10-22	A61B5/151	全文	1-20
A	CN104981203A	2015-10-14	A61B5/155	全文	1-20
A	CN1717280A	2006-01-04	B01L3/00	全文	1-20

相 关 非 专 利 文 献					
类型	书名（包括版本号和卷号）	出版日期	作者姓名和出版者名称	相关页数	涉及的权利要求
类型	期刊或文摘名称 （包括卷号和期号）	发行日期	作者姓名和文章标题	相关页数	涉及的权利要求
类型	网址	网络发布日 或公开日	作者姓名和网页标题	相关部分	涉及的权利要求

表格填写说明事项：

1. 审查员实际检索领域的 IPC 分类号应当填写到大组和/或小组所在的分类位置。
2. 期刊或其它定期出版物的名称可以使用符合一般公认的国际惯例的缩写名称。
3. 相关文件的类型说明：

   X：单独影响权利要求的新颖性或创造性的文件；

   Y：与本检索报告中其他 Y 类文件组合后影响权利要求的创造性的文件；

   A：背景技术文件，即反映权利要求的部分技术特征或者有关的现有技术的文件；

   R：任何单位或个人在申请日向专利局提交的、属于同样的发明创造的专利或专利申请文件。

   P：中间文件，其公开日在申请的申请日与所要求的优先权日之间的文件，或者会导致需要核实该申请优先权的文件；

E：单独影响权利要求新颖性的抵触申请文件；

T：申请日或优先权日当天或之后公布的，可以对所要求保护发明的理论或原理提供清楚解释的文件，或者可显示出所要求保护发明的推理或事实不成立的文件；

L：除 X、Y、A、R、P、E 和 T 类文件之外的文件。

审 查 员：李媛媛　　审查部门：专利审查协作河南中心
2023 年 09 月 25 日

21 May 2024

PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
McLean, VA 22102
USA

By Email Only:
james.conley@pillsburylaw.com
benjamin.hudson@pillsburylaw.com
suzanne.simpson@pillsburylaw.com
Docket_ip@pillsburylaw.com

To the attention of Jim Conley

P.K. 26 – First Office Action of:

IL Patent Application No.: 286812
Title: NON-VENTING BODILY FLUID SAMPLE OPTIMIZATION DEVICE AND SYSTEM
Filing Date: 29 September 2021
App. date: 1 April 2020
IL NP of PCT Patent Application No.: PCT/US2020/26276
Applicant(s): KURIN, INC.

Your ref.: 069366-0572161_KUR7N01IL Our ref.: 1000-020-01

1

Dear Jim:

The Israel Patent Office (ILPO) has issued its first Office Action (substantive examination report) dated 20 May 2024, notifying the Applicant of the beginning of the examination process of the above identified IL Patent Application.

A response to the Office Action should be filed within four months and before **20 September 2024**. Monthly extensions (up to four months) are available upon payment of government fees of about $60 per month. Kindly note that the maximum extension period which can be obtained during substantive examination cannot exceed 12 months.

The examination is based on the following documents:

Description dated 29 September 2021

Claims dated 29 September 2021

Drawings dated 29 September 2021

The references hereunder relate to the following publications:

D1: US2018271425A1 [KURIN INC [US]] - 27/09/2018
D2: GB1378602A [BECTON DICKINSON CO] - 27/12/1974
D3:US2014112841A1 [BOEHRINGER INGELHEIM MICROPART [DE]] - 24/04/2014

In accordance with details below the following are the examiner's remarks regarding the allowability of the claims:

Defects were found in claims 1-20:

1. **Novelty and Inventive Step**

1.1. Claims 1-3,5-7,10,14-17 do not define a novel invention as per section 4 of the law, in light of D1, as detailed in the International Search Report.

1.2. Claims 1-20 do not define an invention with an inventive step as per section 5 of the law, in light of D1, D2, D3, as detailed in the International Search Report.

2 **Duty of Disclosure**

The applicant is hereby reminded that any change in the list of prior art or status of corresponding application (section 18c of the law) regarding oppositions, procedures to cancel corresponding applications / registrations must be reported to the ILPO up to the payment of the allowance fee.

We look forward to receiving your instructions in due course.

Yours sincerely,

Dr. Sarah Presenti, Adv
Katz, Presenti & Co

Submitted herewith

> The original OA (p.k. 26) in Hebrew.

> D1, D2, D3

> Our invoice number 3465

3

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Primary Examiner
Name: Nielsen, Michael
Tel: +49 30 259 01 - 554

Carroll, Christopher P.
Burns & Levinson London LLP
4-12 Regent Street, 4th Floor
London SW1Y 4PE
ROYAUME UNI

Application No.	Ref.	Date
22 181 212.6 - 1122	KUR-19212-P-EP	28.09.2023
Applicant: Kurin, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and in sofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11(b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered Letter

Nielsen, Michael
Primary Examiner
For the Examining Division

Enclosure(s): 3 page/s reasons (EPO Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

1, 2, 4-46	as originally filed	
3, 3a, 3b	filed in electronic form on	19-05-2023

Claims, Numbers

1-8	filed in electronic form on	19-05-2023

Drawings, Sheets

1/69-69/69	as originally filed

1). The applicants arguments with regard to neither of the documents cited hinting to "a chamber connected with the inlet port and the outlet port, and configured to collect a first portion of the blood sample, **the chamber including a material that is air permeable and blood impermeable**" are agreed upon.

Applicants arguments with regard support for the claims on file, their novelty and inventiveness are likewise agreed upon.

Therefore:

2). The applicant should **bring the description into conformity** with the claims of the present divisional application (Article 84 EPC). In particular should features that are present in the independent claim not be referred to as options in the form of e.g. "in some instances", "in some embodiments", "in a preferred embodiment", "in one implementation" and so forth, but be clearly identified as forming part of the invention. T**his applies to the description as a whole**, not only to the introductory part. The "Summary of The Invention" should likewise be amended, i.e. **recitation of superseded claims and subject-matter be removed or adapted** to the wording of the claims on file.

Anything referred to as "**embodiment**" or "**implementation**" and which is not covered by the claims on file should be **excised or clearly referred to as examples not covered by the invention**. This throughout the description and drawings.

- The technical field of the invention (Rule 42(1)(a) EPC; Guidelines F-II.4.2) must correspond to the amended set of claims.

- The summary of the invention (Rule 42(1)(c) EPC; Guidelines F-II.4.5) must correspond to the amended set of claims. Where appropriate, statements such as "The invention is set out in the appended set of claims" or "The invention is as defined in claim X" may be used instead of repeating the claims verbatim.
- **Embodiments which are no longer covered by the claims must be** deleted, unless they can reasonably be considered to be useful for highlighting specific aspects of the amended subject-matter. If this is the case, they must be clearly marked as not being part of the present invention (T 1808/06 and Guidelines F-IV, 4.3)]:
  - Any combinations of features which do not fall under the scope of the amended independent claims must be clearly marked as not being part of the present invention.
  - Statements such as "The following examples/aspects/embodiments X, Y, Z are not according to the invention and are present for illustration purposes only" may be used **at the start of the description or in the list of figures**.
- The technical features of the independent claims may not be presented as optional in the description. Where they precede a feature of an independent claim, terms such as "for example", "may", "can", "exemplary", "optionally", "preferably" and the like must be removed.
- The **"claim-like" clauses** in paragraphs [0014] to [0023] and at pages 43 to 46 **must be deleted prior to grant**. Claim-like clauses are clauses present in the description which use claim language such as "according to the preceding clause" or "characterised in that" (Guidelines F-IV, 4.4). Claim-like clauses include examples, embodiments or aspects which are presented as claim-like clauses. The simple conversion of these clauses into separate optional features will not be admitted either.

3). The unit inches expressed in paragraphs [0099], [00115] and [00156] does not meet the requirements of Rule 49(10) EPC and should be replaced by the appropriate SI unit (see Guidelines F-II, Annex, 2). The present expression should, however, be retained in parentheses after the replacement expression.

4). Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Articles 76(1) and 123(2) EPC).

5). Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Articles 76(1) and 123(2) EPC and the Guidelines H-V, 2.2 to 2.5).

PTO/SB/08a (01-22)
Approved for use through 05/31/2024. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	18783088
	Filing Date	2024-07-24
	First Named Inventor	Bobby E. ROGERS
	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	104107054	CN		2014-10-22	BECTON DICKINSON CO		☒
	2	104981203	CN		2015-10-14	MAGNOLIA MEDICAL TECHNOLOGIES INC		☒
	3	1717280	CN		2006-01-04	SECR DEFENCE		☒

PC 6.1.24

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	Filing Date	2024-07-24
	First Named Inventor	Bobby E. ROGERS
	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

	4	2015150742	WO		2015-10-08	UNIV HULL		☒
	5	0448795	EP		1991-02-10	BECTON DICKINSON CO		☒
	6	2013082301A1	WO		2013-06-06	TELEFLEX MEDICAL INC		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Meissner, George F. , et al., "The Standard Clotting Time, A Method Based on the Use of Whole Venous Blood in Capillary Tubes," The American Journal of Clinical Pathology, vol. 39, No. 3., pp. 321-323, Mar. 1963.	☐
	2	European Patent Application No. EP23155927.9 extended European Search Report dated Jul. 26, 2023, 8 pages.	☐
	3	Office Action (Final Rejection) dated 08/25/2023 for US App. No. 18113710 (pages 1-50)	☐
	4	Notice of Allowance mailed 09-08-2023; Attorney Docket No. 069366-0574153_KUR2C04US. 35 page.	☐
	5	Notice of Allowance mailed 09-14-2023; Attorney Docket No. 069366-0574152_KUR2D02IL. 90 pages.	☐
	6	Office Action (Non-Final Rejection) dated 10/04/2023 for US App. No. 17538990 (pages 1-47)	☐

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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

	7	JP Notice of Allowance mailed 06-20-2023; Attorney Docket No. 069366-0572231_KUR3D01JP. 6 pages.	☐
	8	Examination Report dated Sep. 28, 2023, for European Patent Application No. 22181212.6. 5 pages.	☐
	9	Office Action (Non-Final Rejection) dated 09/27/2023 for CN App. No. 202080000666.0 (pages 1-28).	☐
	10	Office Action (Notice of Section 18) dated 12/20/2023 for IL App No. 309380 (pages 1-5).	☐
	11	Notice of Allowance mailed 01-17-2024; Attorney Docket No. 069366-0572201_KUR2C03US. 16 pages.	☐
	12	JP Office Action mailed 02/27/2024; Attorney Docket No. 069366-0575273_KUR2D03JP. 11 pages.	☐
	13	Office Action (Non-Final Rejection) dated 01/25/2024 for IL App. 302893 (pages 1-3).	☐
	14	Li, Yiwen, et al. "Direct labeling and visualization of blood vessels with lipophilic carbocyanine dye DiI." Nature protocols 3.11 (2008): 1703-1708.	☐
	15	Abbott Point of Care, Cartridge and Test Information, Art: 714258-010; Rev. Date: 15-Aug-16,1-6 pages.	☐
	16	NCCLS. Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fifth dition. H3-A5, vol. 23, No. 32. Replaces H3-A4; vol. 18, No. 7. 1-52 pages. http://demo.nextlab.ir/Organization/ Documents/CLSI-Standards/CLSI-H3-A5.aspx.	☐
	17	Perez, P., et al. "Multivariate analysis of determinants of bacterial contamination of whole-blood donations." Vox Sanguinis 82.2 (2002): 55-60.	☐

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	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

	18	Sheppard, et al., Bacterial Contamination of Platelets for Transfusion: Recent Advances and Issues, LABMEDICINE, vol. 36, No. 12, Dec. 2005 ("Sheppard 2005").	☐
	19	Office Action (Non-Final Rejection) dated 04/25/2023 for US App. 16838017 (pages 1-20).	☐
	20	Office Action (Final Rejection) dated 01/29/2024 for US App. 16838017 (pages 1-44).	☐
	21	"Membrane Definition & Meaning," Merriam-Webster, Merriam-Webster, 22 Apr. 2009, www.merriam-webster.com/ dictionary/ membrane. (Year: 2009).	☐
	22	Office Action (Advisory Action) dated 02/09/2024 for US App. 16838017 (pages 1-6).	☐
	23	Office Action (Non-Final Rejection) dated 04/16/2024 for US App. 16838017 (pages 1-19).	☐
	24	Office Action (Non-Final Rejection) dated 05/21/2024 for IL App. 286812 (pages 1-3).	☐
	25	First Office Action (Non-Final Rejection) dated 01/16/2024 for JP App. 2021-558648 (pages 1-6).	☐
	26	First Office Action (Non-Final Rejection) dated 09/27/2023 for CN App. 202080000666.0 (pages 1-11).	☐
	27	Second Office Action (Non-Final Rejection dated 04/28/2024 for CN App. 202080000666.0 (pages 1-11).	☐
	28	European Patent Office, Extended European Search Report for European Patent Application 21818838.1-1122, dated April 22, 2024, 11 pages.	☐

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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

	29	Australian Patent Office, Examination Report No. 1 for for Australian Patent Application 2021202622, dated March 18, 2022, 3 pages.	☐
	30	Office Action (Final Rejection) dated 08/25/2023 for US Application No. 18113710 (pages 1-50).	☐
	31	European Patent Office, Extended European Search Report for European Patent Application 23155927.9-1122, dated July 26, 2023, pages 1-8.	☐
	32	Notice of Allowance mailed 04-17-2024; Attorney Docket No. 069366-0572201_KUR2C03US. 16 pages.	☐
	33	Office Action (Non-Final Rejection) mailed 10/04/2023 for US Application No. 17538900 (1-47).	☐
	34	First Office Action (Non-Final Rejection) dated 08-03-2023 for CN Application No. 202010300942.7. 21 pages.	☐
	35	Office Action (Non-Final Rejection) dated 02/21/2023 for US Application No. 17893079, pages 1-32.	☐
	36	Office Action (Final Rejection) dated 07/19/2023 for US Application No. 17893079, pages 1-21.	☐
	37	Advisory Action dated 09/29/2023 for US Application 17893079, pages 1-24.	☐
	38	European Patent Office, Examination Report for European Patent Application 22181212.6-1122, dated September 28, 2023, pages 1-5.	☐
	39	European Patent Office, Extended European Search Report for European Patent Application 20781928.5-1122 dated October 28, 2022, pages 1-10.	☐

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	First Named Inventor	Bobby E. ROGERS
	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

	40	Rule 70(a) Communication for European Application No. 20781928.5-1122 dated November 15, 2022, 1 page.	☐
	41	International Search Report and Written Opinion dated 19 March 2020 for PCT application no. PCT/US2020/023617. pages.	☐
	42	International Search Report and Written Opinion dated 28 September 2021 for PCT application no. PCT/ US2021/035294. 7 pages.	☐
	43	European Patent Office, Extended European Search Report for European Patent Application 22181212.6-1122 dated October 24, 2022, pages 1-10.	☐
	44	Australian Patent Office, Australian Examination Report No. 1 for Application No. 2021120 622 dated March 18, 2022, 3 pages.	☐
	45	Notice of Allowance mailed 03-01-2023; Attorney Docket No. 069366-0572419_KUR2D01AU. 3 pages.	☐
	46	First Office Action dated 11/24/2021 for IL Application No. 286030, pages 1-3.	☐
	47	Notice of Allowance mailed 01-29-2023; Attorney Docket No. 069366-0572425_KUR2D01IL. 87 pages.	☐
	48	Office Action (Non-Final Rejection) dated 08/10/2021 for Japanese Application No. 2020-118498, pages 1-7.	☐
	49	Office Action (Non-Final Rejection) dated 03/28/2022 for Japanese Application No. 2020-118498, pages 1-3.	☐
	50	Office Action (Non-Final Rejection) dated 09/01/2022 for Japanese Application No. 2020-118498, pages 1-4.	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

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EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	18783088
	Filing Date	2024-07-24
	First Named Inventor	Bobby E. ROGERS
	Art Unit	OPAP
	Examiner Name	DOCKET CENTRAL
	Attorney Docket Number	069366-0580418_KUR2C06US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97(e) to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ A certification statement is not submitted herewith.

FEE

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

COPIES

☐ An identification of an earlier application pursuant to 37 CFR 1.98 (d) (1) is attached.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Benjamin F. Hudson/	Date (YYYY-MM-DD)	2024-08-26
Name/Print	Benjamin F. Hudson	Registration Number	71,474

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PC 6.1.24

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Application No.	Ref.	Date
20 781 928.5 - 1122	KUR-007EP1	31.07.2024
Applicant: Kurin, Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and in sofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

In case you withdraw the application within the above-mentioned period, the examination fee will be refunded at a rate of 50% (Art. 11(b) RFees).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

Registered Letter

Coja, Michael
Primary Examiner
For the Examining Division

Enclosure(s): 4 page/s reasons (EPO Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

3-28	as published	
1, 2, 3b	filed in electronic form on	12-05-2023

Claims, Numbers

1-9	filed in electronic form on	12-05-2023

Drawings, Sheets

1/16-16/16	as published

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1	US 2018/271425 A1 (ROGERS BOBBY E [US] ET AL) 27 September 2018 (2018-09-27)
D2	EP 3 324 845 A1 (KURIN INC [US]) 30 May 2018 (2018-05-30)
D3	WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 5 December 2019 (2019-12-05)

D3 published on 05-12-2019 claims the priority date of 31-05-2018. Its content as filed is therefore considered to be comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) EPC. Furthermore, the present application claims a priority date of 01-04-2019, which appears not to be valid since the content of the priority document (US201962827783P, see document filed on 26-10-2020 by the applicant) does not support the subject matter of the present application, in particular the claims as filed. D3 is therefore considered to be comprised in the state of the art, pursuant to Article 54(2) EPC.

1. The amendments filed with the letter dated 12-05-2023 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendments concerned are the following:

- In claims 1 and 5, replacing the expression "**A fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source, a first portion of the fluid sample potentially having contaminants**" with the expression "**A device**", which is broader than what is supported by the original description.

- In claims 1 and 5, replacing the expression "**contaminant containment reservoir**" with the expression "**chamber**", which is broader than what is supported by the original description.

- In claim 1, removing the features "**wherein the resistive plug includes a film that is pierceable by a first of the subsequent pressure differentials**" (original claim 11) and "**wherein the resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film**" (original claim 11), while these features are clearly essential for solving the technical problem of sequestrating a first portion of the fluid sample from a subsequent portion of the fluid sample (see Guidelines H-V.3.1).

- In claim 5, removing the features "**wherein the resistive plug includes a mesh with a dissolvable material that dissolves upon contact with a first of the subsequent portions of the fluid sample**" (original claim 13), while these features are clearly essential for solving the technical problem of sequestrating a first portion of the fluid sample from a subsequent portion of the fluid sample (see Guidelines H-V.3.1).

2. The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1, 5 is not new within the meaning of Article 54(1) and (2) EPC.

2.1 D3 discloses **a device** (see fig.8-12, par.[0135]-[0150]) **comprising:**
an inlet (512) **configured to connect with a fluid source;**
an outlet (516) **configured to connect with a fluid collection device;**
a sample path (524) **connected between the inlet and the outlet, the sample path further having a resistive plug** (574) **that is configured to inhibit at least a part of a first portion of a fluid sample from entering the sample path;**
a chamber (514) **connected between the inlet and the outlet, the chamber further having an air permeable fluid resistor** (515) **proximate the outlet, the chamber being arranged to receive, when a pressure differential is applied between the inlet and the outlet, the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet, such**

that upon receipt of the first portion of the fluid sample in the chamber (see fig.9, par.[0142]), **subsequent portions of the fluid sample can be forced through the resistive plug and conveyed by the sample path from the inlet to the outlet, the resistive plug including a membrane** (574) **that is pierceable; and**
a piercing member (578) **configured to pierce the membrane** (see fig.10, par. [0145]).

The subject-matter of claim 1 is therefore not new (Article 54(1) and (2) EPC).

2.2. D3 discloses **a device** (see fig.3, par.[0098]-[0112]) **comprising:**
an inlet (312) **configured to connect with a fluid source;**
an outlet (316) **configured to connect with a fluid collection device;**
a sample path (324) **connected between the inlet and the outlet, the sample path further having a resistive plug** (323) **that is configured to inhibit at least a part of a first portion of the fluid sample from entering the sample path, the resistive plug including a mesh; and**
a chamber (314) **connected between the inlet and the outlet, the chamber further having an air permeable fluid resistor** (315) **proximate the outlet, the chamber being arranged to receive, when a pressure differential is applied between the inlet and the outlet, the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet, such that upon receipt of the first portion of the fluid sample in the chamber** (see par. [0106]), **subsequent portions of the fluid sample can be forced through the resistive plug and conveyed by the sample path from the inlet to the outlet** (see par.[0111]).

The subject-matter of claim 5 is therefore not new (Article 54(1) and (2) EPC).

3. Dependent claims 2-4,6-9 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty and/or inventive step.

3.1 The features of claims 2,7 are merely some straightforward possibilities which the skilled person would select, depending on the circumstances, without exercising inventive skill, in order to solve the problem posed.

3.2 The subject matter of claims 3,8 is already known from D3 (see par.[0021]).

3.3 The subject matter of claims 4,9 is already known from D3 (see par.[0108]:"the selectively permeable member 315 is placed in a sealed configuration when transitioned to the second state").

3.4 The subject matter of claim 6 is already known from D3 (see par.[0103]).

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Medical device used for collecting biological samples

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Also published as: CN104107054 (B) BR112015026154 (A2) BR112015026154 (B1) CA2909186 (A1) CA2909186 (C) more

Abstract of CN104107054 (A)

The invention relates to a biological fluid sampling device used for collecting a blood sample from an independent vascular access device and discharging a part of the collected sample to a point-of-care testing device used for analysis. The biological fluid sampling device comprises a body surrounding a storage device with an internal volume for receiving an enough amount of blood used for diagnosis and test. The sampling device comprises an access pipe cavity extending from the distal end of the body and providing fluid communication between the independent vascular access device and the storage device, a flow-out pipe cavity in fluid communication with the storage device and a detachable discharge cover attached to the flow-out pipe cavity and comprising a vent hole for gas communication between the storage device and the

ambient air. In addition, a plurality of sampling and transfer devices are provided for obtaining samples from people under test and transferring the samples to the point-of-care testing device.

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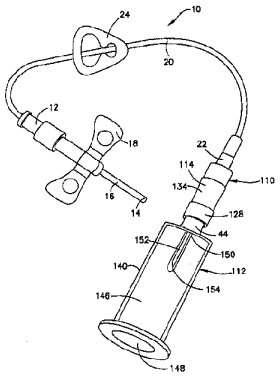
权利要求书2页 说明书8页 附图12页

(54)发明名称

用于收集生物样品的医学装置

(57)摘要

本发明涉及一种生物流体取样装置，其用于从单独血管通路装置收集血液样品及排出一部分收集的样品至用于分析的即时检验装置。该生物流体取样装置包括包围储存器的主体。该储存器具有足以容纳足够量的用于诊断检验的血液的内部容积。该取样装置还包括：通路管腔，其自主体的远端延伸，在单独血管通路装置与储存器之间建立流体连通；流出管腔，其也与储存器流体连通；可移除式排出盖，其附接至流出管腔，并且包括在储存器及环境空气之间气体连通的透气口。此外，还提供了数个取样及转移装置，用于从受验者获取样品并且将样品转移至即时检验装置。



CN 104107054 A

1. 一种生物流体取样装置，其能够与单独的血管通路装置接合，并包括：

壳体，其包围生物流体储存器，该储存器限定一内部；

通路管腔，其自壳体的一部分延伸，并且在单独的血管通路装置与储存器的内部之间建立流体连通；

流出管腔，其自壳体的一部分延伸，并且具有第二端以及设置成与储存器的内部流体连通的第一端；以及

排气盖，其可移除地安置在流出管腔的第二端上，并包括在储存器的内部及周围环境之间气体连通的透气口。

2. 根据权利要求 1 所述的生物流体取样装置，其还包括至少部分地包围通路管腔的鲁尔锁。

3. 根据权利要求 1 所述的生物流体取样装置，其中，排气盖包括用于插入至流出管腔内的鲁尔锁。

4. 根据权利要求 3 所述的生物流体取样装置，其中，排气盖包括紧固件，用于将排气盖的一部分可移除地连接至壳体的一部分。

5. 根据权利要求 1 所述的生物流体取样装置，其中，储存器的内部构造成在其内接收流体样品。

6. 根据权利要求 5 所述的生物流体取样装置，其中，壳体包括可压缩部，其中，对可压缩部的压缩将使流体样品通过通路管腔从储存器的内部排出。

7. 根据权利要求 1 所述的生物流体取样装置，其中，通路管腔安置在壳体的远端，流出管腔安置在壳体的近端。

8. 根据权利要求 1 所述的生物流体取样装置，其中，储存器含有样品稳定剂。

9. 根据权利要求 8 所述的生物流体取样装置，其中，壳体具有与特定样品稳定剂相对应的可视标识。

10. 根据权利要求 9 所述的生物流体取样装置，其中，可视标识为特定的颜色。

11. 根据权利要求 1 所述的生物流体取样装置，其中，排气口包括多孔塞、渗透膜及小排气孔中的至少之一。

12. 一种生物流体取样及收集组件，其包括：

生物流体取样装置，其包括：

壳体，其包围生物流体储存器，该储存器限定一内部；

通路管腔，其自壳体的一部分延伸，并且在储存器的内部与单独的血管通路装置之间建立流体连通；和

流出管腔，其自壳体的一部分延伸，并且具有第二端以及设置成与储存器的内部流体连通的第一端；以及

样品收集装置，其包括：

接头，用于进入样品容器的内部，并在生物流体储存器及样品容器的内部之间建立流体连通，从而允许储存器的内部与样品容器的内部之间的流体连通；以及

限流器，其与接头结合，并且可从打开位置转换至关闭位置，其中，在打开位置时生物流体储存器和样品容器内部之间容许流体连通，在关闭位置时生物流体储存器与样品容器内部流体隔离。

13. 根据权利要求 12 所述的生物流体取样及收集组件，其中，生物流体储存器容纳流体，并且其中，当限流器处在打开位置时，流体从生物流体储存器流至样品容器的内部。

14. 根据权利要求 12 所述的生物流体取样及收集组件，其中，当样品容器与接头接合时限流器处在打开位置，当将样品容器从接头移除时限流器处在关闭位置。

15. 根据权利要求 12 所述的生物流体取样及收集组件，其还包括可移除地布置在流出管腔的第二端上的排气盖，该排气盖包括在储存器的内部与周围环境之间气体连通的透气口。

16. 根据权利要求 12 所述的生物流体取样及收集组件，其中，样品容器为真空容器。

17. 根据权利要求 12 所述的生物流体取样及收集组件，其还包括与通路管腔流体连通的单独血管通路装置。

18. 根据权利要求 17 所述的生物流体取样及收集组件，其还包括在单独血管通路装置与生物流体取样装置之间连接的接头。

19. 根据权利要求 18 所述的生物流体取样及收集组件，其中，接头包括：

壳体；

主管腔，其被包围在壳体内，具有主流出端口；

侧端口，其包括自主管腔延伸并且与主管腔流体连通的侧管腔；以及

阀，其能够从第一位置转换至第二位置，其中在第一位置处允许流体通过主管腔流动同时阻止流体通过侧管腔流动，在第二位置处允许流体通过主管腔及侧管腔二者流动。

20. 根据权利要求 19 所述的生物流体取样及收集组件，其中，通过从侧端口插入管状构件至侧管腔内，将阀从第一位置转换至第二位置。

用于收集生物样品的医学装置

技术领域

[0001] 本发明涉及适用于与血管通路装置一起使用、适用于收集生物样品以用在即时检验中、以及适用于填充样品收集容器以用在常规实验室检验中的装置、组件和系统。

背景技术

[0002] 血液取样是一种常见的医疗过程，包括从患者至少取出一滴血。血液样品通常通过手指针刺、足跟针刺或者静脉穿刺的办法取自住院、家庭护理以及急诊室的患者。一旦被采集，可分析血液样品以获得医学上有用的信息，包括化学成分、血液学、凝血等。

[0003] 血液检验可确定患者的生理生化状态，例如疾病、矿物质含量、药物有效性以及器官功能。血液检验可在临床实验室进行或者在患者附近即时检验。即时血液检验的一个示例是患者血糖水平的常规检验，其包括通过手指针刺提取血液以及机械地收集血液进入诊断板卡。之后，诊断板卡分析血液样品并且向临床医生提供患者的血糖水平读数。可使用其他分析血气电解质水平、锂水平及离子钙水平的装置。一些其他的即时检验设备可确定急性冠脉综合征 (ACS) 和深静脉血栓 / 肺栓塞 (DVT/PE) 的标记物。

[0004] 尽管即时检验和诊断有了快速的发展，但是血液取样技术相对仍保持无改变。通常，通过采用附接至针或者导管组件近端的皮下针头或者真空管来抽取血液样品。在一些情况下，临床医生采用插入导管中的针和注射器从患者经由插入的导管抽血而自导管组件收集血液。这些过程使用针和真空管作为中间装置，通常在检验前从该中间装置抽取收集的血液样品。因此，上述程序是装置密集型的，即在血液样品的获得、准备和检验的过程中使用多个装置。每种额外的装置增加了检验过程的时间和成本。因此，所期望的是获得一种为即时检验提供血液的简化装置。此外，由于即时检验常常补充有其他的常规实验室检验，因此也期望获得能用于收集常规实验室检验用的血液样品和收集即时检验用的第二份样品的血液取样和收集组件。通过本发明的装置、组件和系统能实现上述特性。

发明内容

[0005] 鉴于现有技术中的上述缺点，本文中提供了用于即时检验的生物流体取样装置、用于收集流体样品的血管外系统以及其使用方法。通过下面结合附图的详述，本发明的其他详情和优点将会被理解。

[0006] 根据本发明的实施例，生物流体取样装置（如血液取样装置）包括壳体以及通路管腔，其中，该壳体包围限定一内部的生物流体储存器，该通路管腔自壳体的一部分延伸并且在单独血管通路装置与储存器的内部之间建立流体连通。该生物流体取样装置也包括自壳体的一部分延伸的流出管腔，该流出管腔具有第二端以及设置成与储存器的内部流体连通的第一端。该生物流体取样装置还包括可移除地安置在流出管腔的第二端上的排气盖，该排气盖包括在储存器的内部与周围环境之间气体连通的透气口。

[0007] 在某些构型中，该生物流体取样装置也包括至少部分地包围通路管腔的鲁尔锁。排气盖可包括用于插入流出管腔中的鲁尔锁。排气盖也可包括用于将排气盖的一部分可移

除地连接至壳体的一部分的紧固件。储存器的内部可构造成在其中接收流体样品。壳体也可包括可压缩部，并且对可压缩部压缩可使流体样品通过通路管腔从储存器的内部排出。

[0008] 在某些构型中，通路管腔布置在壳体的远端，流出管腔布置在壳体的近端。储存器也可含有样品稳定剂。在其他的实施例中，壳体可具有与特定的样品稳定剂相对应的可视标识。该可视标识可以是特定的颜色。可选择地，排气口可包括多孔塞、渗透膜及小排气孔中的至少之一。

[0009] 根据本发明的另一个实施例，生物流体取样及收集组件（例如血液取样及收集组件）可包括生物流体取样装置。该生物流体取样装置包括壳体及通路管腔，其中，壳体包围限定一内部的生物流体储存器，通路管腔自壳体的一部分延伸并且在储存器的内部与单独血管通路装置之间建立流体连通。该生物流体取样装置也可包括流出管腔，该流出管腔自壳体的一部分延伸，并且具有第二端以及设置成与储存器的内部流体连通的第一端。该组件也可包括样品收集装置，该样品收集装置包括接头，接头用于进入样品容器的内部并在生物流体储存器及样品容器的内部之间建立流体连通。这样就允许储存器的内部与样品容器的内部之间的流体连通。该样品收集装置也可包括与接头接合的限流器。该限流器可从打开位置转换至关闭位置，其中，在打开位置时生物流体储存器与样品容器的内部之间流体连通，在关闭位置时生物流体储存器与样品容器的内部流体隔离。

[0010] 在某些构型中，生物流体储存器容纳流体，并且当限流器处在打开位置时，流体从生物流体储存器流至样品容器的内部。当样品容器与接头接合时限流器处在打开位置，当将样品容器从接头移除时限流器处在关闭位置。

[0011] 在其他构型中，该生物流体取样及收集组件还包括可移除地布置在流出管腔的第二端上的排气盖。该排气盖包括在储存器的内部与周围环境之间气体连通的透气口。样品容器可为真空容器。该组件还可包括与通路管腔流体连通的单独血管通路装置。

[0012] 在其他构型中，该生物流体取样及收集组件包括在单独血管通路装置与生物流体取样装置之间连接的接头。该接头可包括壳体、主管腔、侧端口以及阀，其中，主管腔包围在壳体内并具有主流出端口，侧端口包括自主管腔延伸并且与主管腔流体连通的侧管腔，阀可从第一位置转换至第二位置，在第一位置处允许流体流经主管腔同时阻止流体流经侧管腔，在第二位置处允许流体流经主管腔及侧管腔二者。通过从侧端口插入管状构件至侧管腔内，将阀从第一位置转换至第二位置。

附图说明

[0013] 进行以下说明以使本领域的技术人员能够制造和使用为实现本发明而构思的所描述的实施例。然而，对于本领域的技术人员而言，各种修改、等同物、变化和替代例将仍然是显而易见的。修改、等同物、变化和替代例中的任一及全部都旨在涵盖在本发明的精神和范围内。

[0014] 图 1 是根据本发明的一个实施例的生物流体取样装置、样品容器收集装置以及单独血管通路装置的透视图。

[0015] 图 2 是图 1 的包括排气盖的生物流体取样装置的透视图。

[0016] 图 3 是图 1 的生物流体取样装置的透视图，其中，将排气盖从装置的主体拆卸。

[0017] 图 4 是图 1 的生物流体取样装置的透视剖面图，其中，将排气盖从装置的主体拆

卸。

[0018] 图 5 是根据本发明的另一实施例的包括生物流体取样装置和含样品收集容器的样品容器收集装置的组件的透视图。

[0019] 图 6 是图 5 的组件的剖面透视图。

[0020] 图 7 是图 5 的剖面透视图，从组件移除了样品收集容器。

[0021] 图 8 是根据本发明的又一实施例的包括生物流体取样装置、样品容器收集装置、侧端口连接器及单独血管通路装置的系统的透视图。

[0022] 图 9 是图 8 的组件的透视图，其中，侧端口、取样装置和收集装置彼此拆开。

[0023] 图 10 是图 8 的侧端口、取样装置和收集装置的侧视图。

[0024] 图 11 是图 8 的侧端口的剖视图。

[0025] 图 12 是图 8 的侧端口的剖视图，其中，取样装置自该侧端口延伸。

[0026] 图 13 是根据本发明的另一实施例的包括两个生物流体取样装置、侧端口连接器以及连接至侧端口装置的单独血管通路装置的系统的透视图。

[0027] 图 14 是根据本发明一实施例使用者将生物流体从图 1 的的取样装置分送至检验设备的示意性透视图。

具体实施方式

[0028] 为便于理解本发明，附图和描述说明了本发明的优选实施例，并且通过附图和描述使得本发明、本发明不同结构及构型的实施例、操作的方法以及许多优点可被理解和领会。

[0029] 为了后面的描述，术语“上”、“下”、“右”、“左”、“竖直的”、“水平的”、“顶”、“底”、“横向的”、“纵向的”及其衍生词将指的是本发明在附图中的定向。然而，应当理解，除了相反地特指之处之外，该发明可为替代的变例及步骤顺序。也应当理解，在附图中示出的及在以下的说明书中描述的特定装置和方法仅为本发明的示例性实施例。因此，与文中公开的实施例相关的特定尺寸及其他物理特性不应被认为是限制性的。

[0030] 本发明涉及一种生物流体取样装置，例如血液取样装置 110，用于收集血液样品以用于即时检验和分析。血样取样装置 110 构造为较大的血管外系统 10 的一部分，并且构造为从单独的血管通路装置 12 接收流体样品。图 1 描述了示例性的血管外系统。该系统包括血液取样装置 110、样品容器收集装置 112 以及血管通路装置 12。血管通路装置 12 可包括多个在现有技术中已知的构件，例如血管内针 14、套在针之上的导管 16、针遮蔽结构 18 以及末端为鲁尔通路接头 22 或者端口的一体化延伸管 20。

[0031] 示例性的血管通路装置包括直通且带端口的 (ported) 静脉内导管（如 AUTOGUARD™ 遮蔽式导管，可从 Becton，Dickinson，and Company 商购获得）、一体化的外周静脉内导管、翼状针套件以及血液收集套件。IV 通路套件（例如可从 Becton，Dickinson，and Company 商购获得的 BD NEXIVA™ 封闭式静脉内 (IV) 导管系统）也可用来形成封闭式通路系统。类似的，包封式鲁尔接头端口（例如也可从 Becton，Dickinson，and Company 商购获得的 BD Q-SYTE™ 鲁尔通路分式隔膜）可用于完全包封介于取样装置 110 和血管通路装置 12 之间的鲁尔通路接头 22。替代地，在没有诸如延伸管 20 的额外构件的情况下，取样装置 110 可直接地连接至静脉内导管座，以减少构件的数量并且简化收集及取样的过程。

[0032] 血管通路装置 12 还可包括限流器（如夹具 24），从而在取样装置 110 和 / 或收集装置 112 从血管外系统 10 移除时，限制血液流经延伸管 20。替代地，鲁尔通路接头 22 可包括一体化的阀或隔膜，在取样装置 110 从血管外系统 10 移除后，该阀或隔膜自动地关闭以限制流体流动。如下文中将更加详细说明的，本发明旨在包括各种模块化构件，根据要被收集的血液样品的类型可组合这些模块化构件以形成多个血管外系统。本发明也旨在于，在本发明的范围内提供鲁尔通路接头 22 及取样装置 110 的一体化单元。图 8 及图 13 描述了在本发明的范围内的包括多个血液取样装置和 / 或样品容器收集装置的血管外系统 10 的替代构造。

[0033] 如图 2 所示，血液取样装置 110 包括壳体 114 及可移除的排气式端盖 116，其中，壳体 114 可通过注射成型或者吹塑成型的方法来形成。在一些情况下，血液取样装置 110 可减少从患者抽取诊断用血液样品所需的构件的数量。这是因为，该血液取样装置 110 把执行将血管外系统排气的步骤以及获得血液样品的步骤的能力结合在单一装置中。更加具体地，血液取样装置 110 构造成从血管外系统 10 排气，从而通过延伸管 20 从血管通路装置 12 抽取血液至取样装置 110。也可使用在现有技术中已知的外部动力源（如机动泵）来推动血液经由血管外系统 10 至取样装置 110。血液取样装置 110 也可通过芯吸装置来接收血液，该芯吸装置安置在血液取样装置的远端内，用于抽取血液进入该血液取样装置。如图 4 所示，血液保留在取样装置 110 的储存器 118 中。

[0034] 如下文将更加详细地说明的，一旦将血液取样装置 110 从血管外系统 10 移除，就可将血液从取样装置 110 排出至即时检验装置 30（如图 14 所示），如检验条、载玻片、诊断板卡或其他用于检验和分析的检验装置。检验条、载玻片以及检验板卡是接收血液样品并且检验该血液的一个或多个生理和生化状态的即时检验装置。检验板卡的示例包括可从 Abbot 集团公司商购获得的**i-STAT®**检验板卡。诸如**i-STAT®**板卡的检验板卡可用于检验各种状况，包括化学物和电解质、血液学、血气浓度、凝血或心脏标志物的存在情况。采用这种板卡的检验结果能很快地提供给临床医生。

[0035] 参考图 2-4，现将更加详细的描述生物取样装置的结构。生物取样装置 110 的壳体 114 包括狭窄管状部 120，该管状部 120 具有构造成与单独的血管通路装置 12 建立流体连通的通路管腔 122。例如，该狭窄管状部 120 可为公鲁尔锁定连接器 124，适于插入血管通路装置 12 的母鲁尔通路接头 22。储存器 118 被包围在壳体 114 内，并且包括足以容纳足够用于诊断检验的血液的内部容积，例如，该内部容积为大致 0.1ml 至大致 0.4ml。由于不同的血液检验需要不同量的血液，因此在一些实施例中，储存器 118 的尺寸设定成能保留特定检验或特定数量的检验所需的血液量。储存器 118 可具有各种样品稳定剂，例如血液保藏剂、试剂或抗凝剂（例如肝素），以保存血液并且保证血液用于某些预期血液检验的有效性。可选择地，血液取样装置 110 的壳体 114 可设置为特定的颜色，以告知使用者取样装置 110 的储存器 118 含有血液保藏化学制剂。不具有保藏剂的血液取样装置可为一不同的壳体颜色，以告知使用者血液取样装置不含有该化学制剂。

[0036] 储存器 118 与通路管腔 122 及流出管腔 126 流体连通，流出管腔 126 相对于通路管腔 122 布置在壳体 114 的另一端。流出管腔 126 可由如螺纹端口 128 的连接结构包围。如图 2-4 描述的实施例中示出的，螺纹端口 128 及流出管腔 126 连接至可移除式端盖 116。

[0037] 可移除式端盖 116 构造成附接至螺纹端口 128，并且包括贯穿端盖 116 的一部分延

伸的内通路 130，该内通路 130 与流出管腔 126 及储存器 118 流体连通。内通路 130 设置有透气孔 132，其允许气体通过但是阻止流体（如血液）通过。透气孔 132 可包括能提供上述特性的各种结构，例如多孔塞、渗透膜和 / 或含有多个小排气孔的结构。透气孔 132 可包括由玻璃、聚对苯二甲酸乙二醇酯 (PET)、微纤维材料和 / 或其他由高密度聚乙烯纤维制成的合成材料的组合形成的透气部。透气孔 132 可为疏水的或者亲水的。可选择地，透气孔 132 可包括多层不同的材料，以使得透气孔 132 为疏水的且透气的。

[0038] 当在取样装置 110 中收集了足够量的用于检验的血液之后，将取样装置 110 从血管外系统 10 移除。在如图 1 描述的血管外系统 10 的某些构型中，在将取样装置 110 移除之前，可关闭夹具 24 以限制血液进一步流经延伸管 20。替代地，血管外系统 10 可包括阀或隔膜，一旦将取样装置 110 移除，该阀或隔膜自动地限制流体从血管通路装置 12 流动。

[0039] 一旦从血管外系统 10 移除，血液取样装置 110 构造成从储存器 118 排出至少一部分收集的血液样品。例如，在优选的且非限制性的实施例中，血液取样装置 110 包括可压缩部 134。在某些实施例中，壳体 114 由柔性或半柔性材料制成，使得整个壳体 114 为可压缩的。替代地，可压缩部 134 可仅包括在受压时弯曲的壳体 114 的一小部分。可压缩部 134 可包括脊部或者其他的抓握构件 136，以便于使用者抓握、把持及操纵。在另一非限制性的实施例中，可压缩部 134 安置在两个基本上刚性的部分之间，从而当使用者按压该刚性部分时，可压缩部 134 压缩。在这种构型中，刚性部分为取样装置 110 提供了结构强度及稳定性。壳体 114 的可压缩部 134 可通过减薄壳体 114 的壁而获得以增加柔性。替代地，可采用双射成型技术形成壳体 114，其中，柔性材料围绕壳体 114 的远端部分包塑成型。在任一情况中，可压缩部 134 比刚性部分更具有柔性，并且被构造成朝储存器 118 向内弯曲。

[0040] 在某些构型中，取样装置 110 被构造成当未被压缩时保留血液，而在被压缩时排出一定量的血液。照此，一旦将取样装置 110 从血管外系统 10 移除，血液自然地保留在血液取样装置 110 的储存器 118 内，直到可压缩部 134 被临床医生压缩为止。当处在未压缩的位置时，通过血液对通路管腔 122 周边的表面张力及储存器 118 内的流体压力的结合，血液被保留在储存器 118 内。相应地，管状部 120 的纵向长度及通路管腔 122 的周长被选定成使得当压力在一定的范围内时，血液被保留在储存器 118 内。当储存器 118 的内部容积减少时，压力增加到超出能够保留血液的范围，进而使血液通过通路管腔 122 从取样装置 110 流出。血液可被排出到即时检验装置 30，例如血液检验条、诊断板卡或其他类型的血液检验 / 分析装置上。

[0041] 在取样装置 110 的某些实施例中，取样装置 110 可包括多个在储存器 118 内的腔室。每个腔室可具有单独且相应的可压缩部 134，用于分配仅容纳在对应腔室内的流体。这样，取样装置 110 可容纳用于不同类型检验的各个单独的样品。例如，各腔室可具有特定检验所需的不同容积。此外，一些腔室可包括化学制剂、血液保藏剂或特定检验所需的特定试剂。

[0042] 同样需要指出的是，在取样装置 110 仍然连接至血管外系统 10 时，取样装置 110 的可压缩部 134 可用于辅助从血管通路装置 12 抽取血液至储存器 118。例如，使用者可“泵吸”取样装置 110 的可压缩部 134，以辅助把血液样品抽至储存器 118。

[0043] 参考图 5-7，在某些构型中，血液取样装置 110 的可移除式端盖 116 被移除，替代地，取样装置 110 经由螺纹端口 128 及流出管腔 126 连接至样品容器收集装置 112。样品

容器收集装置 112 可为真空管收集系统（例如，Vacutainer）。样品容器 138 可为具有可刺穿封盖的真空试管或者其他的合适的医用容器，正如现有技术中已知的。样品容器收集装置 112 构造成通过取样装置 110 在单独的血管通路装置 12 及样品容器 138 之间建立流体连通，使得样品容器 138 可填充血液样品。需要指出的是，当该样品容器为真空管时，血管外系统 10 与该真空管内部之间的压差可辅助抽取流体经由血管外系统 10 进入样品容器 138。充满的样品容器 138 可被送至临床实验室，以进行某些在医疗行业中通常进行的血液检验。

[0044] 样品容器收集装置 112 包括大致圆筒形的主体 140，该主体 140 具有紧固件 142，用于把收集装置 112 连接至取样装置 110 的主体。例如，该收集装置 112 可被构造成通过相应的螺纹盖 144 而附接至取样装置 110 的螺纹端口 128。圆筒形主体 140 限定了内部区域 146，其具有可接收样品容器 138 的开口端 148。填充接头 150 在内部区域 146 内延伸，从位于收集装置 112 基部的螺纹盖 144 延伸进入内部区域 146。填充接头 150 可包括带锋利尖端 154 的细长针插管 152，该尖端 154 用于刺穿样品容器 138 的封盖 139。

[0045] 收集装置 112 被构造成使得样品容器 138 通过内部区域 146 的开口端 148 插入，封盖 139 侧在前，然后与填充接头 150 的针尖 154 接触。针插管 152 的尖端 154 能穿透封盖 139，以进入样品容器 138 的内部。这样，血液能通过取样装置 110 及填充接头 150 从血管通路装置 12 流入样品容器 138 的内部容积，由此填充样品收集容器 138。

[0046] 在某些构型中，诸如隔膜 156 的限流器安置在填充接头 150 的管腔内。当将样品容器 138 附连至收集装置 112 时，隔膜 156 转换到打开位置，以允许流体流过隔膜填充样品容器 138。当将样品容器 138 移除时，隔膜 156 能转换至关闭位置，从而阻挡流体通过针插管 152。需要指出的是，隔膜 156 以类似的方式对上述取样装置 110 的实施例的排气端盖 116 起作用。更加具体地，当隔膜 156 处在打开位置时，在真空管连接至取样装置的情况下，空气能从血管外系统排入至真空管或者样品收集容器，使得在血管外系统 10 内的空气通过针插管 152 从血管外系统 10 排出。当隔膜 156 处在关闭位置时，限制了流体流动及空气流动，从而防止空气从系统排出并且防止血液填充取样装置。实质上，当将接头 150 与血液取样装置连接时，一旦与接头连接，血液取样装置便通过真空管而填充血液。

[0047] 一旦在储存器 118 内保留了足够量的血液，就可将取样装置 110 及连接的收集装置 112 从血管外系统 10 移除。血液可通过取样装置 110 的通路管腔 122 排出，以用于根据上述方法进行检验和分析。正如上述的生物取样装置 110 的情况，储存器 118 及通路管腔 122 被构造成在预定的流体压力范围内保留血液。当使取样装置 110 的可压缩部朝储存器 118 向内弯曲时，储存器 118 内的压力增加，从而导致流体经由通路管腔 122 从取样装置 110 排出。通过关闭的隔膜 156 防止血液经由流出管腔 126 排出。

[0048] 现参考图 8-10，描述血管外系统 10 的另一个实施例，其包括血管通路装置 12，血管通路装置 12 具有流通部 210 及侧端口 212。除了侧端口 212 外，流通部 210 还包括主流出端口 214。如图 8 所示，主流出端口 214 和 / 或侧端口 212 可包括母鲁尔锁连接器，其被构造成接收相应的血液取样装置 110 的狭窄管状部 120。

[0049] 通过在主流出端口 214 及侧端口 212 上都包括血液取样装置 110，可收集用于不同类型检验和分析的血液样品。例如，取样装置 110 可被构造成收集不同量的血液。替代地，一个血液取样装置 110 可包括保藏剂或抗凝剂，以改变收集的血液的成分；而第二个取

样装置 110 可不包括任何这种化学成分。在某些实施例中，侧端口 212 可用于在血液取样装置保持连接至接头及血管通路装置时获取血液样品。

[0050] 在一个非限制性的实施例中，不含化学保藏制剂的取样装置 110 可连接至样品容器收集装置 112。在该构型中，通过同样的血管通路装置 12 可同时收集用于即时检验的含保藏剂的血液样品、用于另外的即时检验的不含保藏剂的血液样品、以及容纳在样品容器 138 内用于常规实验室检验的血液样品。不需要额外的刺手指或插入针来从患者获得所需的样品。在某些实施例中，取样装置 110 可具有色码，以便使用者可容易地区分哪个取样装置 110 包括额外的化学保藏制剂以及哪个取样装置 110 不包括额外的化学保藏制剂。

[0051] 参考图 11 及 12，描述了具有流通部 210 及取样装置 110 的血液取样装置 110 的剖面图。流通部 210 包括自主流出端口 214 的鲁尔通路接头 22 延伸的主管腔 216，血液取样装置 110 也包括延伸至侧流出端口 212 的侧管腔 218。该取样装置还可包括内部的可转换阀 220。如图 11 所示，阀 220 构造成使得当其处在不偏压且关闭的位置时，容许流体经由主管腔 216 从鲁尔通路接头 22 流动至主流出端口 214，同时阻止流体经由侧管腔 218 流动至侧端口 212。该构型允许血液直接流至样品容器收集装置 112，使得样品容器 138 可容易地（如果需要的话连续地）填充。如图 12 所示，当取样装置 110 的狭窄管状部 120 及通路管腔 122 被插入至侧端口 212 时，阀 220 转换至第二位置。更加具体地，狭窄管状部 120 与阀 220 的一部分接触，并且把阀 220 推开。当阀 220 被推开时，主管腔 216 与侧管腔 218 之间建立流体连通，由此使通过侧端口 212 插入的取样装置 110 填充用于检验的血液。

[0052] 参考图 13，描述包括主流出端口 214 及侧端口 212 的血管外系统 10 的又一个实施例，其中主流出端口 214 和侧端口 212 都连接至取样装置 110，取样装置 110 上连有端盖 116。取样装置 110 不是如图 8 中所示的那样连接至样品容器收集装置 112。在该构型中，取样装置 110 可被填充并用于不同的检验及分析过程。如上所述，一个取样装置 110 可包括化学保藏制剂，而另一个可不包括化学保藏制剂。取样装置 110 可含有色码，以区分哪个取样装置将用于哪种检验或分析过程。

[0053] 在已经描述了血液取样装置 110、样品容器收集装置 112 的构件以及血管外系统 10 的不同构型后，现描述利用血管外系统 10 收集血液样品的方法。临床医生利用任何已知的确立血管通路的工具（例如针 14、导管 16 或在现有技术中已知的血液收集套件）在患者身上确立血管通路位置。针 14 和 / 或导管 16 可包括用于将使用者与针 14 遮蔽开的遮蔽结构 18 及其他在现有技术中已知的安全结构。延伸管 20 连接至血管通路装置 12，并且自血管通路位置延伸至具有端口或鲁尔通路接头 22 的管的打开端。鲁尔通路接头 22 可包括阀或隔膜 156，以在鲁尔通路接头 22 未连接至其他装置时防止流体从该血管通路位置流动。替代地，该管可具有如夹具 24 的限流器，可将其手动地从允许流体流动的位置转换至限制流体流动的位置。临床医生可按需转换夹具 24 以进行所需的过程。

[0054] 一旦血管通路装置 12 准备就绪，临床医生可将取样装置 110 的狭窄管状部 120 插入至血管通路装置 12 的母鲁尔通路接头 22，从而在取样装置 110 与血管通路装置 12 之间建立流体连通。在某些构型中，取样装置 110 设置有已经附接的排气端盖 116。当血液抽入至血管外系统 10 时，在该系统内的空气从端盖 116 排出，从而向取样装置 110 抽取血液。替代地，取样装置 110 可设置有附接至其上的样品容器收集装置 112。在该情况下，空气通过取样装置 110 排出，然后通过收集装置 112 的针插管 152 从血管外系统 10 出来。

[0055] 如果将收集装置 112 连接至血管外系统 10，临床医生将允许血液经由取样装置 110 流入样品容器 138 内。当容器 138 填充了所需量的血液时，将样品容器 138 从收集装置 112 移除。样品收集容器 138 的移除将引起收集装置 112 的隔膜 156 封闭，从而阻止血液通过针插管 152 进一步流动。临床医生可将另外的样品容器 138 插入至收集装置 112，以收集另外的血液样品。一旦填充完所需数量的样品容器 138，隔膜 156 关闭，血液收集在取样装置 110 的储存器 118 内。

[0056] 在任一上述的构型中，下一步骤是将取样装置 110 从血管通路装置 12 移除。在某些构型中，在将取样装置 110 移除之前，临床医生必须关闭限流器或夹具 24，以阻止额外的流体流经延伸管 20。替代地，母鲁尔通路接头 22 可包括自动关闭型阀或隔膜 156，该阀或隔膜 156 关闭以阻止流体进一步流经血管外系统 10。当将取样装置 110 从母鲁尔通路接头 22 移除时，血液通过其相对于通路管腔 122 的内周壁的表面张力而保留在取样装置 110 的储存器 118 内。然后，临床医生将取样装置 110 移至例如检验条的即时检验装置 30。如图 14 所示，临床医生压缩取样装置 110，使可压缩部 134 朝储存器 118 向内弯曲，由此减少储存器 118 的内部容积并且增加储存器 118 内的流体压力。当达到一定的内部流体压力时，容纳在储存器 118 内的血液的一部分经由取样装置 110 的通路管腔 122 及狭窄管状部 120 从储存器 118 排出。排出的血液可收集在检验条上或者诊断检验板卡内。然后，临床医生可采用即时检验装置 30 分析血液样品，并记录相关结果以进行进一步分析。

[0057] 本血液取样装置 110、血管外系统 10 及其使用方法显著地减少了在采用 IV 或类似血液收集套件创建血管通路之后获得诊断用血液样品所需的构件的数量。如本文中所述，血液取样装置 110、样品容器收集装置 112 及血管外系统 10 的实施例可用于在创建静脉通路的常规过程中获得、准备及直接检验血液样品。血管外系统 10 也可用于填充标准样品容器 138，以送至实验室进行常规检验。通过减少过程步骤的数量并减少取样及获得检验结果之间的时长，这些实施例有利于临床医生的整个血液取样过程。

[0058] 如上所述，在现有技术中已知各种即时检验装置 30。这类即时检验装置 30 包括检验条、载玻片、诊断板卡、或其他检验及分析的检验装置。检验条、载玻片及诊断板卡是接收血液样品并检验该血液样品的一个或多个生理和生化状态的即时检验装置 30。许多即时检验装置 30 可采用基于板卡的体系结构来分析非常少量的血液，不需要将样品送至实验室进行分析。从长远来看，这节约了获得结果的时间，但是对高度常规化的实验室环境产生了一系列不同的挑战。这类检验板卡的示例包括 Abbot 集团公司的 **i-STAT®** 检验板卡。诸如 **i-STAT®** 板卡的检验板卡可用于检验各种状况，包括化学物和电解质、血液学、血气浓度、凝血或心脏标记物的存在情况。采用所述板卡的检验结果能很快地提供至临床医生。

[0059] 尽管已经基于目前认为是最实用且最优选的实施例详细地描述了本发明以作为示例，但是应当理解，这些细节仅是为了示例，本发明不限于所披露的实施例；相反地，本发明旨在涵盖在所附权利要求范围和精神内的修改和等同布置。例如，应当理解，本发明构思的是在可能的情况下任何一个实施例的一个或多个特征能与任何其他实施例的一个或多个特征组合。

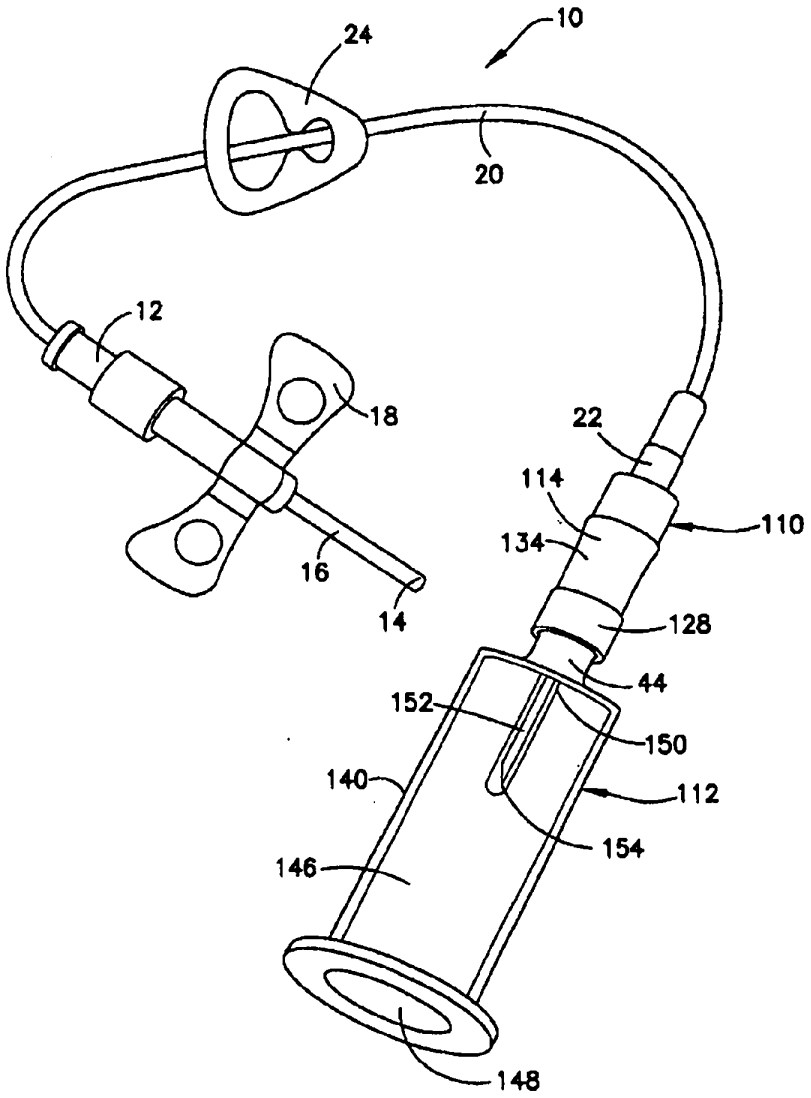

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图 1

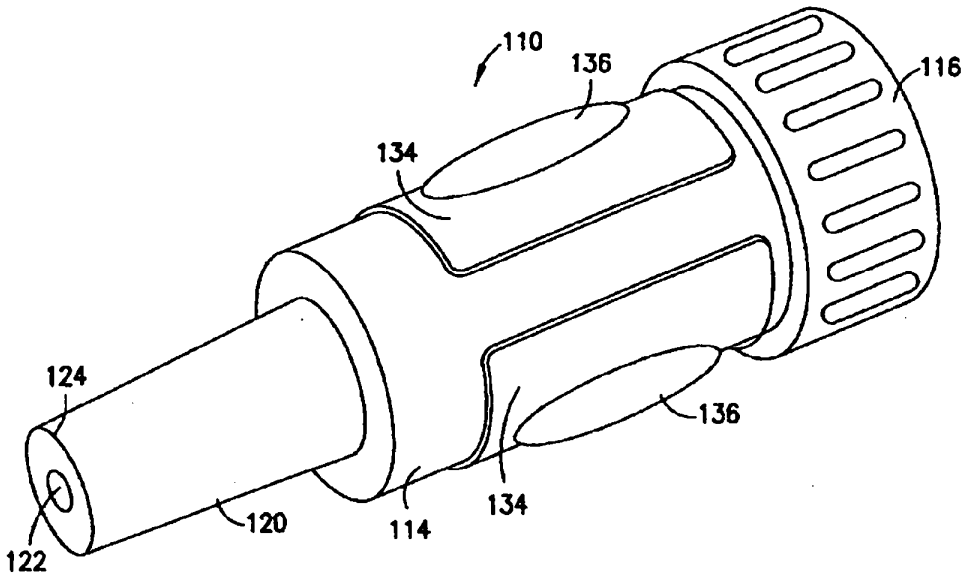

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图 2

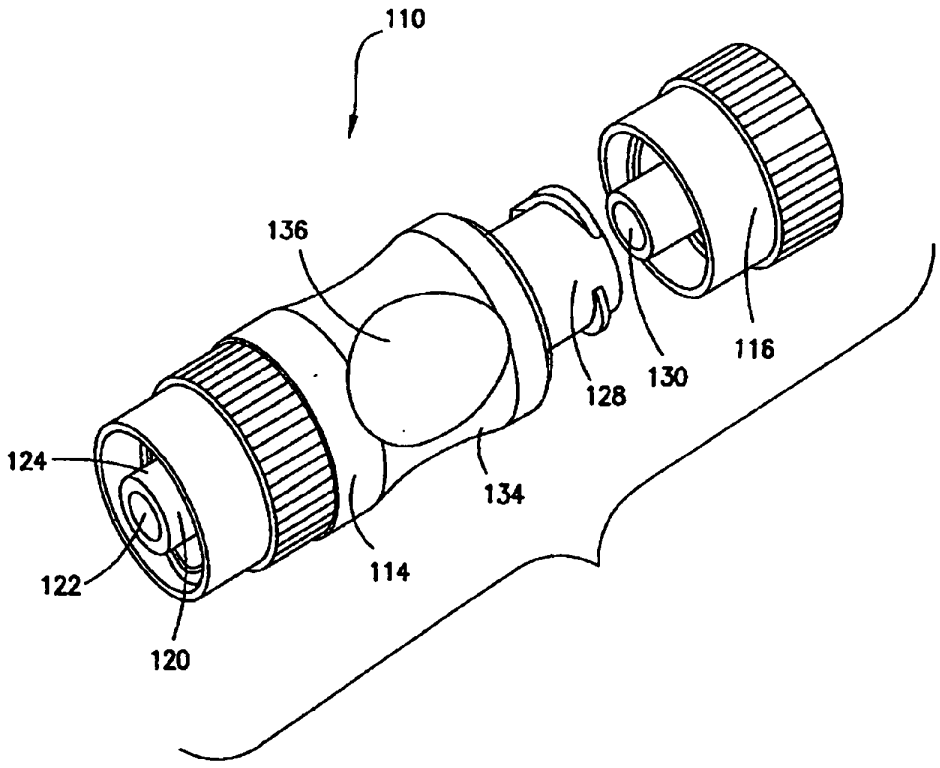

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图 3

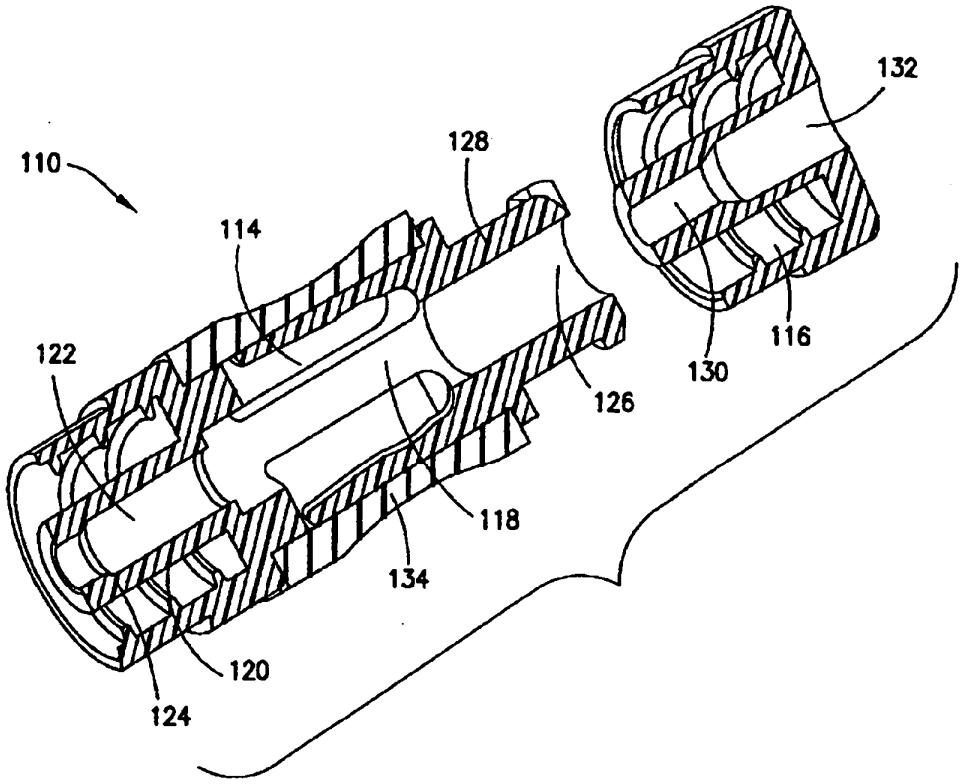


图 4

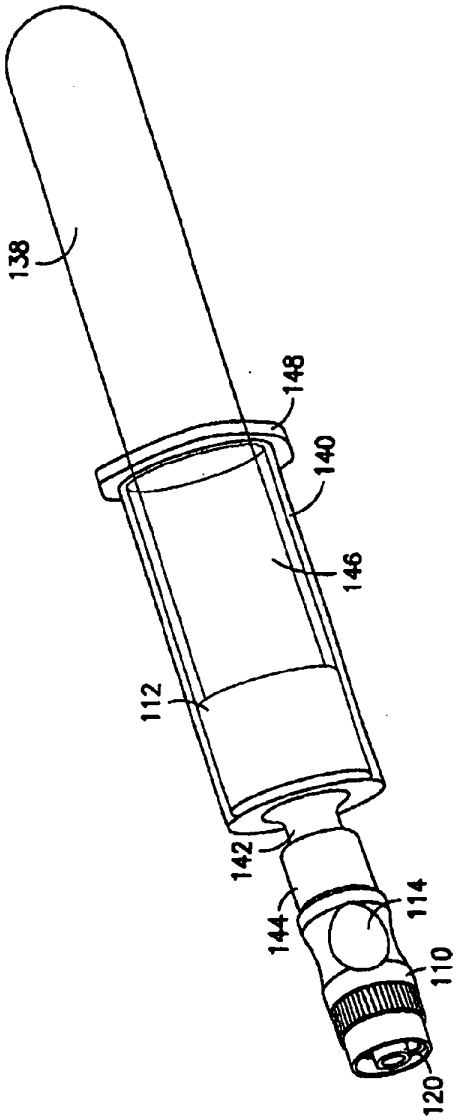


图 5

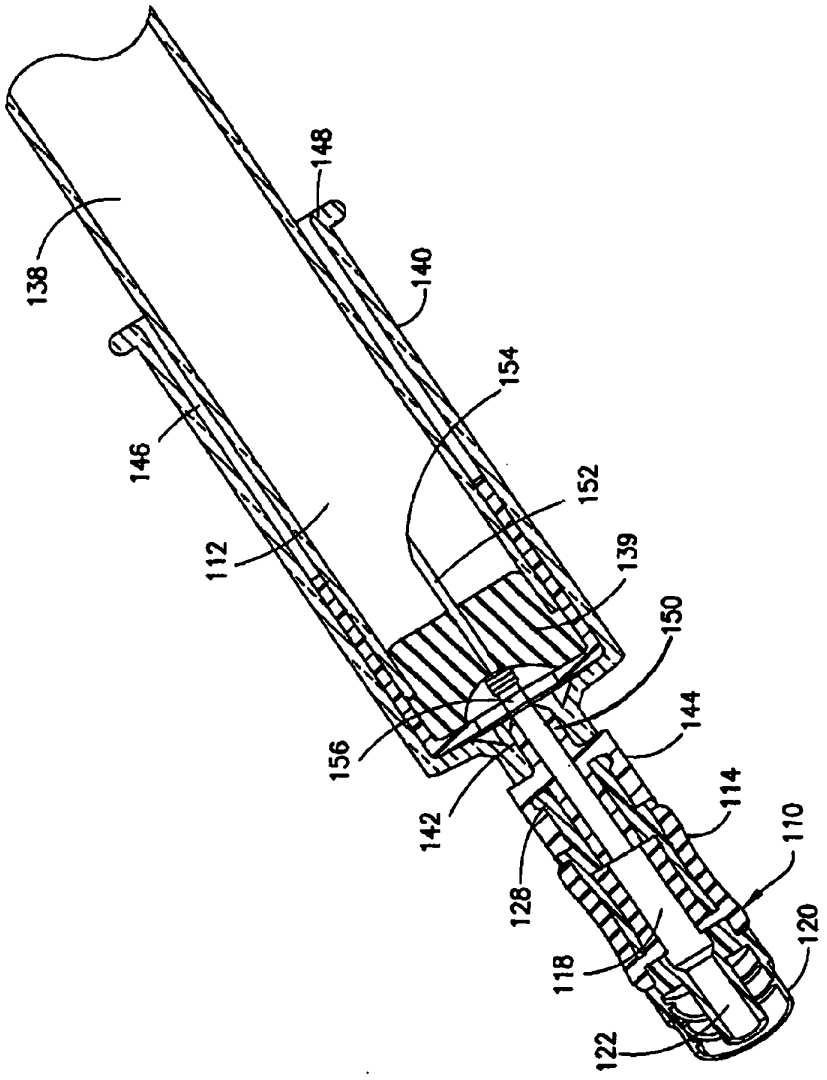

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图 6

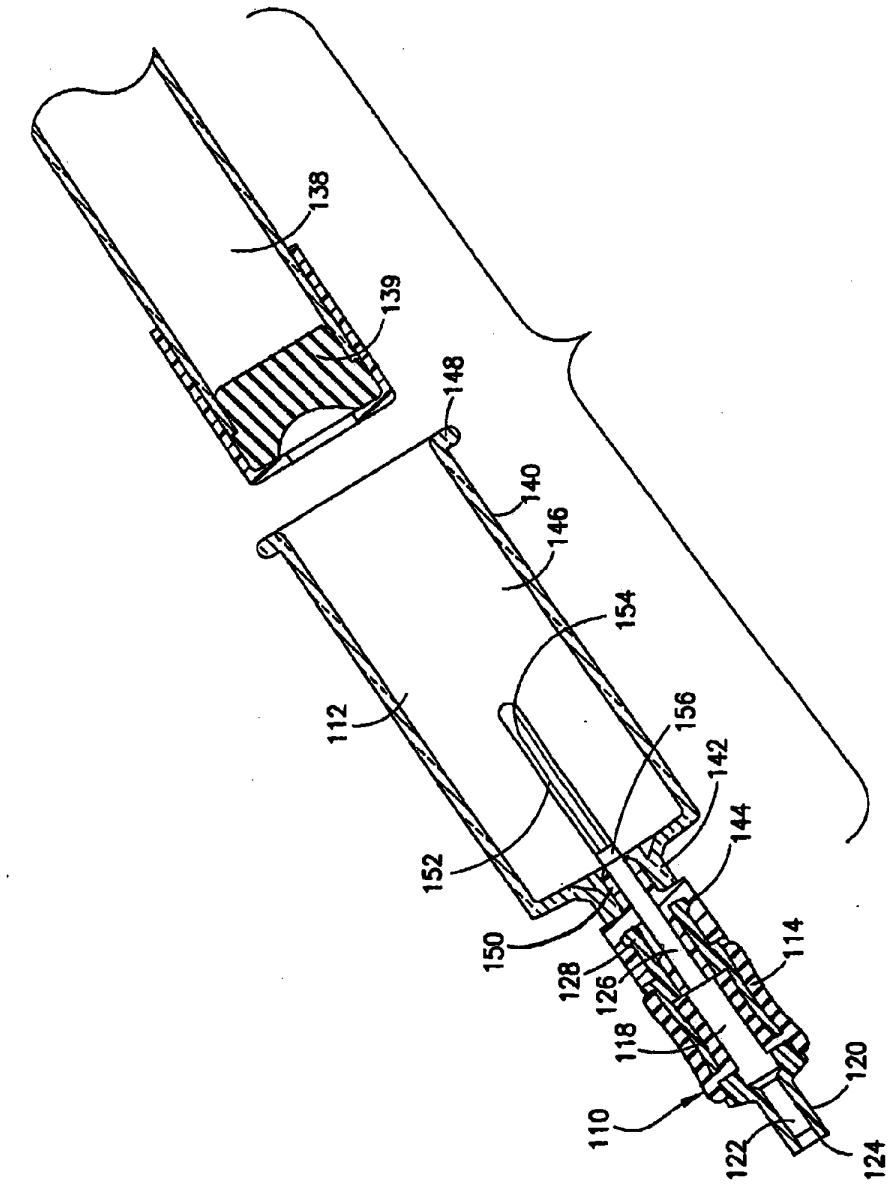

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图 7

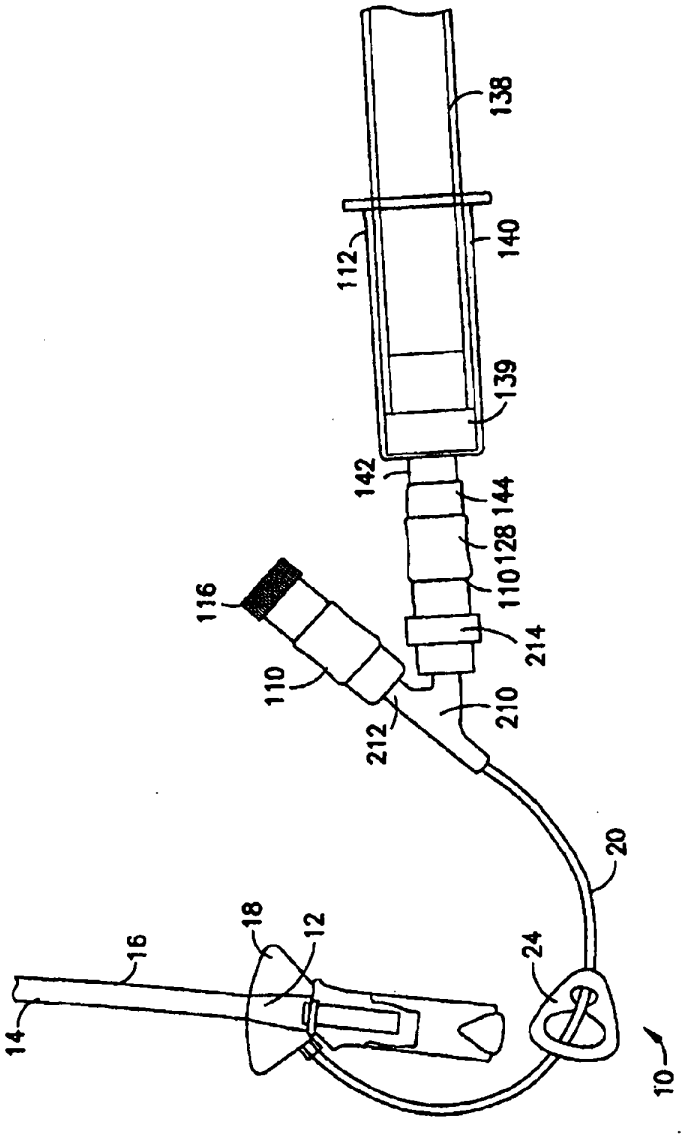

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图 8

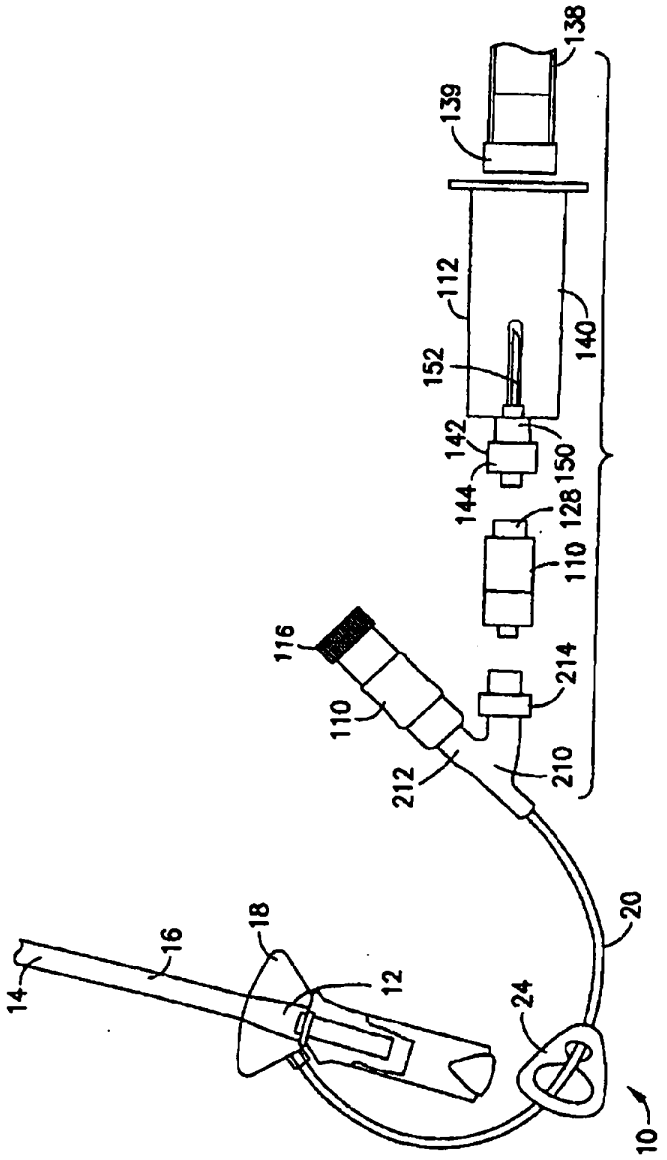

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图 9

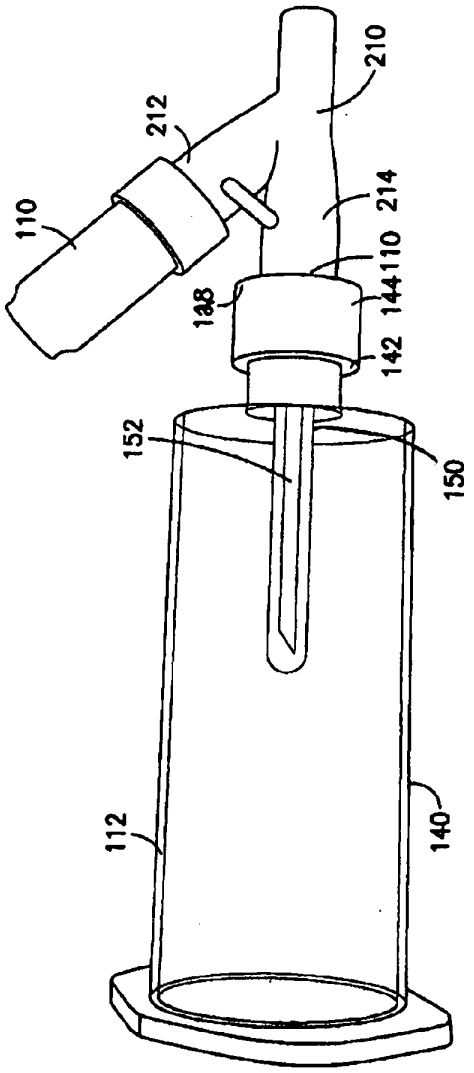

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图 10

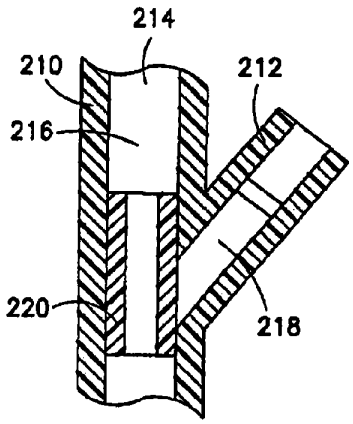

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图 11

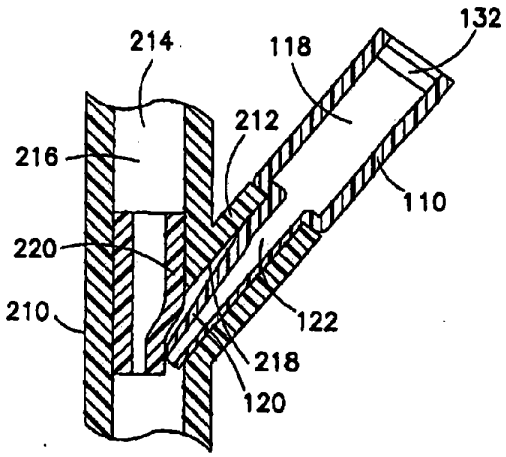


图 12

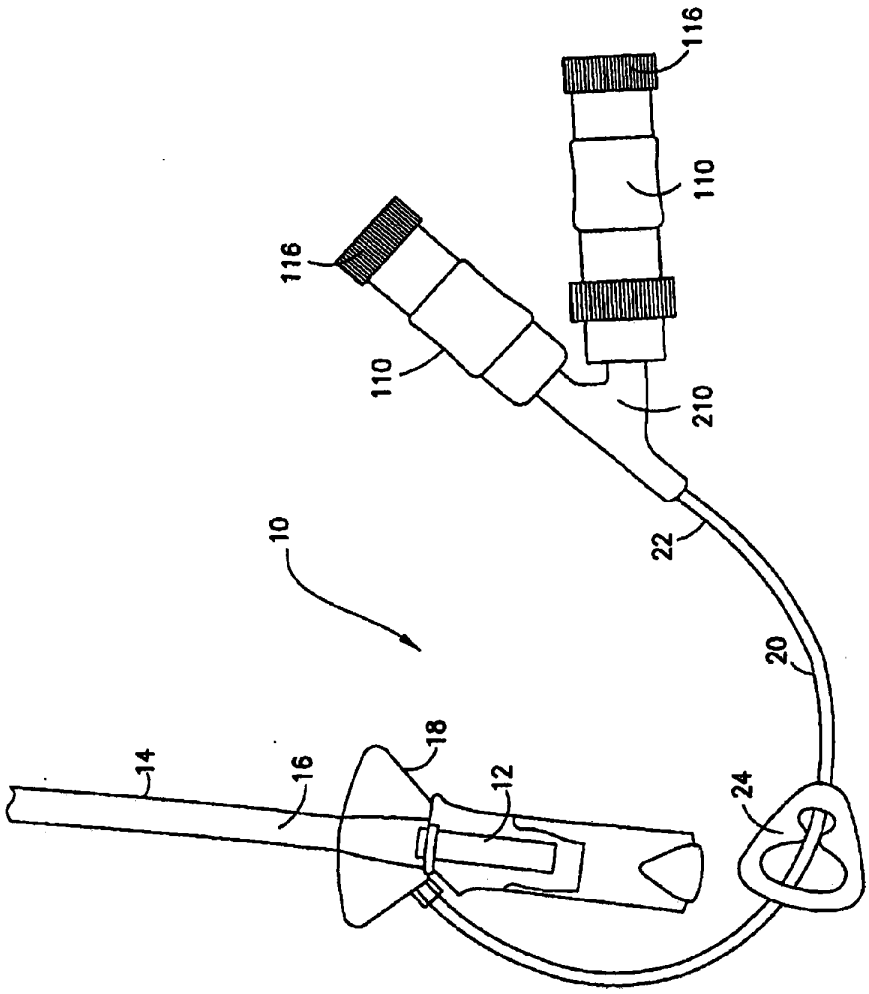


图 13

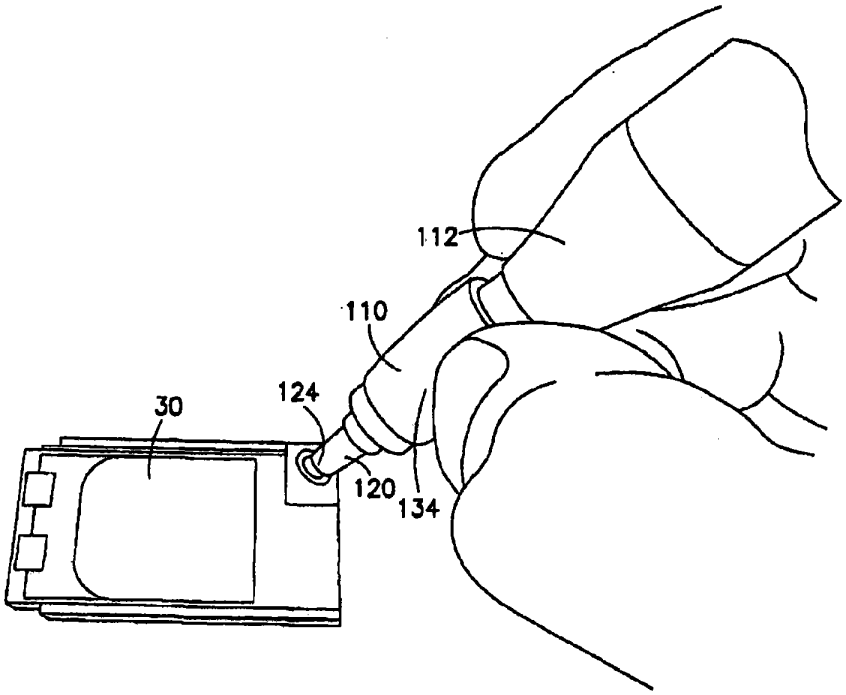


图 14

Espacenet

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Apparatus for processing a fluid sample

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This invention relates to an apparatus for an apparatus for processing a fluid sample comprising: (i) a sample processing chamber comprising a fluid inlet and a fluid outlet; (ii) a waste chamber downstream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and wherein the fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path; (iii) at least two further chambers up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet; (iv) a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path; and (v) a passive means for restricting the flow of fluid. This invention also relates to a method and use of the same.

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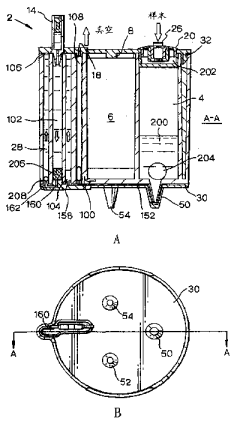
权利要求书 4 页 说明书 21 页 附图 7 页

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用于处理流体样本的设备

[57] 摘要

本发明涉及一种用于处理流体样本的设备，其包括：(i)样本处理腔室，其包括流体入口和流体出口；(ii)废物腔室，其位于样本处理腔室的下游并与样本处理腔室的流体出口流体连通，并且其中在样本处理腔室出口和废物腔室之间的流体连通包括分叉的分析物流动通道；(iii)至少两个附加腔室，其位于样本处理腔室的上游并与样本处理腔室的流体入口流体连通；(iv)用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中的装置；以及(v)用于限制流体的流动的被动装置。 本发明还涉及一种方法及其用途。



1、一种用于处理流体样本的设备，该设备包括：

（i）样本处理腔室，其包括流体入口和流体出口；

（ii）废物腔室，其位于样本处理腔室的下游并与样本处理腔室的流体出口流体连通，并且其中在样本处理腔室出口和废物腔室之间的流体连通包括分叉的分析物流动通道；

（iii）至少两个附加腔室，其位于样本处理腔室的上游并与样本处理腔室的流体入口流体连通；

（iv）用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中的装置；以及

（v）用于限制流体的流动的被动装置。

2、根据权利要求 1 所述的设备，其特征在于，所述用于使流体从所述至少两个附加腔室中的至少一个腔室运动通过样本处理腔室的装置包括用于产生真空的装置。

3、根据权利要求 2 所述的设备，其特征在于，所述废物腔室包括一出口部，该出口部与所述用于产生真空的装置相连。

4、根据权利要求 2 所述的设备，其特征在于，所述分析物流动通道包括一出口部，该出口部与所述用于产生真空的装置相连。

5、根据权利要求 1 所述的设备，其特征在于，所述用于使流体从所述至少两个附加腔室中的至少一个腔室运动通过样本处理腔室的装置包括活塞，该活塞能够压下以从至少一个附加腔室中排出流体。

6、根据权利要求 5 所述的设备，其特征在于，所述用于使流体从所述至少两个附加腔室中的至少一个腔室运动通过样本处理腔室的装置还包括用于产生真空的装置。

7、根据权利要求 1 至 6 中任一项所述的设备，其特征在于，所述用于使流体从所述两个附加腔室中的每一个运动通过样本处理腔室的装置，使流体顺序地从所述至少两个附加腔室中的第一腔室运动通过样本

处理腔室，并进入废物腔室中，然后从所述至少两个附加腔室中的第二腔室运动通过样本处理腔室，并进入废物腔室或者分叉的分析物流动通道中。

8、根据权利要求 1 至 7 中任一项所述的设备，其特征在于，所述用于限制流体流动的被动装置包括阀，该阀位于在所述样本处理腔室和废物腔室之间的流体连通中。

9、根据权利要求 8 所述的设备，其特征在于，所述阀位于分叉的分析物流动通道的下游。

10、根据权利要求 8 所述的设备，其特征在于，所述阀包括小珠，该小珠通过施加正压或负压而打开。

11、根据权利要求 1 至 10 中任一项所述的设备，其特征在于，所述用于限制流体流动的被动装置包括容器，该容器位于在所述至少两个附加腔室中的至少一个腔室和样本处理腔室之间的流体连通中。

12、根据权利要求 1 至 11 中任一项所述的设备，其特征在于，所述用于限制流体流动的被动装置包括小直径的流体通道，从而流体不会在没有施加正压或负压的情况下而流过该通道，该流体通道位于在所述至少两个附加腔室中的至少一个腔室和样本处理腔室之间的流体连通中。

13、根据权利要求 1 至 12 中任一项所述的设备，其特征在于，该设备包括收集腔室，该收集腔室位于所述分析物流动通道的下游并与分析物流动通道出口流体连通。

14、根据权利要求 13 所述的设备，其特征在于，所述收集腔室包括试剂，该试剂优选地为包括一种或多种核酸扩增试剂的试剂，更优选地为从下组中选择的试剂，该组包括核酸引物、核酸探针、荧光染料、酶缓冲剂、核苷酸、镁盐、牛血清白蛋白和变性剂。

15、根据权利要求 13 所述的设备，其特征在于，所述收集腔室包括出口部，该出口部可选择地与用于产生真空的装置相连。

16、根据权利要求 15 所述的设备，其特征在于，该设备包括后处理腔室，所述后处理腔室位于所述收集腔室的下游并与收集腔室出口流体连通，并且其自身可选择地包括出口，该出口可以与用于产生真空的装

置相连。

17、根据权利要求 1 至 16 中任一项所述的设备，其特征在于，所述样本处理腔室包括活动元件，所述活动元件优选地为从下组中选择的捕获元件，该组包括微流体芯片、固相材料、过滤器、过滤器组、亲和性基质、磁分离基质、体积排阻柱、毛细管及它们的混合物。

18、根据权利要求 17 所述的设备，其特征在于，所述样本处理腔室包括玻璃纤维过滤膜。

19、根据权利要求 1 至 18 中任一项所述的设备，其特征在于，所述至少两个附加腔室中的至少一个腔室预填充有缓冲剂溶液，优选地为从下组中选择的缓冲剂溶液，该组包括乙酸钾和三羟甲基氨基甲烷盐酸盐的水溶液，或者乙酸钾和三羟甲基氨基甲烷盐酸盐的乙醇水溶液。

20、根据权利要求 1 至 19 中任一项所述的设备，其特征在于，所述至少两个附加腔室中的至少一个腔室用作样本腔室，所述样本腔室包括入口部，通过该入口部将样本引入设备中。

21、根据权利要求 20 所述的设备，其特征在于，所述样本腔室入口部包括过滤膜。

22、根据权利要求 20 或 21 所述的设备，其特征在于，所述样本腔室包括试剂，所述试剂优选地为包括溶解试剂的试剂，更优选地为离液序列高的盐。

23、根据权利要求 1 至 22 中任一项所述的设备，其特征在于，该设备包括至少一个位于设备主体外部的腔室。

24、根据权利要求 23 所述的设备，其特征在于，所述位于设备主体外部的腔室为所述收集腔室。

25、根据权利要求 23 所述的设备，其特征在于，所述位于设备主体外部的腔室为所述至少两个附加腔室中的至少一个腔室。

26、根据权利要求 23 所述的设备，其特征在于，位于外部的至少一个腔室具有涂覆有导电聚合物的壁。

27、一种处理流体样本的方法，包括：

（i）将样本放置在根据权利要求 1 的设备的样本处理腔室中；

（ii）施加正压或负压以使流体运动通过该设备；

（iii）对该样本进行一个或多个处理步骤；以及

（iv）从所述分叉的分析物流动通道收集处理过的样本。

28、根据权利要求 1 所述设备的用途，用于从流体样本中纯化并浓缩核酸材料。

29、根据权利要求 28 所述的用途，其特征在于，然后对所述核酸材料进行聚合酶链反应扩增。

用于处理流体样本的设备

技术领域

本发明涉及一种用于处理流体样本的设备以及相关方法。

背景技术

可以由于种种原因而对流体样本（例如，临床或者环境样本）进行分析。目前所关注的领域是在流体样本（例如，临床或者环境样本）中正确识别生物材料的方法的发展。其之所以重要是因为其将有助于病状的早期诊断，这样就能进行快速治疗和感染控制，或者有助于识别环境污染物等。尽管对于生物材料的正确识别，核酸扩增（例如，聚合酶链反应（PCR））是非常有用且常用的方法，但是当试图将其成功地开发为在日常非实验室环境中用于在多种个别的流体样本中快速识别生物材料时，例如在所关心的疾病诊断的病人或地点附近时，会出现一些问题。

其中一个关键问题在于，在对典型的临床或环境样本进行核酸扩增之前，需要用试剂进行一系列处理步骤（其中一些是危险的）来纯化并浓缩生物材料。然而，核酸扩增只是这样一种技术的多种不同的可行示例中的一种，在所述技术中需要处理样本（尤其是样本样本），其中涉及大量同时或者连续的处理步骤。这些处理步骤本身可以很多且可以变化，并且除了可能的稀释和浓缩步骤外还可包括例如化学、光学、电、热、机械、声学、加工、传感或者监测。迄今为止，这种复杂的处理是在实验室中进行，其中可依次手动处理样本，或者通过使用专家机器人设备并行加工许多不同样本。然而，存在一些与这些方法相关的问题。这些问题包括速度慢、资源密集、昂贵、易出错和易交叉样本污染。此外，传统的流体处理系统需要流体样本顺序流过一系列不同的腔室，其中各个腔室依次用于单个步骤，这会导致样本的损失，并且这些过程的自动化需要使用复杂的流体组件和处理算法。

这样，仍需要开发一种改进的设备，从而可以使用一系列的预定的连续步骤来处理流体样本，以获得期望的最终产物。这种设备应该易适用于非实验室环境并且由具有很少或没有实验室训练的操作者使用，从而其可以在例如通过核酸扩增进行分析之前，用于操纵流体样本，例如临床或环境样本。这种设备将确保可以快速获得分析结果、使熟练的工作人员免于重复任务并降低成本。另外，这种设备应具有足够的一致性和准确度以防止后面试验的失败，这种设备应能便宜地生产并且是一次性的，从而使交叉污染的可能性最小化并不必对大量装置进行消毒。

现有技术的检索发现了 US 6,374,684，其中公开了一种流体控制和处理系统，该系统包括多个腔室和可运动的阀体，该阀体可以用于根据给定的规程（protocol）来促进对流体样本的处理。尽管这为用于处理流体样本的设备领域中提供了进展，但是仍存在一些问题。一个问题是，为了使流体样本顺序地暴露于不同的溶液，有必要使阀体旋转以通过一些外部端口将样本处理腔室与各溶液的容器依次相连。这种设备并不十分适于由非熟练的实验室工作人员在非实验室环境中使用，这是因为需要将外部端口与各所需溶液的容器相连，而这是不切实际的并且当为危险化学药品时可能有安全隐患，以及其他原因。此外，这种设备由于其复杂性而具有较高的相关成本，并且不可能作为一次性设备节省成本，这导致潜在的交叉样本污染。另外，该设备采用单独的流体移动腔室来依次将各处理溶液传递到样本，并除去任何废料，这可导致在流体移动腔室中剩余材料的混合以及可能破坏灵敏的处理顺序。仍需要开发一种能克服上述问题的用于处理流体样本的设备。

WO 00/62931 公开了一种微流体设备，其具有样本入口，该入口通过一微通道与检测模块相连。在该设备中的流体运动由接通或断开施加电场的芯片泵来控制。该设备可选择地包括存储模块、废物模块、反应模块等，并且该申请以示例的方式公开了将该设备用于核酸扩增反应。该设备可用于对微量体积样本进行核酸扩增反应，但是仍存在关于如何开发这样一种设备的问题，该设备可用于这样的领域中，其中如在临床或环境样本的情况下样本容积为几毫升。

另外，US 6,391,541 公开了一种用于从流体样本分离所需分析物的药筒（cartridge），该药筒包括样本流动通道、样本溶解腔室、废物腔室、分析物流动通道以及用于引导流体流动的流动控制器。该专利还以示例的方式公开了将该设备用于从流体样本中分离核酸样本。该设备还展示了处理流体样本领域中的进展，但是仍存在一些问题。这些问题包括，为了可以以期望的方式（包括所期望的化学和物理处理步骤）来处理样本，该设备包括复杂的流体通道。这需要使用多个贯穿设备的阀，这些阀需要机械打开/关闭，以确保流体以期望的方式行进。另外，该复杂的结构可使得一些样本留在流体药筒内，从而减少了最终处理的样本量。这在大容量的、保留有低浓度的期望分析物的样本的情况下会导致不准确的结果。最后，该药筒的复杂性使得该设备更难于由该领域中不熟练使用者操作。

已经开发了一种克服上述问题的设备以及相关方法。该设备包括：样本处理腔室，其包括流体入口和流体出口；废物腔室，其位于样本处理腔室的下游并与样本处理腔室的流体出口流体连通，并且其中在样本处理腔室出口和废物腔室之间的流体连通包括分叉的分析物流动通道；至少两个附加腔室，其位于样本处理腔室的上游并均与样本处理腔室的流体入口流体连通；用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室，并进入废物腔室或者分叉的分析物流动通道中的装置；以及用于限制流体的流动的被动装置。

将流体样本可选择地通过样本腔室而引入样本处理腔室中，其中该样本腔室可选择地与功能性试剂相互作用。然后，使一种或多种流体处理溶液同时或顺序地从所述附加腔室中的至少一个腔室运动通过样本处理腔室（在那里它们与流体样本相互作用），然后进入废物腔室中。通过确保两个附加腔室都与样本处理腔室连通，可在不必依次形成各个流体连通路径的情况下使流体运动通过该设备。通过控制用于使流体运动通过流体连通路径的装置，可确保各个流体通过预定的规程流动进入样本处理腔室中，并且如果必要可使各流体在到达样本处理腔室之前与另一

流体的相互作用最小化。通过采用用于施加正压或负压以使流体运动通过该设备的装置，可以以最小的复杂性形成正确的流体流动通道，并且通过使用用于限制流体流动的被动装置，可以简单地控制流体通道。可以以多种方式来改进该设备。这些方式可选择地包括：采用施加正压和负压（即真空）的组合，以使流体以受控的方式运动通过该设备；在生产期间使腔室预先加载任何试剂或流体，因此使得该设备的使用者不必处理这些材料；使用多个被动阀，以防止流体通过该设备回流；以及将收集腔室集成入该设备中，从而可以直接收集处理过的样本用于进一步使用，例如用于核酸扩增。另外，可以选择性地使用一个或者多个腔室，使得可以对一种或多种流体（包括流体样本）进行物理处理，例如热、声学、光学、电处理、传感或者监测技术。

本发明的设备具有一些优点。这些优点包括：其可被容易地设计成适应多种预定的处理顺序，包括化学和物理步骤，从而能够简单地使用流体处理装置；该设备采用单个处理腔室，因此使样本损失最小；该设备、包括所有的化学试剂和任何生成的废物可完全集成在单个单元中，因此使样本污染最小化并且减少了使使用者暴露于潜在危险材料的可能性；由于减少了所使用的运动部件的数量，因此可能提高可靠性和使用简单性，即使对于具有很少或者没有实验室训练的使用者来说也是如此；以及制造廉价，这意味着该设备可设计为一次性的，从而进一步减少样本交叉污染的危险。

本发明的一个目的是开发一种用于处理流体样本的设备以及相关方法。本发明的另一目的是设计这样一种设备，其能够对流体样本以预定的顺序进行一系列的顺序的化学或物理处理步骤，优选在核酸扩增反应之前醇化并浓缩流体样本。本发明的另一目的是设计这样一种设备，其易于由具有很少或者没有实验室训练的使用者在非实验室环境下使用。本发明的又一目的是设计这样一种设备，使得任何所需的化学药品或废弃产物都保持集成在设备中，以使得使用者暴露于样本、化学品或者废物的可能性最小化。本发明的又一目的是设计这样一种设备，其制造廉价，从而在一次使用后可被处理掉，因此减少了样本交叉污染的可能性

并不必对大量设备进行消毒。从如下公开中将明白本发明的这些和其它目的。

发明内容

根据第一方面，本发明涉及一种用于处理流体样本的设备，其包括：

（i）样本处理腔室，其包括流体入口和流体出口；

（ii）废物腔室，其位于样本处理腔室的下游并与样本处理腔室的流体出口流体连通，并且其中在样本处理腔室出口和废物腔室之间的流体连通包括分叉的分析物流动通道；

（iii）至少两个附加腔室，其位于样本处理腔室的上游并均与样本处理腔室的流体入口流体连通；

（iv）用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中的装置；以及

（v）用于限制流体的流动的被动装置。

根据第二方面，本发明涉及一种处理流体样本的方法，包括：

（i）将样本放置在根据本发明的设备的样本处理腔室中；

（ii）施加正压或负压以使流体运动通过该设备；

（iii）对该样本进行一个或多个处理步骤；以及

（iv）从所述分叉的分析物流动通道收集处理过的样本。

根据第三方面，本发明涉及将根据本发明的设备用于从流体样本提纯并浓缩核酸材料的用途。

在这里引用的所有出版物除非另有说明，其全部内容均已参考的方式在此引用。

这里使用的术语“流体连通”是指存在于所关心腔室之间的通道，尽管流体流受到用于限制流体流动的一个或多个被动装置的限制，但流体可原则上可以流过该通道。

这里使用的术语“连续的流体连通”是指始终存在于所关心腔室之间的通道，流体可流过该通道。

这里使用的术语“用于限制流体流动的被动装置”是指限制流体流过给定通道的装置，但是其中可通过被动地，即纯粹地向装置或者流动通道自身施加正压或负压来克服该限制，从而允许流体沿着给定的通道流动。可选地，这些装置可由被动动作打开或由被动动作关闭。另外，根据施加压力的位置，该装置可允许流体沿着任一方向流过该装置所处的流体流动通道，或者该装置仅允许流体沿着单一方向流过流体流动通道。

这里使用的术语“流体样本”是指任何以气体、液体、包括由溶剂溶解的样本的溶液、或者包括一个或多个相的流体体系（例如，乳剂）存在的样本。“流体样本”还可指这样的样本，其最初以固态或者粘性液体被引入该设备中，但是然后通过添加一定量的溶剂被稀释或者溶解。

这里使用的术语“功能性试剂”是指用于本发明的设备或方法中的固态化学或物理试剂。其可包括以固态粉末、小珠、胶囊、压片等定量的一种或多种化学试剂，包括与流体样本相互作用的试剂。这种试剂的适当示例包括但并不限于溶解试剂，例如离液序列高的盐、核酸靶、核酸合成对照物、噬菌体、冻干的酶、染料、清洁剂等。然而，功能性试剂还应该理解为包括用于与流体样本相互作用的物理工具。这些物理工具可包括但并不限于磁力搅拌珠、加热装置、包被有抗体的磁性珠等。

下面将更详细地描述所述设备的元件。

本发明涉及一种用于处理流体样本的设备，包括样本处理腔室、废物腔室、至少两个附加腔室、和用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室，并进入废物腔室或者分叉的分析物流动通道中的装置；其特征在于，所述至少两个附加腔室中的各个腔室均与样本处理腔室流体连通，并且样本处理腔室与废物腔室流体连通。本发明的实施方式便于根据预定的规程来处理流体样本。

样本处理腔室是在其中对流体样本自身进行一个或多个处理步骤的设备区域。这些处理步骤可包括化学处理步骤，例如稀释样本、使用一种或多种缓冲剂溶液来顺序清洗样本、使样本与一种或多种化学试剂反

应，但是也可包括物理步骤，例如用一种或多种热辐射来照射流体样本、对流体样本进行声学处理等。样本处理腔室可选择地包括活动部件，优选地为从下组中选择的捕获元件，该组包括微流体芯片、固相材料、过滤器、过滤器组、亲和性基质、磁分离基质、体积排阻柱、毛细管以及它们的混合物。优选地，样本处理腔室包括能够捕获流体样本中的生物材料的捕获元件，例如能够捕获细胞、孢子、病毒、大分子或小分子、蛋白质等。所选择的正确的捕获元件将取决于待捕获材料的性质。这里使用的优选捕获元件为玻璃纤维过滤器，其横跨样本处理腔室的部分或整个内表面区域延伸。

样本处理腔室包括流体入口和流体出口，并且一方面与至少两个附加腔室流体连通，另一方面与废物腔室流体连通。废物腔室位于样本处理腔室的下游并与样本处理腔室的流体出口流体连通，并且至少两个附加腔室位于样本处理腔室的上游并均与样本处理腔室的流体入口流体连通。这些流体连通中的至少一个可以为连续的流体连通。在样本处理腔室出口和废物腔室之间的流体连通包括分叉的分析物流动通道。该流体连通也可以是连续的流体连通。该设备还包括这样的装置，其用于通过向所需的流动通道施加正压或负压，从而按照需要使流体从所述至少两个附加腔室中的各个腔室运动通过样本处理腔室，并进入废物腔室或者分叉的分析物流动通道中。优选地，用于使流体从所述两个附加腔室中的每一个腔室运动通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中的装置，使流体顺序地从至少两个附加腔室中的第一腔室运动通过样本处理腔室并进入废物腔室中，然后从另一附加腔室运动通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中。

用于使流体运动的多种不同装置都是可接受的。这些装置通过向期望的流动通道施加正压或负压而使流体运动。用于施加负压的装置的一个示例为用于产生真空的装置，该真空通过出口部（例如废物腔室上的出口部或者分叉的分析物流动通道上的出口部）与该设备相连，并且能够按需要吸引流体通过该设备。该真空可以使用本领域普通技术人员已知的几种不同的装置中的一种与出口部件相连。将真空与出口部相连的

一种有效的方法是使用风箱，这是因为这些风箱可以容易地与甚至较小的出口部相连，可以提供高容忍度并降低了对于非常准确地处理的需求。如果该设备将以机械的方式或者由非熟练的工作人员操作，则这种布置尤其有用。优选地，设备的废物腔室包括一出口部，用于产生真空的装置可与该出口部相连。这样的结果是，真空能够将流体从附加腔室中的至少一个腔室引导通过样本处理腔室并进入废物腔室中。还优选的是，分叉的分析物流动通道包括出口部，从而可以在这里容易地安装用于产生真空的装置。也可以多种方式来采用用于产生真空的装置。例如，其可以适于以预定顺序将流体引导通过该设备。可选择地，该设备可设计成包括用于限制流体流过该设备的被动装置，从而需要增加的真空力从各个腔室顺序释放流体，由此通过在使用期间增加真空度，可以例如通过控制流体流动通道的尺寸或者通过加入膜或闸门（其需要被动地打开以允许流体流动），来顺序地引导来自第一腔室的流体然后引导来自另一腔室的流体。使用真空也可适于将空气引导通过该设备作为在各流体运动之间的中间步骤，从而清理流体连通路径，并且不同的流体在进入样本处理腔室之前不会彼此相互作用。这对于非常灵敏的样本处理规程是很重要，例如其中在进入样本处理腔室之前第一缓冲剂与第二缓冲剂的相互作用会中和其效果，或者其中非常少量的材料整体到达样本是很重要的。如果使用真空，则还优选的是考虑可通过真空使设备内的任何材料雾化并从该设备排出至大气中。如果该设备适于与这样的试剂一起使用，该试剂如果释放就会造成安全危害，则采用该设备最小化或者消除雾化材料的释放是很重要的。这样一种可行的变化是将过滤膜加入至该设备中，或者加入至用于施加真空的装置中，从而使得雾化材料被捕获并且不会释放到大气中。

用于使流体运动通过该设备的另一合适装置的示例为这样的装置，其用于在流体后面施加正压或者力。同样可以通过本领域普通技术人员已知的多种装置来施加这种力。一个示例为在多个附加腔室中的一个使用活塞，该活塞的压下使得腔室中的任何流体通过流体连通路径排进样本处理腔室中，并然后进入废物腔室中。另外，使用用于在流体后面施

加力的装置，例如使用活塞可适于使得流体从至少两个附加腔室同时或者顺序运动，优选从附加腔室顺序地通过样本处理腔室并进入废物腔室或者分叉的分析物流动通道中。例如，可使一系列活塞中的一个或多个顺序地压下，以使流体顺序地从第一附加腔室运动通过样本处理腔室进入废物腔室，并且然后从另一附加腔室运动等等。在所述的两种情况下，可通过使用注射器、活塞、泵等手动地提供用于使流体运动的装置，或者通过将本发明的设备集成至能够按需要提供动力和装置的另一设备中而机械地提供用于使流体运动的装置。另外，这种用于施加正压的装置可以与用于限制流体流过该设备的被动装置结合使用。

优选地，在本发明的设备中，采用用于产生真空的装置以及用于在流体后面施加力的装置的组合，来使流体从附加腔室中的至少一个腔室运动通过样本处理腔室并进入废物腔室中。一起使用这两个装置的优点在于，在流体后面的初始力促使流体从任何给定腔室释放，真空可引导流体流动通过该设备，因此防止其从期望通道转向。这使得所述设备容易设计成使得流体可根据预定的规程从附加腔室顺序地流过样本处理腔室。

通过贯穿所述设备的、以期望的方式连接腔室的一个或多个通道，来提供本发明的流体连通路径。该设备设计成使得至少两个附加腔室在流体中通过样本处理腔室并进入废物腔室或分叉的分析物流动通道中。例如，可使一系列活塞中的一个或多个顺序地压下，以使流体顺序地从第一附加腔室运动通过样本处理腔室进入废物腔室，并且然后从另一附加腔室运动等等。在所述两种情况下，可通过使用注射器、活塞、泵等手动地提供用于使流体运动的装置，或者通过将本发明的设备集成至能够按需要提供动力和装置的另一设备中而机械地提供用于使流体运动的装置。另外，这种用于施加正压的装置可以与用于限制流体流过该设备的被动装置结合使用。

优选地，在本发明的设备中，采用用于产生真空的装置以及用于在流体后面施加力的装置的组合，来使流体从附加腔室中的至少一个腔室运动通过样本处理腔室并进入废物腔室中。一起使用这两个装置的优点

在于，在流体后面的初始力促使流体从任何给定腔室释放，真空可引导流体流动通过该设备，因此防止其从期望通道转向。这使得所述设备容易设计成使得流体可根据预定的规程从附加腔室顺序地流过样本处理腔室。

通过贯穿所述设备的、以期望的方式连接腔室的一个或多个通道，来提供本发明的流体连通路径。该设备设计成使得至少两个附加腔室与样本处理腔室流体连通。这些腔室可选择地设计成各自具有单独的流出通道，它们在进入样本处理腔室之前在同一点处相连。优选地，只有一个用于使溶液进入样本处理腔室中的进入点，即样本处理腔室入口，以降低设计的复杂性。这样，优选地，来自各个附加腔室的流出通道在进入样本处理腔室之前汇合然后流入共同的样本处理通道中。这些流体连通中的一个或多个可以为连续的流体连通。

为了使以不适当的方式流过腔室的流动最小化，优选地该设备包括用于限制流体流动通过该设备的被动装置，该设备设计成具有这样的特征：其限制任何特定流体流动路径直到需要该流动路径之时。否则，将导致流体从多个腔室同时流动，并因此会破坏样本处理顺序或者可导致流体从废物腔室回流通过该设备。控制这种流动的合适方法的示例包括：使用一个或多个覆盖通道的膜，当在它们后面或前面施加压力时所述膜将破裂；使用极小直径的通道，在不施加力的情况下流体由于其表面张力而不能流过所述通道；使用抽吸力预先填充任何包括缓冲剂溶液的腔室，该抽吸力可用于将这种流体保持在适当的位置直到施加释放它的力；使用贯穿该设备的阀，其通过真空、压力、磁体等操作；将流体连通路径设计成包括需要完全填充以形成流体连通的较小的容器，该流体连通允许在没有溢出的情况下容纳较小的泄漏，等等。优选地，该设备包括这些特征中的一个或多个，以确保适当的流体流动。在本发明的设备中，优选地，用于限制流体流动的被动装置包括一容器，该容器位于在至少两个附加腔室中的至少一个腔室与样本处理腔室之间的流体连通中。还优选地，用于限制流体流动的被动装置包括较小直径的流体通道，从而流体不会在没有施加正压或负压的情况下流过该通道，该流体通道位于

在至少两个附加腔室中的至少一个腔室与样本处理腔室之间的流体连通中。更优选地，在至少两个附加腔室中的至少一个腔室与样本处理腔室之间的连续流体连通包括这两个特征。用于限制流体流动的被动装置的该示例允许在设备内形成连续流体连通通道，同时控制设备内的流体流动。这还进一步降低了设备的复杂性。

样本处理腔室同样通过废物通道与废物腔室流体连通。还重要的是，在废物腔室中的材料不能流回到样本腔室中。因此，优选地将该设备设计成在样本处理腔室和废物腔室之间加入用于限制流体流动的被动装置。优选包括被动阀（优选为单向阀），其位于样本处理腔室和废物腔室之间的流体连通中，以防止这种回流。优选地，该被动阀位于分叉的分析物流动通道的下游。一种简单的方案为采用小珠，例如玻璃珠，其位于流体通道中将其与样本处理腔室相连的点处的废物腔室的开口中。当该设备处于使用中且流体从样本处理腔室运动到废物腔室时，流体的流动或者使用真空将会从开口释放小珠，因此允许流体流动。当没有流体流动时，小珠将返回座在废物腔室的开口中，因此防止了液体回流通过该设备。优选地，采用通过废物腔室的真空来操作该阀。

用于限制流体流动的被动装置的另一示例为使用重力来控制流体的流动。优选地，在进入样本处理腔室之前，优选用真空引导流体向上通过预处理通道。然后，流体从上方（在那里其可通过重力而落下经过该腔室）进入样本处理腔室。还优选地，当流体通过废物通道离开样本处理腔室时，其再次向上流动并从顶部进入废物腔室。这种结构也可以防止流体回流通过该设备，例如从废物腔室进入样本处理腔室以及从样本处理腔室进入附加腔室。根据所关心的特定用途，本领域中普通技术人员能够将该设备设计成包括任何从那些所述的以及其它机构中选择的必需的流体流动控制机构。

来自样本处理的废料被收集在废物腔室中。优选地，将该废物腔室完全集成至本发明的设备中，从而不需要额外的瓶子来收集并然后处理掉这种废物。如果所关心材料是危险的或者有传染性的，那么这是尤为优选的，因为这使得对于使用者处理的需要最小化。废物腔室应具有足

够的容积，以能够容易地保持在样本处理过程中使用的所有流体。优选地，废物腔室容纳在该设备内的任何多余空间中，所述空间位于样本处理腔室和至少两个附加腔室之间和周围。这使得能够最有效地利用空间，因此将设备的整体尺寸保持为最小。如前所述，优选地，废物腔室包括一出口，该出口可与用于产生真空的装置相连，从而可以向该设备施加真空以将流体流直接引导通过该设备并进入废物腔室中。

该设备还包括至少两个附加腔室。根据该设备的用途，这些附加腔室可以起到多种作用。这种腔室的可能示例可包括缓冲剂腔室或者样本腔室，该缓冲剂腔室包括在样本处理规程中所需要的缓冲剂溶液或者水，流体或者固体样本可以最初引入该设备的样本腔室中并且该样本腔室可选择地包括与样本相互作用的第一试剂，或者在该样本腔室中固体样本最初溶解在溶剂中，或者可选地将样本在其中进行物理处理。在制造期间，这些腔室可预先填充有所需溶液或试剂。这具有一些优点，包括使用者不必关心从大量化学溶液中准确地测量等分试样，腔室自身不必安装在溶液的容器上，并且腔室可以预载填充有气泡，当吸引流体通过该设备时，该气泡可跟随流体流动，以确保在使用随后的流体之前清理流体通道。这些腔室可选择地包括内部局部障碍物，例如延伸通过内部腔室的一部分的塑料心轴，如果施加真空或者力，则该心轴可用于使腔室内的固体试剂的运动最小化。同样，这些腔室可包括膜，以防止在在前样本处理步骤期间所包含物被过早释放，或者例如通过污染或汽化而破坏了包含物。在本发明的一个实施例中，优选地，至少两个附加腔室中的至少一个腔室预填充有从下组中选择的缓冲剂溶液，该组包括乙酸钾和三羟甲基氨基甲烷盐酸盐的水溶液，或者乙酸钾和三羟甲基氨基甲烷盐酸盐的乙醇水溶液。还优选地，至少两个附加腔室中的至少一个腔室用作样本腔室，其包括一入口部，样本可通过该入口部被引入该设备中。另外，优选地，该样本腔室包括一试剂，优选地为包括溶解试剂的试剂，更优选地为离液序列高的盐。其可以为固体珠的形式或者被冻干到腔室内的一个或多个表面上。

如果需要可以将该设备的腔室（包括一个或多个附加腔室和/或样本

处理腔室）自身设计成，使得在处理顺序中可以对腔室的包含物实施物理步骤。例如，腔室壁可包括加热元件，用于加热其包含物，它们可以为柔性的以允许声学处理，它们可以透过一种或多种波长的光以允许光学处理、传感或者监测等。优选地，该设备腔室中的至少一个腔室涂覆有例如在 WO 98/24548 中披露的导电聚合物。如果需要这种物理处理，则该设备应设计成将腔室定位成易于并有效地接近物理处理源。例如，该腔室可定位成朝向设备的外表面，或者可在设备主体的外侧局部或完全延伸从而该腔室的一部分能够与物理处理源（例如，光源或者热源）相互作用。优选地，该设备的至少一个腔室位于设备主体的外部，且保持与样本处理腔室流体连通，并且还优选地该腔室具有壁，这些壁至少部分涂覆有导电聚合物。可优选地位于设备主体外部的腔室的示例包括其中需要加热分析物或任何缓冲剂的任何腔室。

另外，该设备也可设计成包括一个或多个过滤膜。如前所述，优选地，样本处理包括捕获元件。同样如前所述，如果该设备包括与用于产生真空的装置相连的出口，则优选地将一过滤器加入至该设备中或者用于产生真空的装置中，从而防止雾化材料被释放进大气中。另外，该设备可包括例如在连通路径中的其它过滤器，以防止固体颗粒导致阻塞。过滤器的另一可选用途是，在进入设备前在样本腔室的入口部过滤样本。或者，如果该设备包括一入口部，通过该入口部将空气从大气引入该设备中，则有必要使用过滤膜，以确保来自大气的任何污染不会进入设备中并潜在地污染所处理的样本。优选地，该样本腔室入口部包括过滤膜，该滤膜可以在将样本引入样本处理腔室之前或之后安置。

本发明的设备可选择地包括收集腔室，处理过的样本可直接收集在该收集腔室中。该腔室可以集成至在该设备中，或者如果需要该设备可设计成使得该腔室简单且可靠地夹在适当的位置。当适当时，该腔室可位于分析物流动通道的下游并与分叉的分析物流动通道出口连通并因此与样本处理腔室流体连通。可这样操作该设备，使得可使用用于使流体在设备内运动的装置来将样本引入该腔室中。例如，该设备还可设有用于使处理过的样本从样本处理腔室运动进入收集腔室中的装置。因此，

可通过与用于使流体运动进入废物腔室中的装置断开连接并连接用于使流体运动进入收集腔室中的装置，而将流体从样本处理腔室引入收集腔室中。优选地，这种装置包括用于产生真空的装置，该装置通过第二出口与收集腔室相连，在这种情况下真空路径从样本处理腔室流过收集腔室，因此将来自废物腔室的任何流体转向而进入收集腔室中。如前所述，如果使用真空，则有利地将过滤膜装配在该设备中真空的上游，以防止来自样本的雾化材料进入大气。与其它腔室一样，收集腔室可设计成可以对其进行物理处理、传感或监测，并且可在设备主体外侧完全或部分地延伸，从而便于收集腔室与物理处理源相互作用。高度优选收集腔室适用于核酸扩增。因此，优选地，收集腔室位于设备主体的外部，其包括至少部分涂覆有导电聚合物的壁以便于样本的热循环，并且还包括透明部分，通过该透明部分可以用光学的方式（优选地通过荧光）监测核酸扩增反应。或者，收集腔室是可拆卸的，从而一旦收集了处理过的样本，则可将其移除以用于别处。集成（如果可拆卸）的收集腔室的其中一个主要优点在于，可以在无需任何介入或额外设备的情况下收集处理过的样本。另外，这对于使用者简化了该设备，使交叉样本污染最小化并使使用者暴露于样本的可能性最小。然而，如果收集腔室预先定量有降解试剂，则有用的是单独存储收集腔室，并且如果需要则将其安装在设备上。这种试剂的示例包括本领域技术人员已知的、对于核酸扩增反应和检测体系所需的试剂，例如，核酸引物、核酸探针、荧光染料、酶缓冲剂、核苷酸、镁盐、牛血清白蛋白、变性剂等。

在一些情况下，一旦主样本处理规程完成，则样本有必要在被收集到收集腔室中之前进一步与另一试剂相互作用。可通过选择性地在该设备中包括附加腔室、在样本处理腔室和收集腔室之间的后处理腔室来实现该最后步骤。在已经从样本处理洗提出处理过的样本后，其进入后处理腔室并与试剂相互作用，该试剂例如是在逆转录聚合酶链反应核酸扩增中逆转录酶步骤中所需的试剂。或者，该设备可设有后处理腔室，其位于收集腔室的下游并包含所关心的最终试剂。然后，可施加真空以将处理过的样本从样本处理腔室引导通过收集腔室并进入后处理腔室中，

从而允许处理过的样本进一步与其中的任何试剂相互作用，然后断开真空并将通过废物腔室重新施加真空，以将完全处理的样本引导回到收集腔室中。与其它腔室一样，优选地，该设备可定量有任何这种试剂，以使得使用者必须处理这些材料的必要性最小化。当该设备用于制备用于核酸扩增的样本时，优选地所述试剂包括从下组中选择的一种或多种试剂，该组包括核酸引物、核酸探针、荧光染料、酶缓冲剂、核苷酸、镁盐、牛血清白蛋白、变性剂等。

该设备自身可具有多种不同的设计、形状、尺寸，并且可根据特定用途而由多种不同的材料制成。为了使设备成本最小并且确保对于单一用途而经济可行地生产，优选地，该设备由诸如热塑性材料的廉价材料制成，例如聚乙烯或聚丙烯、聚碳酸脂、丙烯酸、尼龙或丁二烯-苯乙烯共聚物或者它们的混合物。优选地，该设备由尽可能少的元件制成。这样，优选地，设备主要部分制成为单独的注塑单元，包括腔室和主要通道。优选地，通过将注塑单元的基底超声焊接到包括通道路径的板上而形成复杂的通道。稍后增加任何活塞（可以为盖子），以防止在使用后任何材料泄漏以及污染废物的逃逸。进一步优选该设备由可焚化的材料制成，从而在使用后，可容易地处理包括任何废物的该设备，而不会增加废物或者使得使用者暴露于所涉及化学制品的任何危险。该设备可以为透明或者半透明的。有利地，也可以对任何活塞进行颜色标记，以帮助指导不熟练的使用者正确使用该设备。

该设备还可选择地设计成，使其可以与另一额外设备集成，该额外设备例如可以为流体样本瓶，从而一旦从病人或者环境收集流体样本，就可以将其引入流体处理设备中而不会有任何溢出，或者该额外设备是样本收集锥形物，从而样本可以直接收集在流体处理设备中。这两个设备可通过使用密封件（例如，快速配合密封件、螺钉密封件或其它装置）而集成在一起。如果本发明的设备由塑料模制而成，则这些密封装置可以容易地结合成形。这种集成进一步简化了在非实验室环境中具有很少或者没有科学训练的人员对该设备的使用，并且还使得使用者与样本本身的相互作用最小。

另外，该设备可集成有机械设备。这是由于多个原因，包括为了用物理设备（例如，真空或者活塞压下）将该设备用于使流体运动，或者用于对设备的一个或多个腔室实施物理处理步骤，例如热、光学或声学处理、传感或监测。如果需要这种集成，则重要的是确保该设备设计成使其可有效地与这样的额外物理设备相集成。还重要的是，确保这种集成尽可能的简单，以使其可由非熟练工作人员有效地使用。这可包括将该设备设计成使其仅可沿单一取向被集成，使用色标来帮助取向等。

本发明还涉及一种处理流体样本的方法，包括：

（i）将样本放置在根据本发明设备的样本处理腔室中；

（ii）施加正压或负压以使流体运动通过该设备；

（iii）使该样本经受一个或多个处理步骤；以及

（iv）从所述分叉的分析物流动通道收集处理过的样本。

所述处理步骤可以为化学步骤或物理步骤。

根据第三方面，本发明涉及将根据本发明的设备用于从流体样本纯化并浓缩核酸材料。优选可以这样制备这种样本，以使其可经受核酸扩增，例如聚合酶链反应扩增。

附图说明

现在将参照在下列附图中示出的本发明设备的具体实施方式来描述本发明，其中：

图 1 从侧面显示了设备的立体图；

图 2 从底部显示了设备的立体图；

图 3 从顶部显示了设备的立体图，其中移除了顶板从而可看到内部腔室；

图 4 显示了设备底板的内部视图；

图 5 是沿着 A-A 的设备的剖视图，显示了对于 PCR 使用该设备来处理流体样本的第一步骤；

图 6 是沿着 B-B 的设备的剖视图，显示了对于 PCR 使用该设备来处理流体样本的第二步骤；

图 7 是沿着 C-C 的设备的剖视图，显示了对于 PCR 使用该设备来处理流体样本的第三步骤；

图 8 是沿着 D-D 的设备的剖视图，显示了对于 PCR 使用该设备来处理流体样本的第四步骤；以及

图 9 是沿着 E-E 的设备的剖视图，显示了对于 PCR 使用该设备来处理流体样本的第五步骤。

具体实施方式

图 1 显示出本发明的设备 2，其包括样本腔室 4、具有第一活塞 8 的第一缓冲剂腔室 6、具有第二活塞 12 的第二缓冲剂腔室 10。第一活塞 8 和第二活塞 12 包括插口 34，以允许它们与外部设备集成从而在使用过程中使活塞运动。设备 2 还包括小容积水腔室 14，其延伸超过设备 2 的主体。该小容积水腔室可包括环绕该腔室的膜密封件，从而腔室中的水不会在存储期间或者样本处理的初期阶段汽化。该膜例如为 0.1-0.2 mm 的薄塑料片，由丙烯腈丁二烯苯乙烯制成表层。该设备还包括第一出口部 16 和第二出口部 18，通过这些出口可以将一个或多个真空与设备 2 相连。样本腔室 4 包括盖 20，其通过臂 22 安装在设备 2 的主体上，臂 22 可绕着栓 24 枢转。在将样本（未示出）引入样本腔室 4 中后，将盖 20 绕着栓 24 枢转到将样本腔室 4 密封的位置。盖 20 还包括入口 26，空气可通过该入口借助泵（未示出）而被引入设备 2 中。设备 2 还包括通道 28，该通道从设备 2 的底部延伸到顶部，并且位于设备 2 主体的外部。该通道 28 形成了该设备的流体连通网的一部分。将设备 2 的底板 30 和设备 2 的顶板 32 作为单独的单元制造，并且在制造的最后阶段装配在设备 2 上。

参照图 2，设备 2 包括顶板 32、底板 30 以及外部通道 28。该视图显示出该设备具有三个容器 50、52 和 54，它们也位于设备 2 的主体的外部。容器 50 在样本腔室的下方，容器 52 在第一缓冲剂腔室的下方，而容器 54 在第二缓冲剂腔室的下方。这些容器（50、52 和 54）用作机构的一部分，以防止来自这些腔室每一个的样本或缓冲剂以不适当的方式流过该设备的流体连通网。设备 2 的底板 30 还包括收集腔室 56，该收集

腔室也位于设备 2 主体的外部。一旦流体样本（未示出）已经完全纯化，则其就进入分叉的分析物流动通道并然后进入收集腔室 56，在那里可以对其进行 PCR 扩增反应。优选地，收集腔室 56 涂覆有导电聚合物（未示出），并且包括两个透明的面 58，通过这些面可以监测核酸扩增反应。

参照图 3，设备 2 包括样本腔室 4、第一缓冲剂腔室 6 和第二缓冲剂腔室 10。设备 2 包括废物腔室 100，该废物腔室是在设备主体中包围其它内部腔室的死空间。该设备包括样本处理腔室 102。该腔室通过预处理通道 104 与样本腔室 4 和缓冲剂腔室 6、10 流体连通。样本处理腔室 102 通过废物通道 28 与废物腔室 100 流体连通，该废物通道通过废物端口 106 与废物腔室 100 相连。该设备还包括后处理腔室 108，其与第二真空出口部（18，在该立体图中未示出）相连并且还与样本处理腔室 102 相连（连通未示出）。

参照图 4，底板 30 包括样本容器 50、第一缓冲剂容器 52 和第二缓冲剂容器 54。底板还包括样本通道 152、第一缓冲剂通道 154 和第二缓冲剂通道 156，其提供了分别从样本腔室、第一缓冲剂腔室和第二缓冲剂腔室（未示出）通过预处理通道到样本处理腔室（未示出）的流体连通，该预处理通道的基底如 158 所示。样本处理腔室的基底 160 与废物腔室的基底 162 流体连通。样本处理腔室的基底 160 也通过分叉的分析物流动通道和收集腔室（未示出）与后处理腔室的基底 164 流体连通。

参照图 5，样本 200 通过样本腔室 4 被引入设备 2 中。一旦处于样本腔室中，就关闭样本腔室盖 20。该盖包括过滤器 202，该过滤器防止来自空气的污染物进入设备中并还防止雾化样本离开设备。在样本腔室中，该设备与第一试剂珠 204 相互作用，该试剂珠包括溶解试剂，该溶解试剂包含离液序列高的盐（例如，盐酸胍），以溶解样本中的任何细菌。第一试剂可选择地包括核酸靶，其在后来能够用作使随后的 PCR 扩增反应的效率规格化的手段。在样本与第一试剂相互作用后，通过第一真空出口部向设备施加真空（在该剖视图中示出了真空，但是没有示出第一真空出口部 16）。该真空首先将样本引入样本腔室容器 50 中，沿着样本通道 152 到达预处理通道的基底 158。然后样本被沿着预处理通道 104 向

上引入样本处理腔室 102 中。样本处理腔室 102 包括过滤装置 206，例如玻璃纤维过滤器，在样本经过该过滤器时该过滤装置能够从样本中分离任何核酸。然后，真空将样本从过滤器引出到样本处理腔室的基底 160、到达废物通道的基底 162 并然后向上进入废物通道 28 中。在废物通道的顶部处，已经在此除去了所有核酸的样本通过废物通道出口 106 进入废物腔室 100 中。该图并没有显示在废物腔室中的废料。该废物通道包括小珠 208，该小珠位于废物通道的基底 162 中。当施加真空时，小珠 208 在废物通道 28 中上升，使得流体通过通道 28 进入废物腔室 100 中。当除去真空时，小珠 208 下降并覆盖废物通道的基底 162，因此密封了入口。这防止了废物流体回流到样本处理腔室 102 中。该设备的视图还显示出水腔室 14、第一缓冲剂腔室 6 和活塞 8、后处理腔室 108、以及后处理腔室出口部 18，但是在该视图中没有显示这些腔室之间的流体连通。

参照图 6，设备 2 的第一缓冲剂腔室 6 包括第一缓冲剂 252，例如乙酸钾/三羟甲基氨基甲烷盐酸盐的水溶液，例如可在 Promega Wizard™ 试剂盒中获得的缓冲剂。通过废物腔室出口部（未示出，但是在图 5 中显示）向设备施加真空。同时，活塞 8 在第一缓冲剂腔室 6 内压下，这促使第一缓冲剂 252 流过容器 52，并通过在预处理通道的基底 158 处相连的第一缓冲剂通道 154 和预处理通道 104 而进入样本处理腔室 102 中。第一缓冲剂通道 154 设计成在其离开第一缓冲剂容器 52 的点处具有非常窄的直径。这确保了由于第一缓冲剂的表面张力而使其不能够泄漏到第一缓冲剂通道 154 中直到活塞 8 压下为止。一旦处于样本处理腔室 102 中，缓冲剂就与样本一样流过过滤装置 206，因此在过滤膜上清洗核酸材料。然后通过真空（未示出）引导第一缓冲剂 252 经过废物通道 28 以及废物通道出口部 106，以进入废物腔室 100（没有显示在废物通道中的废料）。

参照图 7，第二缓冲剂腔室 10 包括第二缓冲剂 302，例如乙酸钾/三羟甲基氨基甲烷盐酸盐的乙醇水溶液，例如可在 Promega Wizard™ 试剂盒中获得的缓冲剂。通过废物腔室出口部（未示出，但是在图 5 中显示）向设备施加真空。同时，活塞 12 在第二缓冲剂腔室 10 内压下，这促使

第二缓冲剂 302 流过容器 54，并通过在预处理通道的基底 158 处相连的第二缓冲剂通道 156 和预处理通道 104 而进入样本处理腔室 102 中。与前面一样，第二缓冲剂通道 156 设计成在其离开第二缓冲剂容器 54 的点处具有非常窄的直径。这确保了第二缓冲剂 302 不会泄漏。同样，一旦处于样本处理腔室 102 中，缓冲剂就再次流过过滤装置 206，从而在过滤膜上清洗核酸材料。然后通过真空（未示出）引导第二缓冲剂 302 经过废物通道 28 以及废物通道出口部 106，以进入废物腔室 100（没有显示在废物通道中的废料）。

参照图 8，构造该设备以风干包括经纯化的核酸的过滤膜，以从过滤器除去任何过多的溶剂。为了实现这一点，通过第一真空出口部 16（未示出）向设备 2 施加真空。这使得空气通过样本腔室盖 20 中的入口部 26 而被引入设备中。该空气经过过滤器 202 以除去空气中的物质，因此防止了样本污染。然后其通过真空被引导通过样本腔室 4、样本腔室容器 50、样本腔室通道 152、预处理通道 104、样本处理腔室 102、过滤装置 206、废物通道 28，并且通过废物腔室 100 而引出设备。然后除去用于通过出口部 16 向设备 2 施加真空的装置。

参照图 9，小容积腔室 14 包括纯净水，优选地为大约 100 μl。使用用于加热的外部装置（未示出）对其加热，直到水温优选地大于 80℃。然后通过第二真空出口部 18 向设备施加第二真空。将活塞 305 压下，以将加热的水从水腔室 14 释放进入样本处理腔室 102 中。锥形物 315 用于将小量水直接引导到过滤装置 206。将水引导通过过滤装置 206，当其经过时洗提出纯化的核酸物质，并通过第二真空进入收集腔室 56 中。第二真空还将水引导通过分叉的分析物流动通道、收集腔室 56 并进入后处理腔室 108 中。后处理腔室 108 包含有第二固体试剂 310，该第二固体试剂 310 包括另一 PCR 试剂，例如探针、荧光染料和另一核酸对照物。将该试剂 310 溶解在溶液中。然后除去第二真空，以允许溶液由于重力而落进收集腔室 56 中。或者，可再次施加第一真空，以将溶液引导回到收集腔室 56 中。

一旦处于收集腔室中，准备对核酸就进行实施 PCR 扩增所需的热循

环。收集腔室优选地设计成使其壁由导热聚合物制成。然后收集腔室可在原地经受热循环，或者被除去并放置在另一设备中以进行循环。

该设备的实施方式已经被开发出来以从 10 ml 的流体样本中纯化核酸材料。设备的主体具有从大约 70 到大约 80 mm 的高度，并且具有从大约 70 到大约 80 mm 的直径。样本腔室具有大约 20 ml 的容积，并且第一和第二缓冲剂腔室具有大约 30 ml 的容积。小容积水腔室具有大约 500 μl 的容积，而样本处理腔室具有大约 2 ml 的容积并且具有大约 5 mm 的直径。预处理通道和废物通道各自具有大约 3 mm 的直径。由主体内的的死空间形成的废物腔室具有大约 120 ml 的容积。通过将成形的底板超声焊接到腔室的底侧而形成流体连通通道。这些通道具有大约 1 mm 的直径。在通道离开样本容器的点处，该直径减少到大约 0.6 mm，以防止不期望的流体从腔室流到样本处理腔室中。

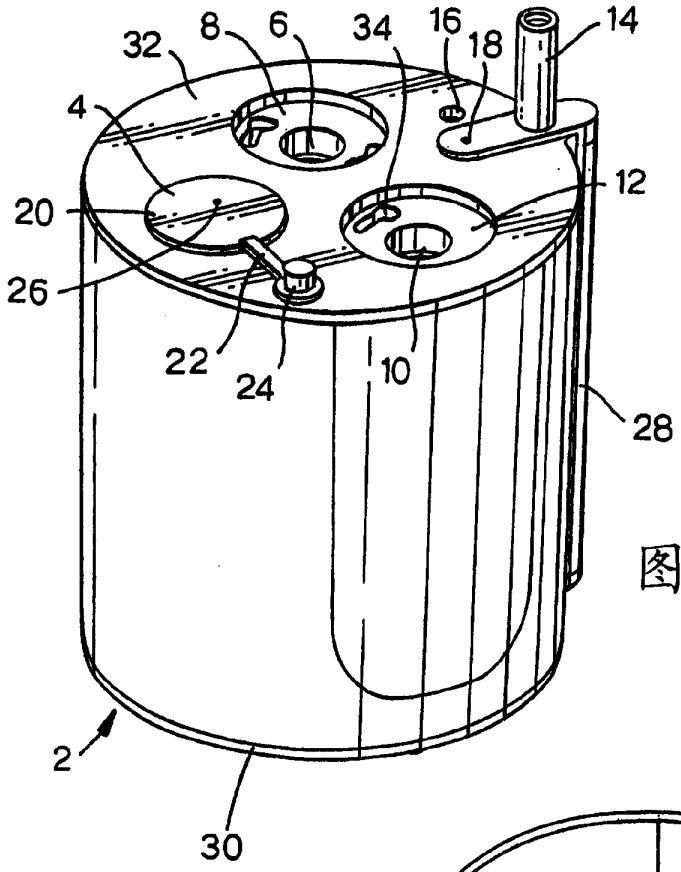


图 1

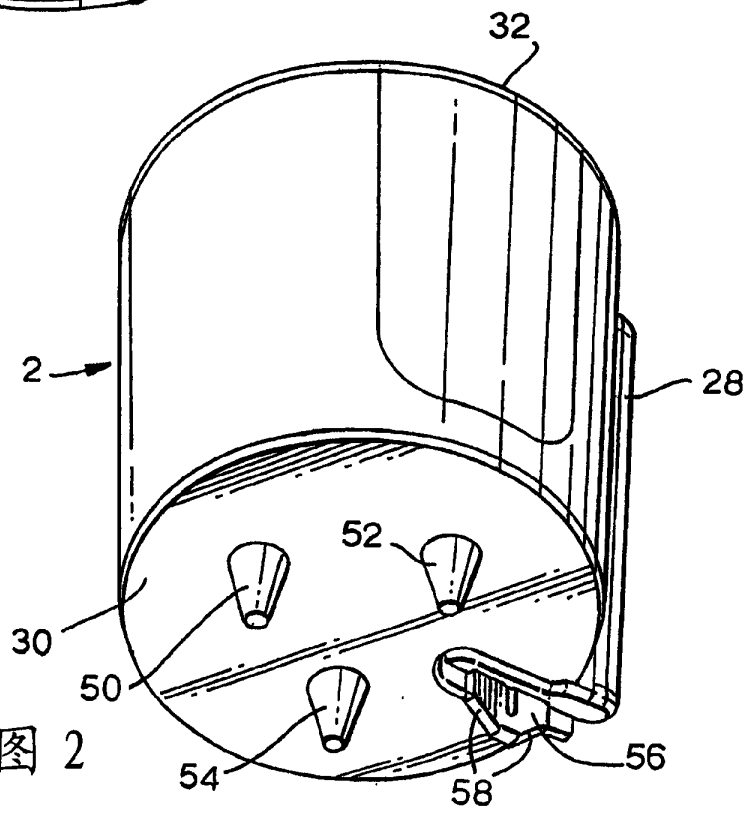


图 2

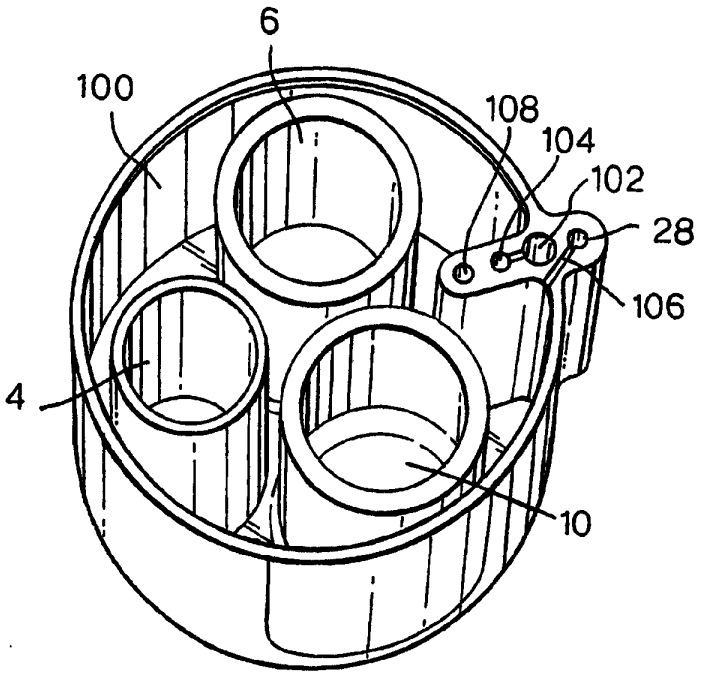

6
100
108
104
102
28
106
4
10

图 3

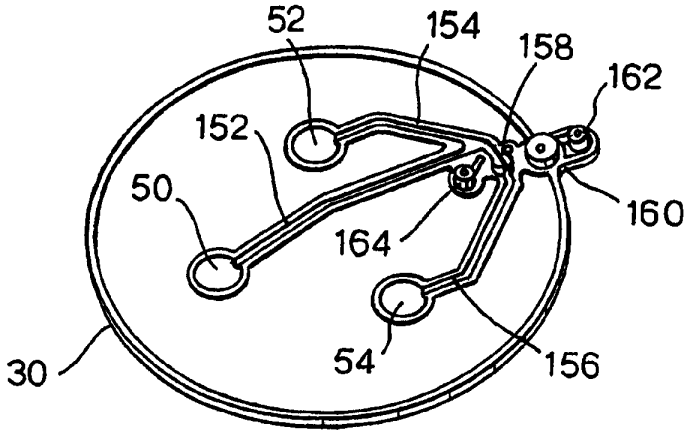

52
154
158
162
152
50
160
164
30
54
156

图 4

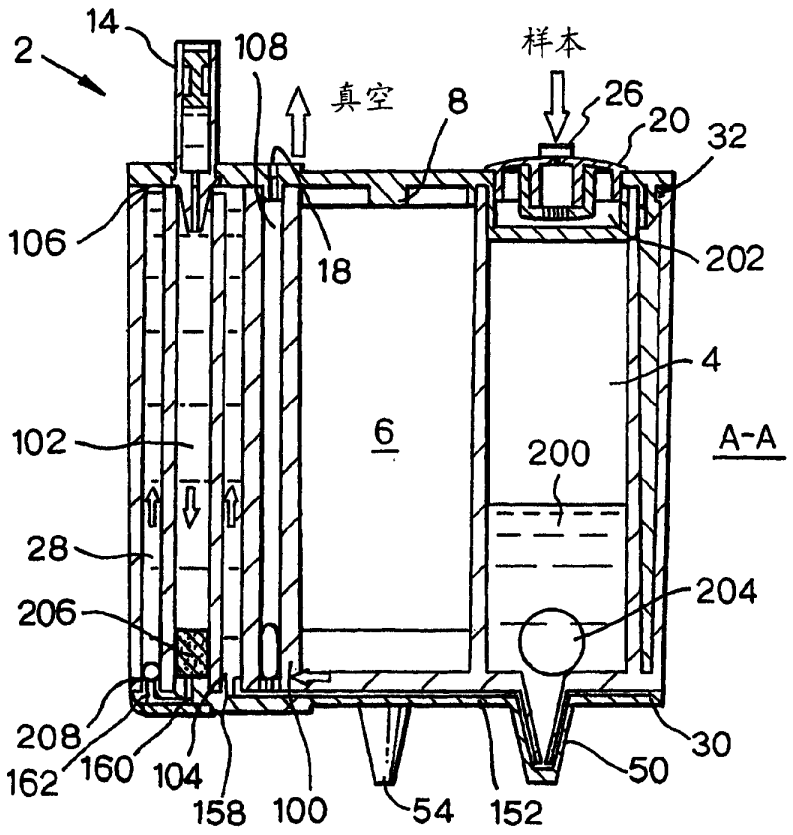

14
2
108
真空
样本
8
26
20
32
106
18
202
4
6
102
A-A
200
28
204
206
208
162
160
104
158
100
54
152
50
30

图 5A

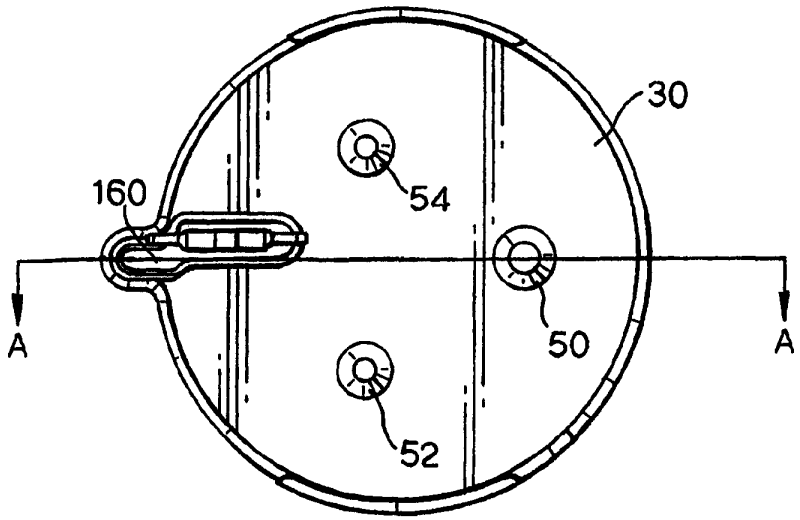

30
160
54
50
A
A
52

图 5B

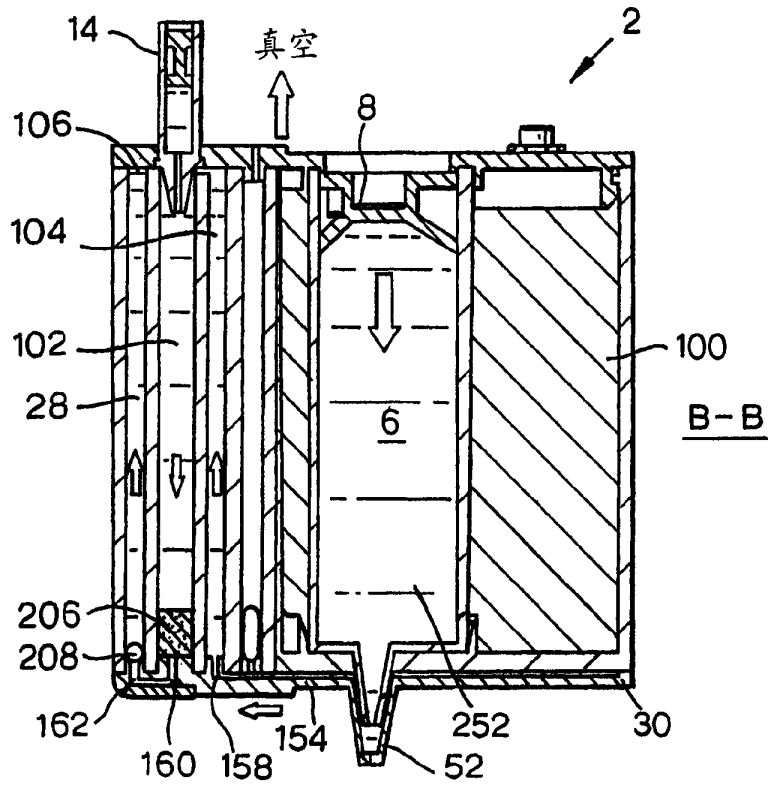

14
真空
2
8
106
104
102
28
100
B-B
6
206
208
162
160
158
154
252
30
52

图 6A

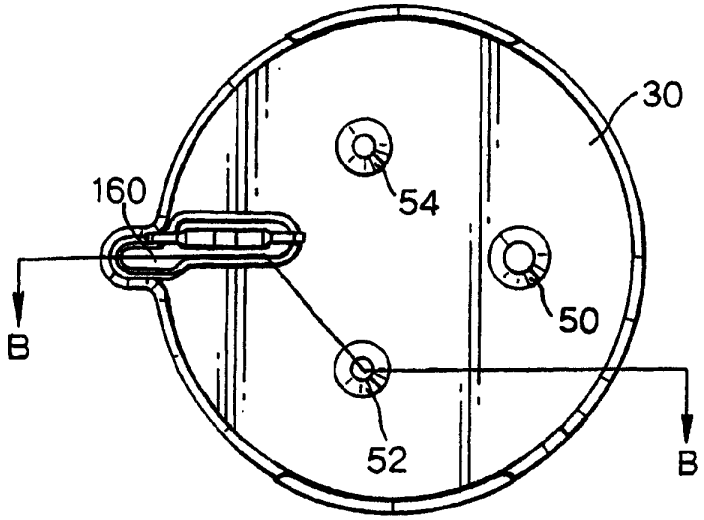

30
160
54
50
B
B
52

图 6B

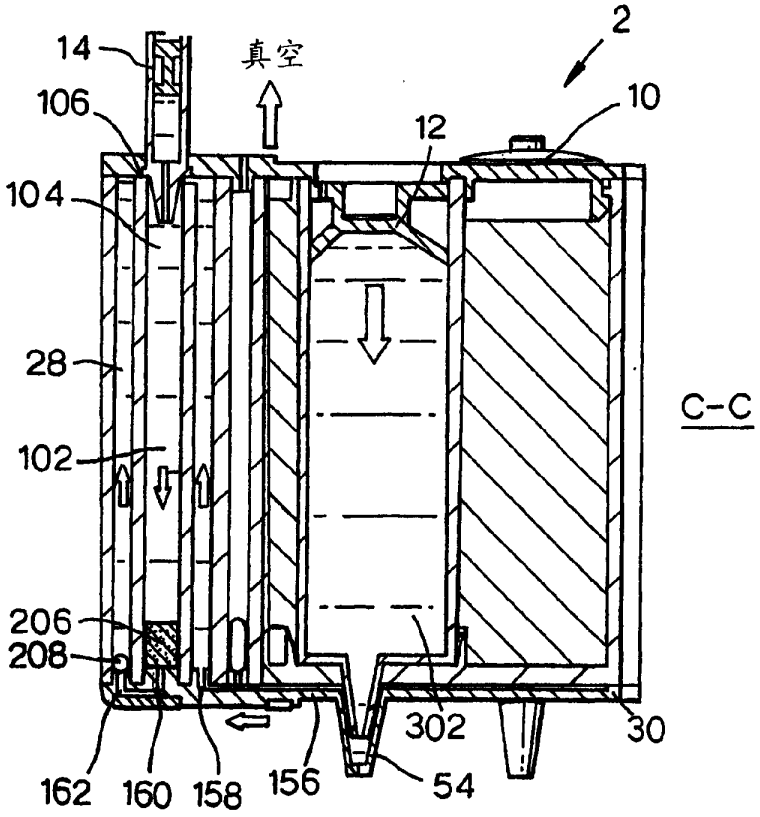

14
真空
2
106
10
12
104
28
C-C
102
206
208
302
30
162
160
158
156
54

图 7A

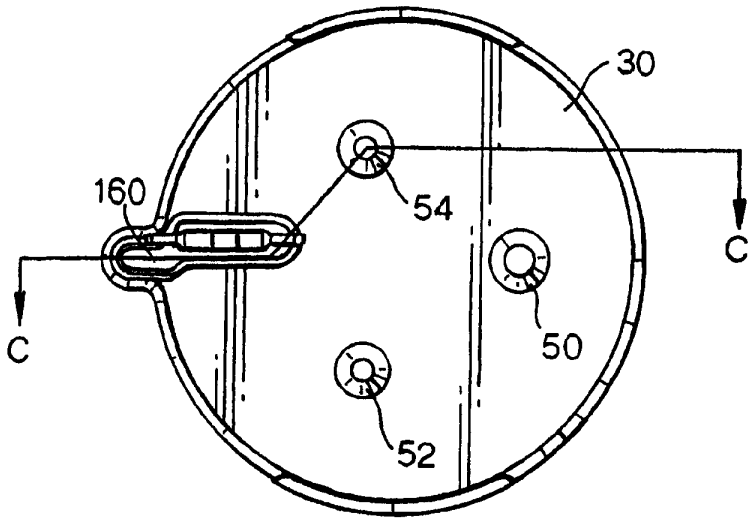

30
160
54
C
C
50
52

图 7B

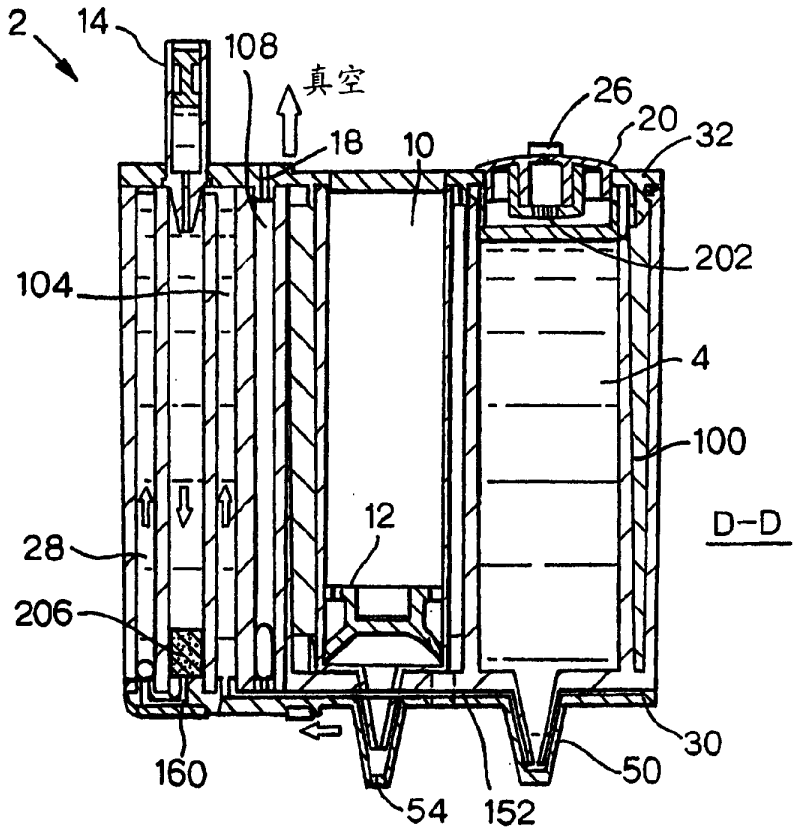

2
14
108
真空
18
10
26
20
32
202
104
4
100
12
D-D
28
206
160
54
152
50
30

图 8A

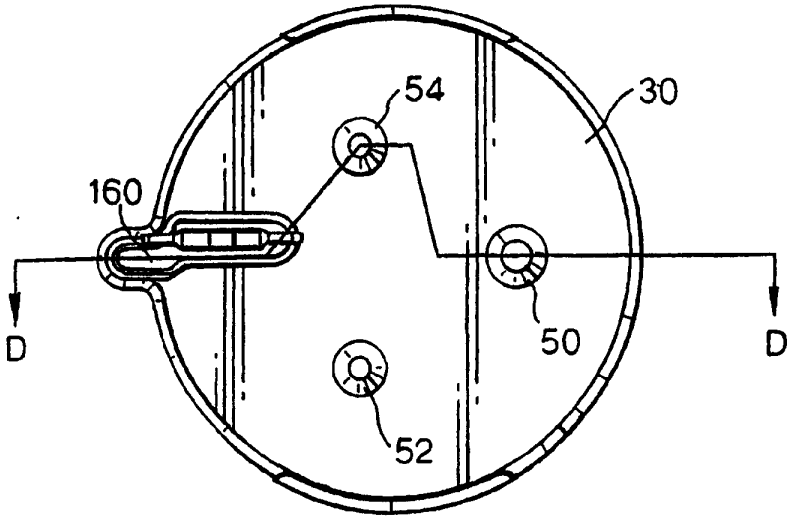

54
30
160
D
D
50
52

图 8B

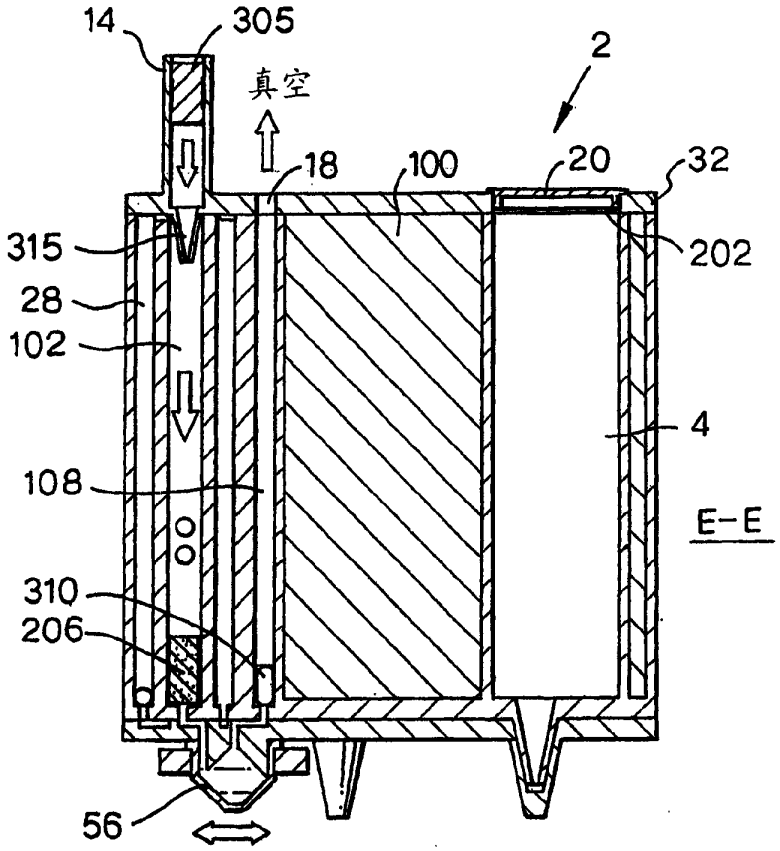

14
305
真空
2
18
100
20
32
315
202
28
102
4
108
E-E
310
206
56

图 9A

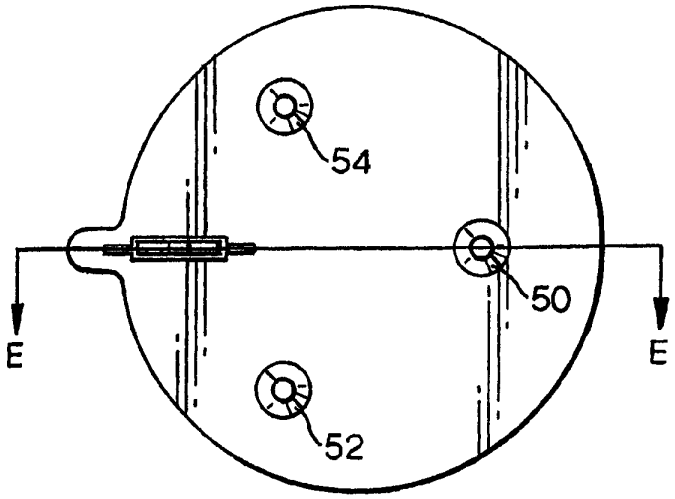

54
50
E
E
52

图 9B

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(72) Inventors; and

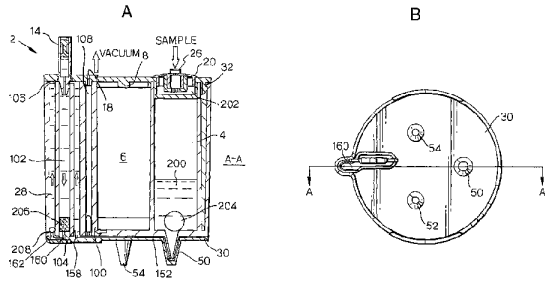
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(54) Title: APPARATUS FOR PROCESSING A FLUID SAMPLE



(57) Abstract: This invention relates to an apparatus for an apparatus for processing a fluid sample comprising: (i) a sample processing chamber comprising a fluid inlet and a fluid outlet; (ii) a waste chamber downstream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and wherein the fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path; (iii) at least two further chambers up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet; (iv) a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path; and (v) a passive means for restricting the flow of fluid. This invention also relates to a method and use of the same.

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Apparatus for Processing a Fluid Sample

This invention relates to an apparatus and associated method for processing a fluid sample.

The analysis of fluid samples, for example clinical or environmental samples, may be conducted for several reasons. One current area of interest is the development of a method to positively identify biological material in a fluid sample, for example a clinical or environmental sample. This is important since it would help in the early diagnosis of disease states, which in turn would enable rapid treatment and infection control, or the identification of environmental contaminants and the like. Although nucleic acid amplification, for example the polymerase chain reaction (PCR) is a very useful and commonly used method for positive identification of biological material, several problems exist when trying to successfully develop it for use on a day to day basis for the rapid identification of biological material in many individual fluid samples in a non-laboratory environment, for example to achieve near patient or point of care disease diagnosis.

One of the key problems lies in the fact that, prior to subjecting a typical clinical or environmental sample to nucleic acid amplification, it needs to undergo a sequence of processing steps using reagents, some of which are hazardous, to purify and concentrate the biological material. However, nucleic acid amplification is just one of many different possible examples of a technique where manipulation of a sample,

especially a fluid sample, is required which involves a number of simultaneous or sequential processing steps. The processing steps themselves may be many and varied and may include for example chemical, optical, electrical, thermal, mechanical, acoustical, processing, sensing or monitoring, in addition to possible dilution and concentration steps. To date such complex processing is conducted in laboratories where samples are either treated manually one by one, or by using specialist robotics facilities to process many different samples in parallel. However, there are several problems associated with these methods. These include that they are slow, resource intensive, expensive, subject to error and to cross sample contamination. In addition, conventional fluid processing systems require fluid samples to flow sequentially through a series of different chambers where each chamber is utilised for a single step in a sequence which may result in loss of sample, and automation of such processes requires the use of complex fluidic assemblies and processing algorithms.

As such there remains a need to develop an improved apparatus whereby a fluid sample can be processed using a series of pre-determined sequential steps, to obtain a desired end product. Such an apparatus should be readily adapted for use in a non-laboratory environment and by an operator with little or no laboratory training such that it can be used to manipulate a fluid sample, for example a clinical or environmental sample, prior to analysis, for example by nucleic acid amplification. Such an apparatus would ensure that analytical results could be rapidly obtained, would free the skilled worker from repetitive tasks and would reduce costs. Furthermore such an apparatus should have sufficient consistency and accuracy to prevent the failure of later tests, should be cheap to produce, and disposable, to

minimise the likelihood of cross contamination and to eliminate the need to sterilise large amounts of equipment.

A prior art search has identified US 6,374,684 which discloses a fluid control and processing system comprising a plurality of chambers and a moveable valve body that can be used to facilitate the processing of a fluid sample according to a given protocol. Although this provides a development in the field of an apparatus for processing a fluid sample, several problems remain. One such problem is that, in order to expose the fluid sample sequentially to different solutions, it is necessary to rotate the valve body to connect in turn, via several external ports, a sample processing chamber with a reservoir of each solution. Such an apparatus is not well suited for use in a non-laboratory environment by a non-skilled laboratory worker because, for among other reasons, there is a need to connect the external ports to reservoirs of each required solution which is impractical and in the case of hazardous chemicals may be a safety risk. In addition such an apparatus, due to its complexity, has a high associated cost, and is unlikely to be cost effective as a disposable apparatus and that result in the potential for cross sample contamination. Furthermore, the apparatus utilises a single fluid displacement chamber to deliver each processing solution to the sample in turn, and to remove any waste materials, which may result in mixing of residual material in the fluid displacement chamber and potential failure of sensitive processing sequences. There remains a need to develop an apparatus for processing a fluid sample that overcomes the above problems.

WO 00/62931 discloses a microfluidic apparatus with a sample inlet port connected via a microchannel to a detection module. Fluidic movement within the apparatus is

controlled by on or off chip pumps which apply an electric field. The apparatus can optionally comprise a storage module, a waste module, reaction modules and the like and the application discloses as an example the use of the apparatus for a nucleic acid amplification reaction. Such an apparatus is useful for conducting nucleic acid amplification reactions on micro-scale volume samples but the problem remains as to how to develop such an apparatus which can be used in the field wherein the volume of the sample is several millilitres as is the case for clinical or environmental samples.

Furthermore US 6,391,541 discloses a cartridge for separating a desired analyte from a fluid sample comprising a sample flow path, a sample lysing chamber, a waste chamber, an analyte flow path and a flow controller for directing fluid flow. Again the patent discloses as an example the use of the apparatus for the separation of a nucleic acid sample from a fluid sample. Again this apparatus presents a development in the field of processing a fluid sample but several problems remain. These include that in order that the sample may be processed in the desired manner, including the desired chemical and physical processing steps, the apparatus comprises complex fluidic channels. This has required the use of many valves through the apparatus which require mechanical opening / closing in order to ensure that the fluid proceeds in the desired manner. Furthermore this complex arrangement may result in some sample remaining inside the fluid cartridge thereby reducing the amount of sample that is ultimately processed. This can lead to inaccurate results in the case of high volumes of sample which retain a low concentration of the desired analyte. Finally the complexity of the cartridge makes the apparatus more difficult to operate in the field by the unskilled user.

An apparatus, and associated method, have now been developed which overcome the above problems. The apparatus comprises a sample processing chamber comprising a fluid inlet and a fluid outlet; a waste chamber downstream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and wherein the fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path; at least two further chambers up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet; a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path; and a passive means for restricting the flow of fluid.

A fluid sample is introduced into the sample processing chamber, optionally via a sample chamber where it may optionally interact with a functional agent. One or more fluid processing solutions are then moved concomitantly or sequentially from at least one of the further chambers, through the sample processing chamber where they interact with the fluid sample, and then into a waste chamber. By ensuring that the further chambers are both in communication with the sample processing chamber, the fluids can move through the apparatus without the need for each fluid communication route to be established in turn. By controlling the means for moving fluid through the fluid communication routes it is possible to ensure that each fluid passes via a pre-determined protocol into the sample processing chamber and if necessary, it is possible to minimise the interaction of each fluid with another prior to reaching the sample processing chamber. By utilising a means for the application of positive or

negative pressure to move fluid through the apparatus the correct fluid flow paths can be established with minimum complexity and by using a passive means for restricting the flow of fluid the fluid pathways can be simply controlled. The apparatus can be enhanced in several ways. These include optionally utilising a combination of application of positive pressure and negative pressure, ie a vacuum, to move fluids through the apparatus in a controlled manner; pre-loading chambers with any reagents or fluids during production thus eliminating the need for the user of the apparatus to handle such materials; using more than one passive valve to prevent the back flow of fluids through the apparatus; and integrating a collection chamber into the apparatus such that the processed sample can be collected directly for further use, for example for nucleic acid amplification. In addition, one or more of the chambers may optionally be adapted such that one or more of the fluids, including the fluid sample, may also be subjected to physical processing for example thermal, acoustic, optical, electrical processing, sensing or monitoring techniques.

The apparatus of the present invention has several advantages. These include that it can be easily designed to accommodate a wide variety of pre-determined processing sequences, including chemical and physical steps, to provide an easy to use fluid processing device; the apparatus utilises a single processing chamber thus minimising sample loss; the apparatus, including all chemical reagents and any waste produced, is completely integrated in a single unit therefore minimising sample contamination and reducing exposure of the user to potentially hazardous materials; due to the use of a reduced number of moving parts the apparatus is likely to have increased reliability and simplicity of use even for a user with little or no laboratory training; and it is

cheap to manufacture which means that the apparatus can be designed to be disposable further reducing the risk of sample cross contamination.

It is an object of the present invention to develop an apparatus, and associated method, for processing a fluid sample. It is a further object of this invention to design such an apparatus which is capable of subjecting a fluid sample to a series of sequential chemical or physical processing steps in a pre-determined sequence, preferably to purify and concentrate a fluid sample prior to a nucleic acid amplification reaction. It is another object of this invention to design such an apparatus to be simple to use by a worker with little or no laboratory training in a non-laboratory environment. It is yet another object of this invention to design the apparatus such that any required chemicals or waste product remain integrated within the apparatus to minimise user exposure to the sample, chemicals or waste. It is yet another object of this invention to design such an apparatus to be cheap to manufacture such that it can be disposed of after a single use thus reducing the likelihood of sample cross contamination and eliminating the need for sterilising large amounts of equipment. These, and other objects of this invention, will become apparent in light of the following disclosure.

Summary of the Invention

According to a first aspect this invention relates to an apparatus for processing a fluid sample comprising:

(i) a sample processing chamber comprising a fluid inlet and a fluid outlet;

(ii) a waste chamber downstream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and wherein the fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path;

(iii) at least two further chambers up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet;

(iv) a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path; and

(v) a passive means for restricting the flow of fluid.

According to a second aspect this invention relates to a method of processing a fluid sample comprising:

(i) placing the sample in the sample processing chamber of an apparatus according to the present invention;

(ii) applying a positive or negative pressure to move fluid through the apparatus;

(iii) subjecting the sample to one or more processing steps; and

(iv) collecting the processed sample from the divergent analyte flow path.

According to a third aspect this invention relates to the use of an apparatus according to the present invention for purification and concentration of nucleic acid material from a fluid sample.

Detailed Description of the Invention

All publications cited herein are hereby incorporated by reference in their entirety, unless otherwise indicated.

As used herein the term "fluid communication" means that a path through which fluid can in principle flow exists between the chambers in question although fluid flow may be restricted by one or more passive means for restricting the flow of fluid.

As used herein the term "continuous fluid communication" means that a path through which fluid can flow exists at all times between the chambers in question.

As used herein the term "a passive means for restricting the flow of fluid" shall be taken to mean a means that restricts fluid flowing through a given path but wherein the restriction can be overcome passively namely purely by the application of positive or negative pressure to either the means or to the flow path itself, thereby allowing fluid flow along the given path. Optionally such means may be opened by passive action or closed by passive action. Furthermore such means may allow flow of fluid

in either direction through the fluid flow path in which the means is situated depending on the position of application of a pressure or alternatively the means may only allow the flow of fluid in a single direction through the fluid flow path.

As used herein the term "fluid sample" means any sample that exists as a gas, a liquid, a solution comprising a sample solvated by a solvent, or a fluid system comprising one or more phases for example an emulsion. A "fluid sample" is also taken to mean a sample which may initially be introduced into the apparatus as a solid or a viscous liquid but which is then diluted or dissolved by the adding of a volume of solvent.

As used herein the term "functional agent" means a solid chemical or physical agent which is used in the apparatus or method of the present invention. It may comprise one or more chemical reagents dosed as a solid powder, bead, capsule, pressed tablet and the like comprising a reagent to interact with the fluid sample. Suitable examples of such reagents include, but are not limited to, lysis reagents for example chaotrophic salts, nucleic acid targets, nucleic acid synthetic controls, bacteriophage, lyophilised enzymes, dyes, detergents and the like. However, the term functional agent should also be understood to comprise physical means for interacting with the fluid sample. These could include, but are not limited to, a magnetic stirrer bead, a heating means, magnetic beads coated with antibodies and the like.

The elements of the apparatus are described in more detail below.

This invention relates to an apparatus for processing a fluid sample comprising a sample processing chamber, a waste chamber, at least two further chambers, a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or divergent analyte flow path; and is characterised in that each of the at least two further chambers are in fluid communication with the sample processing chamber and in that the sample processing chamber is in fluid communication with the waste chamber. Embodiments of the invention facilitate processing of a fluid sample according to a pre-determined protocol.

The sample processing chamber is the region of the apparatus in which the fluid sample itself is subjected to one or more processing steps. These processing steps can include chemical processing steps such as diluting the sample, washing the sample sequentially with one or more buffer solutions, reacting the sample with one or more chemical reagents, but may also include physical steps for example radiating the fluid sample with one or more thermal radiation, subjecting the fluid sample to acoustical processing and the like. The sample processing chamber may optionally comprise a an active member, preferably a trapping member selected from the group consisting of a microfluidic chip, a solid phase material, a filter, a filter stack, an affinity matrix, a magnetic separation matrix, a size exclusion column, a capillary tube and mixtures thereof. It is preferred that the sample processing chamber comprises a trapping member capable of trapping the biological material in a fluid sample for example capable of trapping cells, spores, viruses, large or small molecules, proteins and the like. The exact trapping member chosen will depend on the nature of the material to be trapped. The preferred trapping member for use herein is a glass fibre filter that

extends across part or all of the internal surface area of the sample processing chamber.

The sample processing chamber comprises a fluid inlet and a fluid outlet and is in fluid communication with at least two further chambers on the one hand and a waste chamber on the other hand. The waste chamber is down stream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and the at least two further chambers are up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet. At least one of these fluid communications may be a continuous fluid communication. The fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path. Again this may be a continuous fluid communication. The apparatus also comprises a means for moving fluid from the at least two further chambers through the sample processing chamber into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path. It is preferred that the means for moving fluid from each of the two further chambers through the sample processing chamber and into the waste chamber or the divergent analyte flow path moves the fluid sequentially from the first at least two further chambers through the sample processing chamber and into the waste chamber and then from another further chambers through the sample processing chamber and into the waste chamber or the divergent analyte flow path.

Many different means are acceptable for moving the fluid. The means moves fluid by the application of either a positive pressure or a negative pressure to the desired flow path. One example of a means for the application of negative pressure is a means for generating a vacuum that is attached to the apparatus via an outlet port, for example an outlet port on the waste chamber or an outlet port on the divergent analyte flow path and that is able to draw fluid through the apparatus as desired. The vacuum can be attached to the outlet port using one of several different means known to one of ordinary skill in the art. One effective way of attaching the vacuum to the outlet port is by the use of bellows since these can be readily attached to even a small outlet port giving a high tolerance and reducing the need for very accurate handling. Such an adaptation is particularly useful if the apparatus is to be operated mechanically or by a non-skilled worker. It is preferred that the waste chamber of the apparatus comprises an outlet port to which a means for generating a vacuum can be attached. This has the result that the vacuum is able to draw the fluid from at least one of the further chambers, through the sample processing chamber and into the waste chamber. It is also preferred that the divergent analyte flow path comprises an outlet port such that a means for generating a vacuum can be readily attached here. The means for generating a vacuum can also be adapted in several ways. For example it can be adapted to draw the fluid through the apparatus in a pre-determined sequence. Optionally the apparatus can be designed to comprise a passive means for restricting the flow of fluid through the apparatus such that an increased vacuum force is required to sequentially release the fluids from each chamber, such that by increasing the vacuum during use it is possible to sequentially draw the fluids from first one chamber and then another for example by controlling the dimensions of fluid flow paths or by incorporating membranes or gates which need to be passively opened to

allow fluid flow. The use of a vacuum can also be adapted to pull air through the apparatus as an interim step between the moving of each fluid such that the fluid communication routes are cleared and the different fluids do not interact with each other prior to entering the sample processing chamber. This can be important in sample processing protocols that are very sensitive for example where the interaction of a first buffer with a second prior to entering the sample processing chamber may neutralise its effects, or where it is important that the whole of a very small volume of material reaches the sample. If a vacuum is used it is also preferred to consider that any material within the apparatus may be aerosolised by the vacuum and drawn out of the apparatus into the atmosphere. If the apparatus is adapted for use with reagents which may prove a safety hazard if released it is important to adapt the apparatus to minimise or eliminate release of the aerosolised material. One such possible adaptation is to incorporate filter membranes into the apparatus, or into the means for applying a vacuum, such that the aerosolised material is captured and not released into the atmosphere.

An example of another suitable means for moving fluid through the apparatus is a means for applying positive pressure or force behind the fluid. Again such a force can be applied by many means known to one of ordinary skill in the art. One example is the use of a plunger in one of more of the further chambers, the depression of which would expel any fluid in that a chamber through the fluid communication routes into the sample processing chamber and then into the waste chamber. Again, the use of a means for applying force behind the fluid, for example by the use of a plunger, can be adapted such that the fluids from the at least two further chambers move concomitantly or sequentially, preferably sequentially, from the further chamber

through the sample processing chamber and into the waste chamber or the divergent analyte flow path. For example it would be possible to sequentially depress one or more of a series of plungers to move fluid sequentially from a first further chamber through the sample processing chamber into the waste chamber and then from a another and so on. In both instances described it is possible that the means for moving the fluid could be provided manually by the use of syringes, plungers, pumps and the like or mechanically by integrating the apparatus of the present invention into a further apparatus able to provide the power and means as required. Again such a means for applying positive pressure can be used in conjunction with a passive means for restricting the flow of fluid through the apparatus.

It is preferred in the apparatus of the present invention to utilise a combination of both a means for generating a vacuum and a means for applying force behind the fluid to move fluid from at least one of the further chambers through the sample processing chamber and into the waste chamber. The use of the two together has the advantage that the initial force behind the fluid initiates release of the fluid from any given chamber that the vacuum could direct the fluid flow through the apparatus thus preventing it from being diverted from the desired path. This enables the apparatus to be readily designed such that fluid can flow sequentially from the further chambers through the sample processing chamber according to a pre-determined protocol.

The fluid communication routes of the present invention are provided by one or more channels that pass through the apparatus connecting the chambers in the desired manner. The apparatus is designed such that at least two further chambers are in fluid

through the sample processing chamber and into the waste chamber or the divergent analyte flow path. For example it would be possible to sequentially depress one or more of a series of plungers to move fluid sequentially from a first further chamber through the sample processing chamber into the waste chamber and then from a another and so on. In both instances described it is possible that the means for moving the fluid could be provided manually by the use of syringes, plungers, pumps and the like or mechanically by integrating the apparatus of the present invention into a further apparatus able to provide the power and means as required. Again such a means for applying positive pressure can be used in conjunction with a passive means for restricting the flow of fluid through the apparatus.

It is preferred in the apparatus of the present invention to utilise a combination of both a means for generating a vacuum and a means for applying force behind the fluid to move fluid from at least one of the further chambers through the sample processing chamber and into the waste chamber. The use of the two together has the advantage that the initial force behind the fluid initiates release of the fluid from any given chamber that the vacuum could direct the fluid flow through the apparatus thus preventing it from being diverted from the desired path. This enables the apparatus to be readily designed such that fluid can flow sequentially from the further chambers through the sample processing chamber according to a pre-determined protocol.

The fluid communication routes of the present invention are provided by one or more channels that pass through the apparatus connecting the chambers in the desired manner. The apparatus is designed such that at least two further chambers are in fluid

communication with the sample processing chamber. These chambers are optionally designed to each have an individual outflow channels which connect at a common point prior to entering the sample processing chamber. It is preferred that there is only a single entry point for solutions to pass into the sample processing chamber, ie the sample processing chamber inlet, to allow for reduced design complexity. As such it is preferred that the outflow channels from each further chamber meet and then flow into a common sample processing channel prior to entering the sample processing chamber. One or more of these fluid communications may be a continuous fluid communication.

In order to minimise the flow of fluid through the chamber in an inappropriate manner it is preferred that the apparatus comprises a passive means for restricting the flow of fluid through the apparatus which is designed to contain features which limit any particular fluid flow route until such time as that flow route is required. Failure to do this could result in fluid flowing from more than one chamber simultaneously and thus could destroy the sample processing sequence or could result in fluid flowing from the waste chamber back through the apparatus. Examples of suitable means to control such flow include use of one or more of membranes covering channels that are broken when pressure is applied behind them or in front of them, very small diameter channels through which a fluid is unable to flow due to its surface tension without the application of a force, pre-filling any chambers comprising buffer solutions using suction which then acts to hold such a fluid in place until a force is applied to release it, using valves throughout the apparatus which are operated by vacuum, pressure, magnets and the like, designing the fluid communication routes to comprise a small reservoir which needs to be filled completely in order for fluid communication to be

established which allows for small leaks to be accommodated without overflows, and the like. It is preferred that the apparatus comprise one or more of such features to ensure appropriate fluid flow. In the apparatus of the present invention it is preferred that the passive means for restricting the flow of fluid comprises a reservoir located in the fluid communication between at least one of the at least two further chambers and the sample processing chamber . It is also preferred that the passive means for restricting the flow of fluid comprises a fluid pathway of small diameter such that fluid can not flow through the pathway without the application of a positive or negative pressure, located in the fluid communication between at least one of the at least two further chambers and the sample processing chamber. It is even more preferred that the continuous fluid communication between at least one of the at least two further chambers comprises both of these features. Such examples of passive means for restricting the flow of fluid allow continuous fluid communication pathways to be established within the apparatus whilst at the same time controlling fluid flow within the apparatus. This further reduces the complexity of the apparatus.

The sample processing chamber is similarly in fluid communication with a waste chamber via a waste channel. It is also important that material in the waste chamber is not able to flow back into the sample chamber. It is therefore preferred to design the apparatus to incorporate a passive means for restricting the flow of fluid between the sample processing chamber and the waste chamber. It is preferred that this comprises a passive valve, preferably a 1-way valve, located in the fluid communication between the sample processing chamber and the waste chamber to prevent such back flow. It is preferred that the passive valve is down stream of the divergent analyte flow path. One simple solution is to utilise a small bead, for

example a glass bead, that is positioned in the opening of the waste channel at a point in the fluid path connecting it to the sample processing chamber. When the apparatus is in use and fluid is moving from the sample processing chamber to the waste chamber the movement of fluid, or the use of a vacuum, will release the bead from the opening thus allowing fluid flow. When there is no fluid flow the bead will return to sit in the opening of the waste channel thus preventing the back flow of liquid through the apparatus. It is preferred that the application of a vacuum via the waste chamber is used to operate this valve.

Another example of a passive means for restricting the flow of fluid is to control the flow of fluid by the use of gravity. It is preferred that prior to entering the sample processing chamber the fluid is directed, preferably by a vacuum, up through a pre-processing channel. The fluid then enters the sample processing chamber from above where it can fall by gravity through the chamber. Again it is preferred that when the fluid leaves the sample processing chamber via the waste channel it again passes up and enters the waste chamber from the top. This arrangement can also prevent fluid flowing backwards through the apparatus eg from the waste chamber into the sample processing chamber and from the sample processing chamber into the further chambers. Depending on the particular use in question, one of ordinary skill in the art would be able to design the apparatus to comprise any necessary fluid flow control mechanisms selected from those mentioned and others.

The waste material from the sample processing is collected in a waste chamber. It is preferred that the waste chamber is fully integrated into the apparatus of the present invention such that additional bottles are not required for collecting and then

disposing of such waste. This is especially preferred if the materials in question are either hazardous or infectious since this minimises the need for user handling. The waste chamber should have sufficient volume to be able to readily hold all of the fluids used during the sample processing. It is preferred that the waste chamber is housed within any redundant space inside the apparatus between and around the sample processing chamber and the at least two further chambers. This enables the most efficient use of space thus keeping the overall size of the apparatus to a minimum. As mentioned previously it is preferred that the waste chamber comprises an outlet which can be connected to a means for generating a vacuum such that a vacuum can be applied to the apparatus to direct fluid flow directly through the apparatus into the waste chamber.

The apparatus also comprises at least two further chambers. Depending on the use of the apparatus these further chambers may have several roles. Possible examples of such chambers may include a buffer chamber which comprises a buffer solution or water which are required in the sample processing protocol or a sample chamber into which a sample, either as a fluid or a solid, may be initially introduced into the apparatus and which may optionally comprise a first reagent with which the sample interacts, or optionally where a solid sample is initially dissolved in a solvent, or alternatively where the sample may be subjected to physical processing. The chambers can be pre-filled with the required solutions or reagents during manufacture. This has several advantages including that the user need not be concerned with accurately measuring aliquots of chemical solution from bulk, the chambers do not themselves need to be attached to a reservoir of solution and the chambers can be pre-loaded filled with an air pocket which, when the fluid is drawn through the apparatus,

can follow the fluid flow to ensure that the fluid channels are cleared prior to the use of a subsequent fluid. The chambers may optionally comprise internal partial barriers, for example a plastic spindle extending through part of the internal chamber which can be used to minimise the movement of solid reagents within the chamber if a vacuum or force is applied. Similarly the chambers may comprise a membrane to prevent early release of the contents or disruption, for example by contamination or evaporation, of the contents during prior sample processing steps. In one embodiment of the present invention it is preferred that at least one of the at least two further chambers is pre-filled with a buffer solution selected from the group consisting of an aqueous solution of potassium acetate and Tris.hydrochloride, or an aqueous ethanolic solution of potassium acetate and Tris.hydrochloride. It is also preferred that at least one of the at least two further chambers acts as a sample chamber which comprises an inlet port though which a sample can be introduced into the apparatus. Furthermore it is preferred that the sample chamber comprises a reagent, preferably a reagent comprising a lysis reagent, more preferably chaotrophic salts. This may be in the form of a solid bead or freeze dried onto one or more surfaces inside the chamber.

The chambers of the apparatus, including one or more of the further chambers and or the sample processing chamber itself, can be designed if required such that the contents of the chamber can be subjected to physical steps in the processing sequence. For example the walls of the chamber may comprise heating elements which allow their contents to be warmed, they may be flexible to allow acoustic processing, they may be transparent to one or more wavelengths of light to allow optical processing, sensing or monitoring and the like. It is preferred that at least one of the chambers of the apparatus is coated with an electrically conducting polymer such as that disclosed

in WO98/24548. If such physical processing is required the apparatus should be designed such that the chamber is positioned for easy and efficient access to the source of the physical processing. For example the chamber may be positioned towards the external face of the apparatus or may extend partially or fully outside of the main body of the apparatus such that a part of the chamber is able to interact with a source of the physical processing eg a light source or a heating source. It is preferred that at least one chamber of the apparatus is located externally to the main body of the apparatus whilst remaining in fluid communication with the sample processing chamber and it is further preferred that this chamber has walls which are coated at least partially with an electrically conducting polymer. Examples of chambers which may be preferentially be located externally to the main body of the apparatus include any chamber in which the analyte or any buffers are required to be heated.

In addition the apparatus may also be designed to comprise one or more filter membranes. As already discussed it is preferred that the sample processing comprise a trapping member. Again, as already discussed, if the apparatus comprises an outlet which is attached to a means for generating a vacuum it is preferred that a filter is incorporated either in the apparatus or in the means for generating a vacuum to prevent aerosolised material being released into the atmosphere. Furthermore the apparatus may comprise other filters for example in the communication routes to prevent solid particulate causing blockages. Another optional use of a filter could be at the inlet port of the sample chamber to filter a sample prior to entering the apparatus. Alternatively, if the apparatus comprises an inlet port through which air is drawn from the atmosphere into the apparatus it may be necessary to use a filter

membrane to ensure that any contamination from the atmosphere does not enter the apparatus and potentially contaminate the sample being processed. It is preferred that the sample chamber inlet port comprises a filter membrane which can be positioned either before or after the sample has been introduced into the sample.

The apparatus of the present invention may optionally comprise a collection chamber into which the processed sample can be directly collected. The chamber may be integrated into the apparatus or the apparatus may be designed such that the chamber can be simply and securely clipped into place when required. When in place such a chamber would be downstream of the analyte flow path and in fluid communication with the divergent analyte flow path outlet and thereby the sample processing chamber. The apparatus could be operated such that the sample could be directed into this chamber using a means for moving fluid within the apparatus. For example the apparatus would also be provided with a means for moving the processed sample from the sample processing chamber into the collection chamber. It would therefore be possible to direct fluid from the sample processing chamber into the collection chamber by disconnecting the means for moving fluid into the waste chamber and connecting the means for moving fluid into the collection chamber. It is preferred that such a means comprise a means for generating a vacuum connected to the collection chamber via a second outlet, in this instance where the path of the vacuum flows from the sample processing chamber through the collection chamber thus diverting any fluid from the waste chamber but instead into the collection chamber. As mentioned previously, if a vacuum is used it may be advantageous to fit a filter membrane into the apparatus upstream of the vacuum to prevent aerosolised material from the sample entering the atmosphere. As with other chambers the collection chamber can be

designed such that it can be subjected to physical processing, sensing or monitoring and may extend either in whole or part outside of the main body of the apparatus in order to facilitate the interaction of the collection chamber with a source of the physical processing. It is highly preferred that the collection chamber is adapted for use in a nucleic acid amplification. It is therefore preferred that the collection chamber is external to the main body of the apparatus, comprises walls which are at least partially coated with an electrically conducting polymer to facilitate thermal cycling of the sample and also comprises a transparent section through which the nucleic acid amplification reaction can be optically monitored, preferably by fluorescence. Alternatively the collection chamber may be detachable such that, once the processed sample is collected, it can be removed for use elsewhere. One of the main advantages of an integrated, if detachable, collection chamber, is that the processed sample can be collected without the need for any intervention or additional apparatus. Again this simplifies the apparatus for the user, minimises cross sample contamination and minimises user exposure to the sample. However if the collection chamber is to be pre-dosed with reagents which degrade it may be useful to store the collection chamber separately and attach it to the apparatus when required. Examples of such reagents include those known by one skilled in the art to be required for a nucleic acid amplification reaction and detection system for example nucleic acid primers, nucleic acid probes, fluorescing dyes, enzyme buffers, nucleotides, magnesium salts, bovine serum albium, denaturants, and the like.

In some circumstances it may be necessary that, once the main sample processing protocol is complete, that the sample further interacts with yet another reagent prior to being collected in the collection chamber. This final step could be provided by

optionally including in the apparatus a further chamber, a post processing chamber between the sample processing chamber and the collection chamber. After the processed sample has been eluted from the sample processing, it enters the post processing chamber and interacts with a reagent such as that required for a reverse transcriptase step in reverse transcriptase polymerase chain reaction nucleic acid amplification. Optionally the apparatus could be provided with a post processing chamber downstream from the collection chamber containing the final reagent in question. It is then possible to apply a vacuum to draw the processed sample from the sample processing chamber through the collection chamber and into the post processing chamber, allowing the processed sample to further interact with any reagent therein and then disconnecting the vacuum and reapplying the vacuum through the waste chamber to draw the fully processed sample back into the collection chamber. As with the other chambers it is preferred that the apparatus is pre-dosed with any such reagents to minimise the need for the user to have to handle these materials. When the apparatus is used for preparing a sample for nucleic acid amplification preferably the reagent comprises one or more reagents selected from the group consisting of nucleic acid primers, nucleic acid probes, fluorescing dyes, enzyme buffers, nucleotides, magnesium salts, bovine serum albium, denaturants, and the like.

The apparatus itself can have a wide variety of different designs, shapes, sizes and can be made of many different materials depending on the specific use. In order to minimise the cost of the apparatus and to ensure that it is economically feasible to produce for a single use it is preferred that the apparatus is manufactured from a cheap material such as a thermoplastic material for example polyethylene or polypropylene,

polycarbonate, acrylic, nylon or butadiene-styrene copolymer or mixtures thereof. It is preferred that the apparatus is manufactured from as few components as possible. As such it is preferred that the main bulk of the apparatus is manufactured as a single injection moulded unit containing the chambers and key channels. It is preferred that the intricate channels are formed by the ultrasonic sealing of the base of the injection moulded unit to a plate containing the channel routes. Any plungers are added later, as can be a lid, to prevent the leaking of any materials and the escape of contaminated waste after use. It is further preferred that the apparatus is manufactured from a material which can be incinerated such that after use the apparatus, including any waste, can be easily disposed of without the build up of waste or any risk of exposure of the user to the chemicals involved. The apparatus can be transparent or translucent. Advantageously any plungers can also be colour coded to help direct the unskilled user as to the correct use of the apparatus.

The apparatus may also be optionally designed such that it can integrate with further additional apparatus for example a sample bottle such that the fluid sample, once collected from the patient or environment, can be introduced into the fluid processing apparatus without any spillage, or a sample collection cone such that the sample can be collected directly into the fluid processing apparatus. The two apparatus could integrate via the use of a seal for example a quick fit seal, a screw seal or other means. If the apparatus of the present invention is moulded from plastic then such sealing devices can be integrated easily into the shape. This integration further simplifies the use of the apparatus in a non-laboratory environment for staff with little or no scientific training and again minimises user interaction with the sample itself.

Additionally the apparatus may integrate with a mechanical apparatus. This could be for several reasons including for applying the means for moving the fluid using a physical apparatus, such as the vacuum or plunger depression, or for subjecting one or more of the chambers of the apparatus to a physical processing step for example thermal, optical or acoustical processing, sensing or monitoring. If such integration is required it is important to ensure that the apparatus is designed such that it can integrate effectively with such an additional physical apparatus. It is also important to ensure that such an integration is as simple as possible such that it can effectively be used by a non-skilled worker. This may include designing the apparatus such that it can only be integrated in a single orientation, using colour coding to aid the orientation and the like.

This invention also relates to a method of processing a fluid sample comprising:

(i) placing the sample in the sample processing chamber of an apparatus according to the present invention;

(ii) applying a positive or negative pressure to move fluid through the apparatus;

(iii) subjecting the sample to one or more processing steps; and

(iv) collecting the processed sample from the divergent analyte flow path.

The processing steps can be chemical steps or physical steps.

According to a third aspect this invention relates to the use of an apparatus according to the present invention for purification and concentration of nucleic acid material

from a fluid sample. Such a sample should preferably be prepared such that it can then undergo a nucleic acid amplification, for example polymerase chain reaction amplification.

Figures

This invention will now be described by reference to a specific embodiment of the apparatus of the present invention shown in the following figures in which;

Figure 1 shows a perspective view of the apparatus from the side;

Figure 2 shows a perspective view of the apparatus from the base;

Figure 3 shows a perspective view of the apparatus from the top, with the top plate removed such that the internal chambers can be seen;

Figure 4 shows an internal view of the base plate of the apparatus;

Figure 5 is a cross sectional view of the apparatus along A-A showing the first step of use of the apparatus for processing a fluid sample for PCR;

Figure 6 is a cross sectional view of the apparatus along B-B showing the second step of use of the apparatus for processing a fluid sample for PCR;

Figure 7 is a cross sectional view of the apparatus along C-C showing the third step of use of the apparatus for processing a fluid sample for PCR;

Figure 8 is a cross sectional view of the apparatus along D-D showing the fourth step of use of the apparatus for processing a fluid sample for PCR; and

Figure 9 is a cross sectional view of the apparatus along E-E showing the fifth step of use of the apparatus for processing a fluid sample for PCR.

Figure 1 shows an apparatus of the present invention 2 comprising a sample chamber 4, a first buffer chamber 6 with a first plunger 8; a second buffer chamber 10 with a

second plunger 12. The first plunger 8 and the second plunger 12 comprise sockets 34 that allow them to integrate with an external apparatus to move the plungers during use. The apparatus 2 additionally comprises a small volume water chamber 14 that extends beyond the main body of the apparatus 2. This comprises a membrane seal enclosing the chamber such that the water within the chamber does not evaporate during storage or the initial stages of sample processing. The membrane is a thin plastic sheet for example 0.1mm-0.2mm, skin of acrylonitrile butadiene styrene. The apparatus also comprises a first outlet port 16 and a second outlet port 18 by which one or more vacuums can be attached to the apparatus 2. The sample chamber 4 comprises a lid 20 which is attached to the main body of the apparatus 2 via an arm 22 which is able to pivot around a peg 24. After the introduction of the sample (not shown) into the sample chamber 4 the lid 20 is pivoted around the peg 24 into position to seal the sample chamber 4. The lid 20 also comprises an inlet outlet port 26 through which air can be drawn into the apparatus 2 via a pump (not shown). The apparatus 2 also comprises a channel 28 that extends from the bottom to the top of the apparatus 2 and which is external to the main body of the apparatus 2. This channel 28 forms part of the fluid communication network of the apparatus. The base plate 30 of the apparatus 2 and the top plate 32 of the apparatus 2 are manufactured as separate units and are fitted to the apparatus 2 during the final stages of manufacture.

Referring to Figure 2, the apparatus 2 comprises a top plate 32, a base plate 30, and an exterior channel 28. The view shows that the apparatus has three reservoirs 50, 52 and 54 that are also exterior to the main body of the apparatus 2. The reservoir 50 is below the sample chamber, the reservoir 52 is below the first buffer chamber and the reservoir 54 is below the second buffer chamber. These reservoirs (50, 52 & 54) are

used as part of the mechanism to prevent sample or buffer from each of these chambers flowing through the fluid communication network of the apparatus in an inappropriate manner. The base plate 30 of the apparatus 2 also comprises a collection chamber 56 that is also exterior to the main body of the apparatus 2. Once the fluid sample (not shown) has been fully purified it enters the divergent analyte flow path and then the collection chamber 56 where it is able to undergo the PCR amplification reaction. It is preferred that the collection chamber 56 is coated with an electrically conducting polymer (not shown) and that it comprises two transparent faces 58 through which a nucleic acid amplification reaction can be monitored.

Referring to Figure 3, the apparatus 2 comprises a sample chamber 4, a first buffer chamber 6 and a second buffer chamber 10. The apparatus 2 comprises a waste chamber 100 that is the dead space within the main body of the apparatus surrounding the other internal chambers. The apparatus comprises a sample processing chamber 102. This is in fluid communication with the sample chamber 4 and the buffer chambers 6, 10 via a pre-processing channel 104. The sample processing chamber 102 is in fluid communication with the waste chamber 100 via a waste channel 28 which links with the waste chamber 100 via the waste port 106. The apparatus also comprises a post processing chamber 108 which is linked to the second vacuum outlet port (18, not shown in this perspective) and also to the sample processing chamber 102 (communication not shown).

Referring to Figure 4, the base plate 30 comprises the sample reservoir 50, a first buffer reservoir 52 and a second buffer reservoir 54. It also comprises a sample channel 152, a first buffer channel 154 and a second buffer channel 156, which

provides the fluid communication from the sample chamber, the first buffer chamber, and the second buffer chamber (not shown) respectively to the sample processing chamber (not shown) via the pre-processing channel the base of which is shown at 158. The base of the sample processing chamber 160 is in fluid communication with the base of the waste chamber 162. The base of the sample processing chamber 160 is also in fluid communication with the base of the post processing chamber 164 via the divergent analyte flow path and the collection chamber (not shown).

Referring to Figure 5, the sample 200 is introduced into the apparatus 2 via the sample chamber 4. Once inside the sample chamber the sample chamber lid 20 is closed. This lid comprises a filter 202 that prevents contamination from the air entering the apparatus and also prevents aerosolised sample leaving the apparatus. In the sample chamber the apparatus interacts with a first reagent bead 204, which comprises lysis reagent containing chaotrophic salts, for example guanidium hydrochloride, to lyse any bacteria within the sample. The first reagent may optionally comprise a nucleic acid target that is later able to act as a means for normalising the efficiency of the subsequent PCR amplification reaction. After the sample has interacted with the first reagent a vacuum is applied to the apparatus via the first vacuum outlet port (vacuum shown in this cross section, but first vacuum outlet port 16 is not shown). This vacuum draws the sample firstly into the sample chamber reservoir 50, along the sample channel 152 to the base of the pre-processing channel 158. The sample is then drawn up the pre-processing channel 104 and into the sample processing chamber 102. The sample processing chamber 102 comprises a filter means 206, for example a glass fibre filter, that is capable of isolating from the sample any nucleic acid as the sample passes through. The vacuum then draws the sample out of the filter to the

base of the sample processing chamber 160, to the base of the waste channel 162 and then up into the waste channel 28. At the top of the waste channel the sample, from which all of the nucleic acid has been removed, enters into the waste chamber 100 through the waste channel outlet 106. This figure does not show the waste material in the waste chamber. The waste channel comprises a small bead 208 that is positioned in the base of the waste channel 162. When the vacuum is applied the bead 208 rises within the waste channel 28 allowing the passage of fluid through the channel 28 into the waste chamber 100. When the vacuum is removed the bead 208 falls and covers the base of the waste channel 162 thus sealing the entrance. This prevents waste fluid from flowing back into the sample processing chamber 102. This view of the apparatus also shows the water chamber 14, the first buffer chamber 6 and plunger 8 and the post processing chamber 108, and the post processing chamber outlet port 18, but the fluid communication between these chambers are not shown in this view.

Referring to Figure 6, the first buffer chamber 6 of the apparatus 2 comprises the first buffer 252, for example an aqueous potassium acetate / Tris.hydrochloride solution such as that available in Promega Wizard™ kit. A vacuum is applied to the apparatus via the waste chamber outlet port (not shown but as in Figure 5). Simultaneously the plunger 8 is depressed within the first buffer chamber 6 which initiates the flow of the first buffer 252 through the reservoir 52 and into the sample processing chamber 102 via the first buffer channel 154 and the pre-processing channel 104 which are linked at the base of the pre-processing channel 158. The first buffer channel 154 is designed to have a very narrow diameter at the point it leaves the first buffer reservoir 52. This ensures that, due to the surface tension of the first buffer, it is unable to leak into the first buffer channel 154 until depression of the plunger 8. Once in the sample

processing chamber 102, as with the sample, the buffer flows through the filter means 206 thus washing the nucleic acid material on the filter membrane. The first buffer 252 is then drawn by the vacuum (not shown) via the waste channel 28, and the waste channel outlet port 106, into the waste chamber 100 (waste material in the waste channel is not shown).

Referring to Figure 7, the second buffer chamber 10 comprises the second buffer 302, for example an aqueous ethanolic solution of potassium acetate / Tris.hydrochloride such as that available in Promega Wizard™ kit. A vacuum is applied to the apparatus via the waste chamber outlet port (not shown but as in Figure 5). Simultaneously the plunger 12 is depressed within the second buffer chamber 10 which initiates the flow of the second buffer 302 through the reservoir 54 and into the sample processing chamber 102 via the second buffer channel 156 and the pre-processing channel 104 which are linked at the base of the pre-processing channel 158. As before the second buffer channel 156 is designed to have a very narrow diameter at the point it leaves the second buffer reservoir 54. This ensures that the second buffer 302 does not leak. Again, once in the sample processing chamber 102, the buffer flows through the filter means 206 again washing the nucleic acid material on the filter membrane. The second buffer 302 is then drawn by the vacuum (not shown) via the waste channel 28, and the waste channel outlet port 106, into the waste chamber 100 (waste material in the waste chamber is not shown).

Referring to Figure 8, the apparatus is configured to air dry the filter membrane comprising the purified nucleic acids to remove any excess solvent from the filter. In order to do this a vacuum is applied to the apparatus 2 via the first vacuum outlet port

16 (not shown). This draws air into the apparatus through the inlet port 26 in the sample chamber lid 20. This air passes through a filter 202 to remove material in the air thus preventing sample contamination. It is then drawn by the vacuum through the sample chamber 4, the sample chamber reservoir 50, the sample chamber channel 152, the pre-processing channel 104, the sample processing chamber 102, the filter means 206, the waste channel 28 and out of the apparatus through the waste chamber 100. The means for applying a vacuum to the apparatus 2 via the outlet port 16 is then removed.

Referring to Figure 9, the small volume chamber 14 comprises purified water, preferably approximately 100µl. This is warmed using an external means for heating (not shown) until the temperature of the water is preferably greater than 80°C. A second vacuum is then applied to the apparatus via the second vacuum outlet port 18. A plunger 305 is depressed releasing the warmed water from the water chamber 14 into the sample processing chamber 102. A cone 315 is used to direct the small volume of water directly to the filter means 206. The water is drawn through the filter means 206, eluting the purified nucleic acid material as it passes through, into the collection chamber 56 by the second vacuum. The second vacuum further draws the water through the divergent analyte flow path, the collection chamber 56 and into the post processing chamber 108. The post processing chamber 108 contains a second solid reagent 310 comprising further PCR reagents for example probes, fluorescing dyes and further nucleic acid controls. This reagent 310 dissolves in the solution. Removing the second vacuum then allows the solution to fall by gravity into the collection chamber 56. Alternatively the first vacuum can be reapplied to draw the solution back into the collection chamber 56.

Once in the collection chamber the nucleic acids are ready to be subjected to the heat cycling required to conduct the PCR amplification. The collection chamber is preferably designed such that its walls are made of a heat conducting polymer. The collection chamber can then either be subjected to the heat cycling in situ or removed and placed in a further apparatus for cycling.

This embodiment of the apparatus has been developed to purify the nucleic acid material from a 10ml fluid sample. The main body of the apparatus has a height of from about 70 to about 80mm and has a diameter of from about 70 to about 80mm. The sample chamber has a volume of about 20ml and the first and second buffer chamber have a volume of about 30ml. The small volume water chamber has a volume of about 500µl and the sample processing chamber has a volume of about 2ml and has a diameter of about 5mm. The pre-processing channel and the waste channel each have a diameter of about 3mm. The waste chamber which is formed by the dead space within the main body has a volume of about 120ml. The fluid communication channels are formed by ultrasonically welding a shaped base plate to the underside of the chamber. The channels have a diameter of about 1mm. At the point where the channels leave the sample reservoirs this diameter is reduced to approximately 0.6mm to prevent unwanted fluid flow from the chambers into the sample processing chamber.

CLAIMS

1. An apparatus for processing a fluid sample comprising:

   (i) a sample processing chamber comprising a fluid inlet and a fluid outlet;

   (ii) a waste chamber downstream from the sample processing chamber and in fluid communication with the sample processing chamber fluid outlet and wherein the fluid communication between the sample processing chamber outlet and the waste chamber comprises a divergent analyte flow path;

   (iii) at least two further chambers up stream from the sample processing chamber both of which are in fluid communication with the sample processing chamber fluid inlet;

   (iv) a means for moving fluid from each of the at least two further chambers through the sample processing chamber and into the waste chamber or into the divergent analyte flow path as desired by applying positive or negative pressure to the desired flow path; and

   (v) a passive means for restricting the flow of fluid.

2. An apparatus according to Claim 1 wherein the means for moving fluid from at least one of the at least two further chambers through the sample processing chamber comprises a means for generating a vacuum.

3. An apparatus according to Claim 2 wherein the waste chamber comprises an outlet port which is connected to the means for generating a vacuum.

4. An apparatus according to Claim 2 wherein the analyte flow path comprises an outlet port which is connected to the means for generating a vacuum.

5. An apparatus according to Claim 1 wherein the means for moving fluid from at least one of the at least two further chambers through the sample processing chamber comprises a plunger capable of being depressed to expel fluid from the at least one further chamber.

6. An apparatus according to Claim 5 wherein the means for moving fluid from at least one of the two further chambers through the sample processing chamber additionally comprises a means for generating a vacuum.

7. An apparatus according to any of Claims 1 to 6 wherein the means for moving fluid from each of the two further chambers through the sample processing chamber moves the fluid sequentially from the first at least two further chambers through the sample processing chamber and into the waste chamber and then from the second at least two further chambers through the sample processing chamber and into either the waste chamber or the divergent analyte flow path.

8. An apparatus according to any of Claims 1 to 7 wherein the passive means for restricting the flow of fluid comprises a valve located in the fluid communication between the sample processing chamber and the waste chamber.

9. An apparatus according to Claim 8 wherein the valve is down stream of the divergent analyte flow path.

10. An apparatus according to Claim 8 wherein the valve comprises a bead which is opened by applying a positive or negative pressure.

11. An apparatus according to any of Claims 1 to 10 wherein the passive means for restricting the flow of fluid comprises a reservoir located in the fluid communication between at least one of the at least two further chambers and the sample processing chamber.

12. An apparatus according to any of Claims 1 to 11 wherein the passive means for restricting the flow of fluid comprises a fluid pathway of small diameter such that fluid can not flow through the pathway without the application of a positive or negative pressure, located in the fluid communication between at least one of the at least two further chambers and the sample processing chamber.

13. An apparatus according to any of Claims 1 to 12 comprising a collection chamber downstream of the analyte flow path and in fluid communication with the analyte flow path outlet.

14. An apparatus according to Claim 13 wherein the collection chamber comprises a reagent, preferably a reagent comprising one or more nucleic acid amplification reagents, more preferably a reagent selected from the group consisting of nucleic acid primers, nucleic acid probes, fluorescing dyes, enzyme buffers, nucleotides, magnesium slats, bovine serum albium, and denaturants.

15. An apparatus according to Claim 13 wherein collection chamber comprises an outlet port which optionally may be connected to a means for generating a vacuum.

16. An apparatus according to Claim 15 wherein the apparatus comprises a post processing chamber down stream from the collection chamber in fluid communication with the collection chamber outlet and which optionally itself comprises an outlet which may be connected to a means for generating a vacuum.

17. An apparatus according to any of Claims 1 to16 wherein the sample processing chamber comprises an active member, preferably a trapping member selected from the group consisting of a microfluidic chip, a solid phase material, a filter, a filter stack, an affinity matrix, a magnetic separation matrix, a size exclusion column, a capillary tube, and mixtures thereof.

18. An apparatus according to Claim 17 wherein the sample processing chamber comprises a glass fibre filter membrane.

19. An apparatus according to any of Claims 1 to 18 wherein at least one of the at least two further chambers is pre-filled with a buffer solution, preferably a buffer solution selected from the group consisting of an aqueous solution of potassium acetate and Tris.hydrochloride, or an aqueous ethanolic solution of potassium acetate and Tris.hydrochloride.

20. An apparatus according to any of Claims 1 to 19 wherein at least one of the at least two further chambers acts as a sample chamber comprising an inlet port through which a sample is introduced into the apparatus.

21. An apparatus according to Claim 20 wherein the sample chamber inlet port comprises a filter membrane.

22. An apparatus according to any of Claims 20 to 21 wherein the sample chamber comprises a reagent, preferably a reagent comprising a lysis reagent, more preferably a chaotrophic salt.

23. An apparatus according to any of Claims 1 to 22 wherein the apparatus comprises at least one chamber located externally to the main body of the apparatus.

24. An apparatus according to Claim 23 wherein the chamber located externally to the main body of the apparatus is the collection chamber.

25. An apparatus according to Claim 23 wherein the chamber located externally to the main body of the apparatus is at least one of the at least two further chambers.

26. An apparatus according to Claim 23 wherein at least one chamber located externally has walls which are coated with an electrically conducting polymer.

27. A method of processing a fluid sample comprising:

(i) placing the sample in the sample processing chamber of an apparatus according to Claim 1;

(ii) applying a positive or negative pressure to move fluid through the apparatus;

(iii) subjecting the sample to one or more processing steps; and

(iv) collecting the processed sample from the divergent analyte flow path .

28. Use of an apparatus according to Claim 1 for purification and concentration of nucleic acid material from a fluid sample.

29. Use according to Claim 28 wherein the nucleic acid material is then subjected to a polymerase chain reaction amplification.

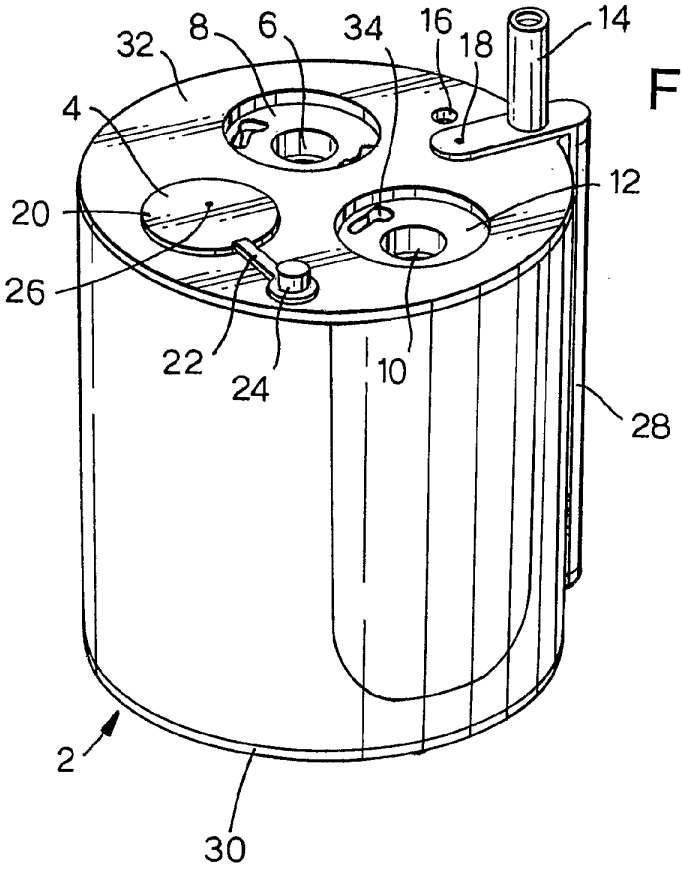


Fig.1.

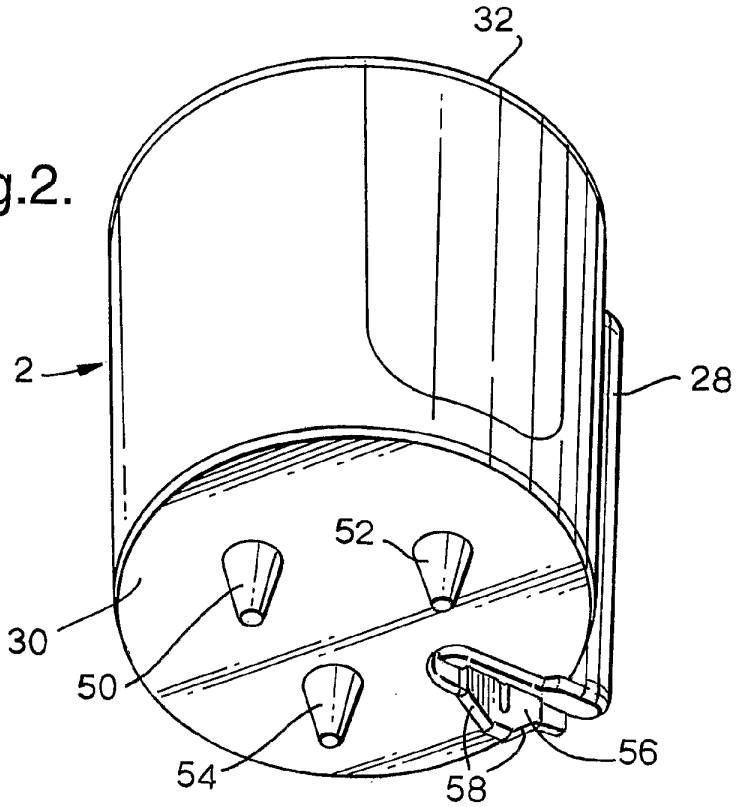


Fig.2.

Fig.3.

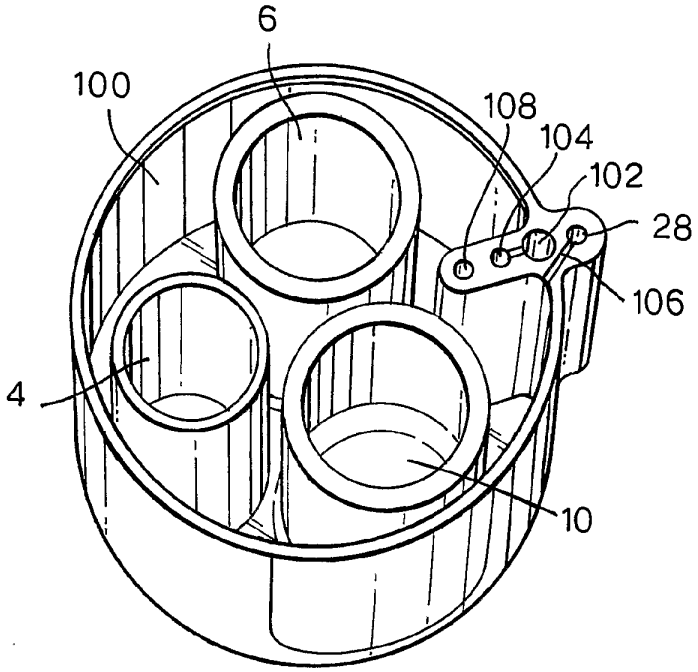

6
100
108
104
102
28
106
4
10

Fig.4.

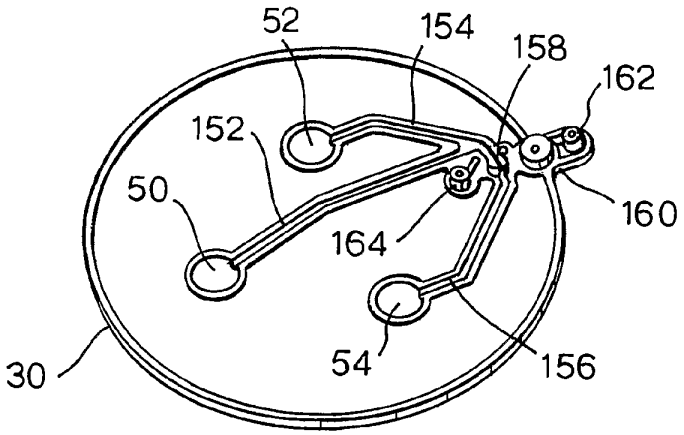

52
154
158
162
152
50
160
164
30
54
156

Fig.5 A.

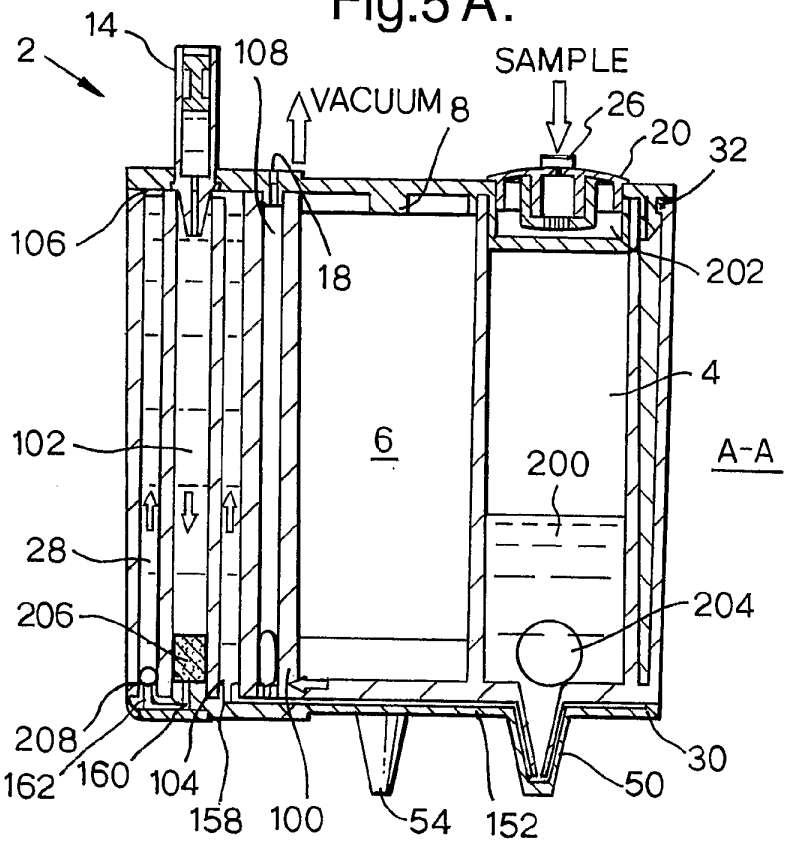

14
2
108
VACUUM
8
SAMPLE
26
20
32
106
18
202
4
102
6
200
A-A
28
206
204
208
162
160
104
158
100
54
152
50
30

Fig.5 B.

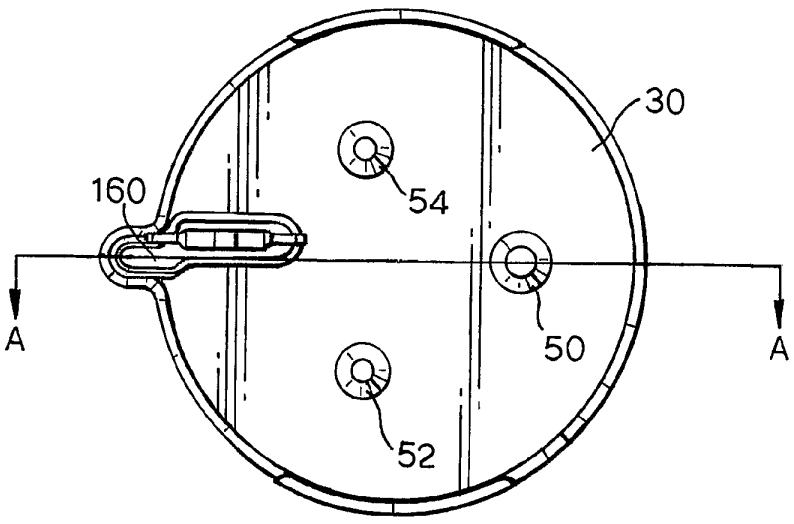

30
160
54
50
A
A
52

Fig.6 A.

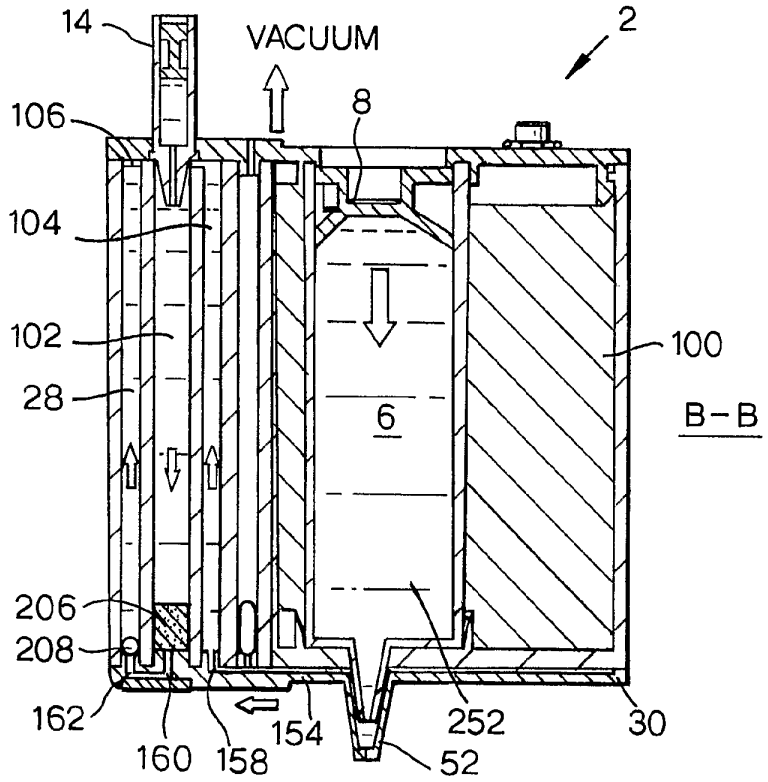

14
VACUUM
2
106
8
104
102
100
28
6
B-B
206
208
162
160
158
154
252
30
52

Fig.6 B.

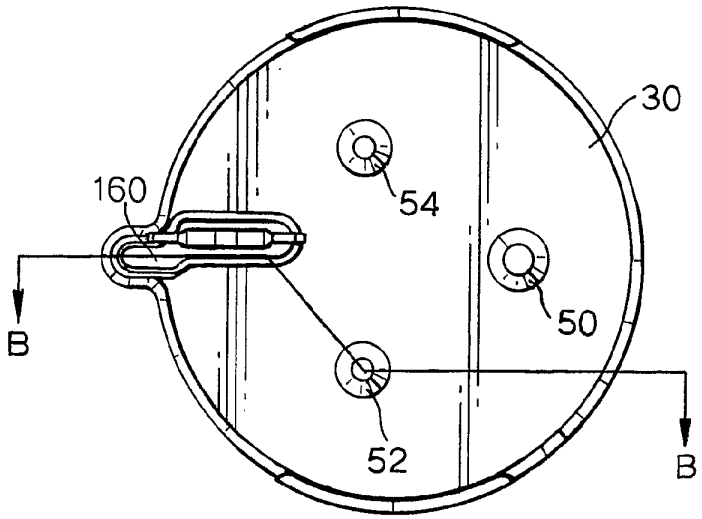

30
160
54
50
B
52
B

Fig.7A.

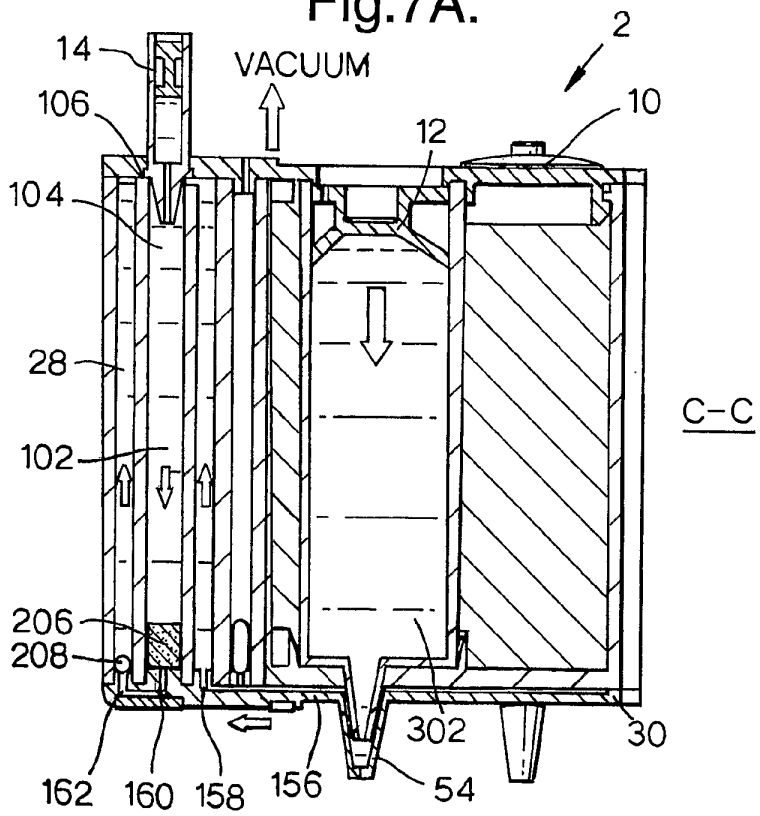

14
VACUUM
2
106
10
12
104
28
C-C
102
206
208
302
30
162
160
158
156
54

Fig.7B.

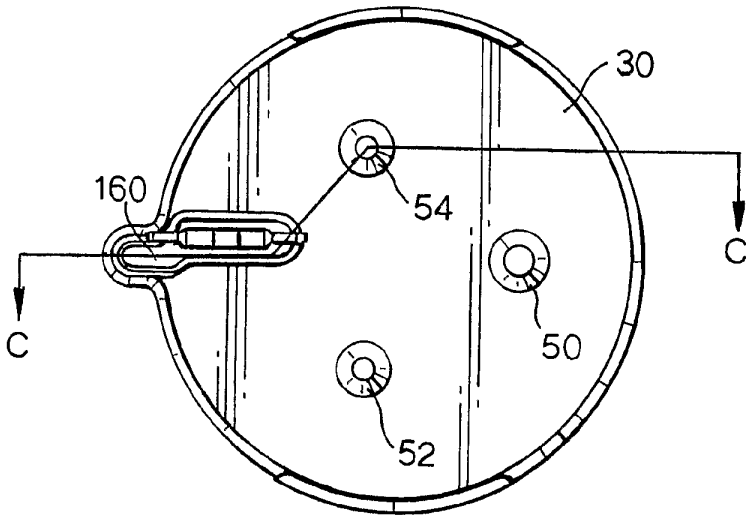

30
160
54
C
C
50
52

Fig.8A.

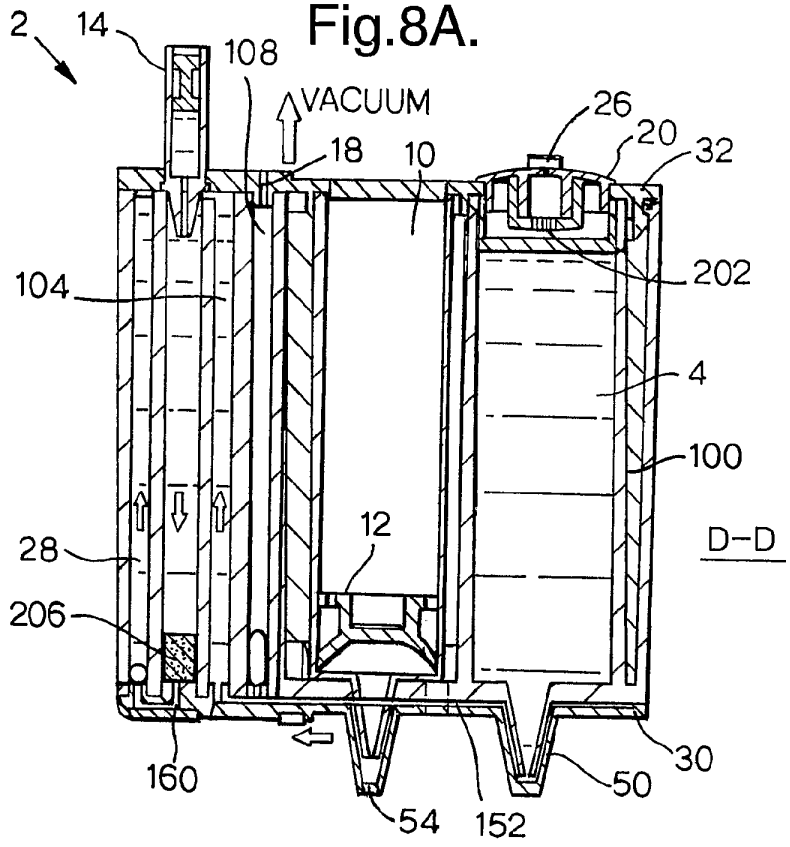

2
14
108
VACUUM
18
10
26
20
32
104
202
4
100
12
D-D
28
206
160
54
152
50
30

Fig.8B.

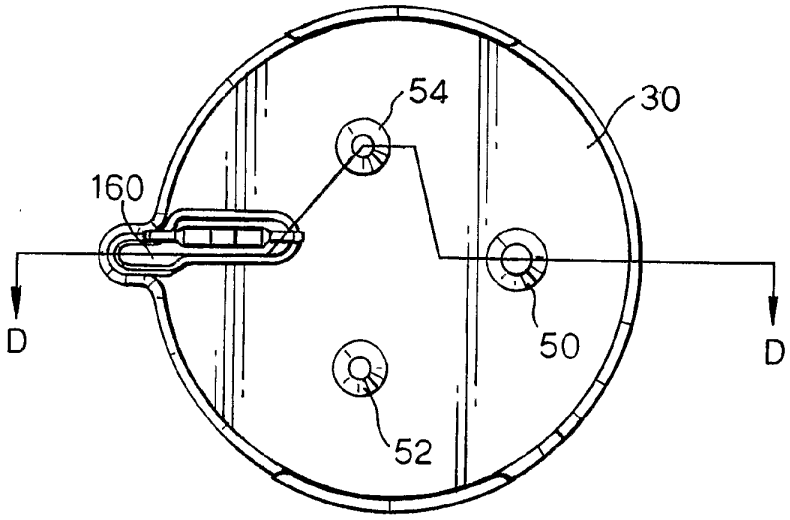

54
30
160
D
50
D
52

Fig.9A.

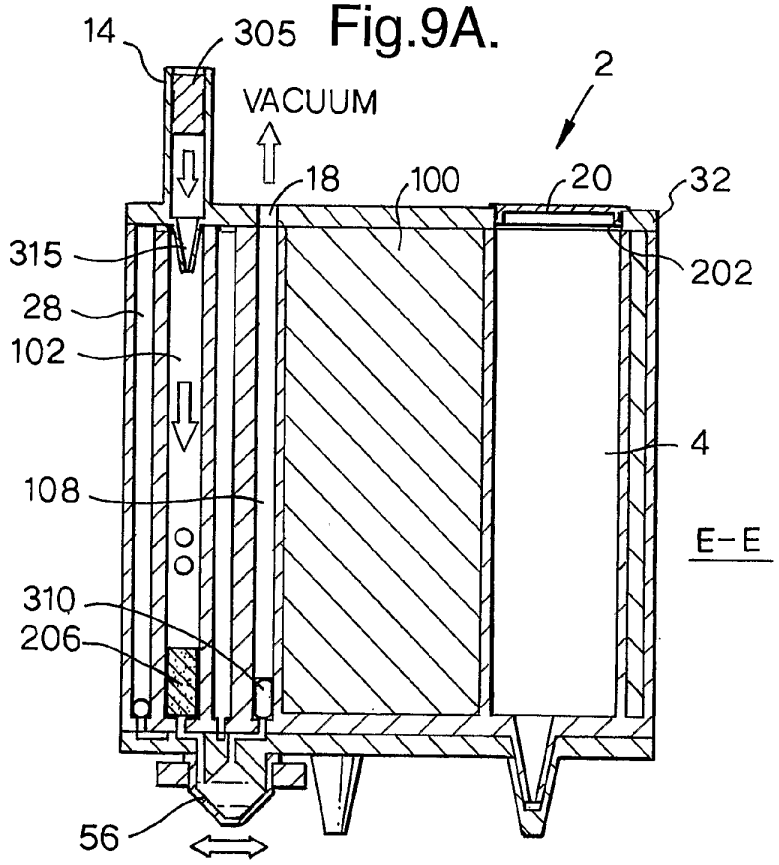
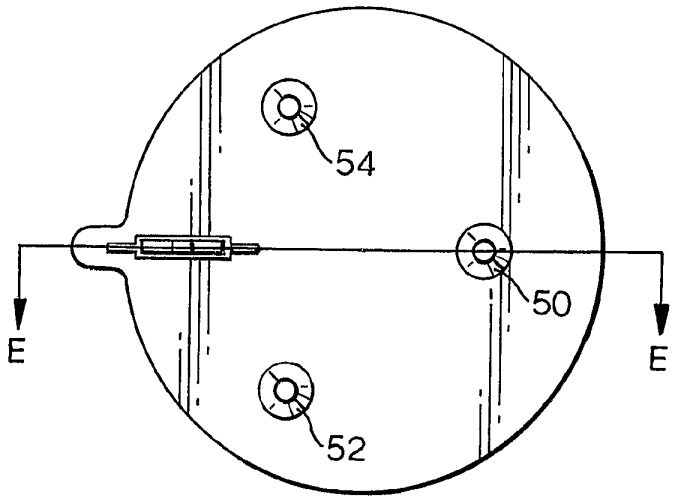

14
305
VACUUM
2
18
100
20
32
315
202
28
102
4
108
E-E
310
206
56

Fig.9B.


54
50
E
E
52

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/GB 03/05173

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00 C12Q1/68 G01N1/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01L C12Q G01N C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/039783 A1 (POURAHMADI FARZAD ET AL) 4 April 2002 (2002-04-04) paragraphs '0011!-'0020! paragraphs '0047!-'0055!,'0066!; figure 2 paragraphs '0074!,'0084!-'0095!,'0100!-'0102!,'0122!-'0126!,'0131!	1-29
X	EP 0 381 501 A (EASTMAN KODAK CO) 8 August 1990 (1990-08-08) column 2, line 20 -column 4, line 3; figures 1-9 column 11, line 37 -column 13, line 4 column 17, line 50 -column 20, line 36	1,2,5,6, 11-14, 16,17, 19,20, 22,27-29

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2004	20/04/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Tiede, R

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 03/05173

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/62931 A (KAYYEM JON FAIZ ;CLINICAL MICRO SENSORS INC (US)) 26 October 2000 (2000-10-26) cited in the application page 2, line 4 -page 2, line 15; figure 1D	1-4,6
A	US 5 637 469 A (WILDING PETER ET AL) 10 June 1997 (1997-06-10) the whole document	1-29
A	US 6 300 142 B1 (ATTRIDGE JOHN WORTHINGTON ET AL) 9 October 2001 (2001-10-09) abstract; figures 1-6	1-29

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 03/05173

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		US 2002045246 A1	18-04-2002
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 03/05173

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CARTRIDGE AND TEST INFORMATION

i-STAT® sensors are available in a variety of panel configurations. Sensors are contained in cartridges with microfluidic components and, in some cartridges, calibration solution. i-STAT cartridges are used with the i-STAT 1 Analyzer* for the simultaneous quantitative determination of specific analytes and coagulation parameters in whole blood.

CARTRIDGE SPECIFICATIONS

Shelf Life:

Refrigerated at 2 to 8 °C (35 to 46 °F) until expiration date.

Refer to the cartridge box for room temperature storage requirements.

Preparation for Use:

Individual cartridges may be used after standing five minutes at room temperature. An entire box of cartridges should stand at room temperature for one hour.

All cartridges should be used immediately after opening pouch. If the pouch has been punctured, the cartridge should not be used.

Sample Type:

Fresh whole blood from arterial, venous, or skin punctures.

(Note: Skin puncture is NOT a recommended sample type for ACT, cTnI, CK-MB, ß-hCG or BNP testing.)

cTnI, ß-hCG and CK-MB cartridges require the use of heparinized whole blood or plasma, or non-heparinized whole blood tested within one minute of patient draw.

BNP cartridges require the use of EDTA whole blood or plasma samples.

Sample Volume:

17 µL, 20 µL, 40 µL, 65 µL, or 95 µL depending on cartridge type.

Test Timing:

Immediately after collection

- Samples for the measurement of ACT, PT/INR and Lactate

Within 3 minutes after collection

- Samples collected in capillary tubes with balanced heparin anticoagulant
- Samples collected in evacuated or non-evacuated tubes and syringes without anticoagulant

Within 10 minutes after collection

- Samples collected with anticoagulant for the measurement of pH, PCO_2, PO_2 and iCa. Maintain anaerobic conditions. Remix before filling cartridge.

Within 30 minutes after collection

- Sodium, potassium, chloride, glucose, BUN/urea, creatinine, hematocrit, troponin I, CK-MB, ß-hCG and BNP. Remix thoroughly before testing.

Abbott Point of Care

Art: 714258-01O Rev. Date: 15-Aug-16

* The cTnI, CK-MB, ß-hCG and BNP cartridges can only be used with the i-STAT 1 analyzer bearing the  symbol.

Analysis Time:

- ACT cartridge: to detection of end point - up to 1000 sec (16.7 min)
- PT/INR cartridge: to detection of end point – up to 300 sec (5 min)
- cTnI, ß-hCG and BNP cartridges: 600 sec (10 min)
- CK-MB cartridge: 300 sec (5 min)
- Other cartridges: typically 130 to 200 sec

Cartridges	Collection Options			
	Syringes	Evacuated Tubes	Capillary Tubes	Directly from Skin Puncture
Cartridges which measure ionized calcium	• Without anticoagulant • With balanced heparin anticoagulant (syringe must be filled to labeled capacity)	• Without anticoagulant • With lithium heparin anticoagulant (tubes must be filled to capacity)	• With balanced heparin anticoagulant	• Not recommended • Not recommended for blood gas analysis; arterial specimens are preferred
Cartridges which perform ACT	• Without anticoagulant ONLY • Syringes must be plastic	• Without anticoagulant, clot activators, or serum separators ONLY • Tubes must be plastic • Devices used to transfer sample to cartridge must be plastic	• Not recommended	• Not recommended
Cartridges which perform PT/INR	• Without anticoagulant ONLY • Syringes must be plastic	• Without anticoagulant, clot activators, or serum separators ONLY • Tubes must be plastic • Devices used to transfer sample to cartridge must be plastic	• Not recommended	• Recommended
Cartridges which measure Troponin I or CK-MB	• With sodium or lithium heparin anticoagulant (syringe must be filled to labeled capacity) • Without anticoagulant if tested within one minute of patient draw	• With sodium or lithium heparin anticoagulant (tubes must be filled to capacity) • Without anticoagulant if tested within one minute of patient draw	• Not recommended	• Not recommended

Cartridges	Collection Options			
	Syringes	Evacuated Tubes	Capillary Tubes	Directly from Skin Puncture
Cartridges which measure Total ß-hCG	• With sodium or lithium anticoagulant (syringe must be filled to labeled capacity) • Without anticoagulant if tested within one minute of patient draw • Syringes must be plastic	• With sodium or lithium heparin anticoagulant (tubes must be filled to capacity)	• Not recommended	• Not recommended
Cartridges which measure BNP	• With EDTA anticoagulant (syringe must be filled to labeled capacity) • Syringes must be plastic	• With EDTA anticoagulant (tubes must be filled to capacity) • Tubes must be plastic	• Not recommended	• Not recommended
All other cartridges	• Without anticoagulant • With lithium or balanced heparin anticoagulant (syringe must be filled to labeled capacity)	• Without anticoagulant • With lithium heparin anticoagulant (tubes must be filled to capacity)	• With balanced heparin anticoagulant • With lithium heparin if labeled for the measurement of electrolytes	• While a sample can be transferred directly from a skin puncture to a cartridge, a capillary tube is preferred • Not recommended for blood gas analysis; arterial specimens are preferred

Note Regarding System Reliability

The i-STAT System automatically runs a comprehensive set of quality checks of analyzer and cartridge performance each time a sample is tested. This internal quality system will suppress results if the analyzer or cartridge does not meet certain internal specifications (see Quality Control section in System Manual for detailed information). To minimize the probability of delivering a result with medically significant error the internal specifications are very stringent. It is typical for the system to suppress a very small percentage of results in normal operation given the stringency of these specifications. If however the analyzer or cartridges have been compromised, results may be persistently suppressed, and one or the other must be replaced to restore normal operating conditions. **Where unavailability of results while awaiting replacement of analyzers or cartridges is unacceptable, APOC recommends maintaining both a backup i-STAT System analyzer and cartridges from an alternate lot number.**

EXPECTED VALUES

Measured:

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
Sodium/Na	mmol/L (mEq/L)	100 – 180	138 – 146	138 – 146
Potassium/K	mmol/L (mEq/L)	2.0 – 9.0	3.5 – 4.9	3.5 – 4.9
Chloride/Cl	mmol/L (mEq/L)	65 – 140	98 – 109	98 – 109
Glucose/Glu	mmol/L mg/dL g/L	1.1 – 38.9 20 – 700 0.20 – 7.00	3.9 – 5.8 70 – 105 0.70 – 1.05	3.9 – 5.8 70 – 105 0.70 – 1.05
Lactate/Lac	mmol/L mg/dL	0.30 – 20.00 2.7 – 180.2	0.36 – 1.25 3.2 – 11.3	0.90 – 1.70 8.1 – 15.3
Creatinine/Crea	mg/dL µmol/L	0.2 – 20.0 18 – 1768	0.6 – 1.3 53 – 115	0.6 – 1.3 53 – 115
pH		6.5 – 8.2	7.35 – 7.45	7.31 – 7.41
***P*CO$_2$**	mmHg kPa	5 – 130 0.67 – 17.33	35 – 45 4.67 – 6.00	41 – 51 5.47 – 6.80
TCO$_2$ (on the CHEM8+ cartridge only)	mmol/L (mEq/L)	5 – 50	23 – 27	24 – 29
***P*O$_2$**	mmHg kPa	5 – 800 0.7 – 106.6	80 – 105 10.7 – 14.0	
Ionized Calcium/iCa	mmol/L mg/dL	0.25 – 2.50 1.0 – 10.0	1.12 – 1.32 4.5 – 5.3	1.12 – 1.32 4.5 – 5.3
Urea Nitrogen/BUN **Urea**	mg/dL mmol/L mg/dL g/L	3 – 140 1 – 50 6 – 300 0.06 – 3.00	8 – 26 2.9 – 9.4 17 – 56 0.17 – 0.56	8 – 26 2.9 – 9.4 17 – 56 0.17 – 0.56
Hematocrit/Hct	%PCV Fraction	15 – 75 0.15 – 0.75	38 – 51 0.38 – 0.51	38 – 51 0.38 – 0.51
Celite Activated Clotting Time / ^{Celite}ACT *The range from 80 - 1000 seconds has been verified through method comparison studies.*	seconds	50 – 1000	74 – 125 (Prewarm) 84 – 139 (Nonwarm)	74 – 125 (Prewarm) 84 – 139 (Nonwarm)
Kaolin Activated Clotting Time / ^{Kaolin}ACT *The range from 77 - 1000 seconds has been verified through method comparison studies.*	seconds	50 – 1000	74 – 137 (Prewarm) 82 – 152 (Nonwarm)	74 – 137 (Prewarm) 82 – 152 (Nonwarm)
Prothrombin Time / PT *Performance characteristics have not been established for INRs above 6.0.*	INR	0.9 – 8.0		
Troponin I / cTnI	ng/mL (µg/L)	0.00 – 50.00		0.00 – 0.03* 0.00 – 0.08**
Performance characteristics have not been established for cTnI values above 35.00 ng/mL. ** Represents the 0 to 97.5% range of results.* *** Represents the 0 to 99% range of results.*				
Creatine Kinase MB / CK-MB ****Represents the 0 to 95% range of results.*	ng/mL (µg/L)	0.0 – 150.0		0.0 – 3.5***

EXPECTED VALUES (CONT.)

Measured: (CONT.)

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
B-Type Natriuretic Peptide / BNP	pg/mL (ng/L)	15 – 5000		<15 – 50#
# Represents the 0 to 95% range of results.				
Total Beta-Human Chorionic Gonadotropin /ß-hCG	IU/L	5.0 – 2000.0		<5.0

Calculated:

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
Hemoglobin/Hb	g/dL	5.1 – 25.5	12 – 17	12 – 17
	g/L	51 – 255	120 – 170	120 – 170
	mmol/L	3.2 – 15.8	7 – 11	7 – 11
TCO_2 (on all cartridges but the CHEM8+)	mmol/L (mEq/L)	5 – 50	23 – 27	24 – 29
HCO_3	mmol/L (mEq/L)	1.0 – 85.0	22 – 26	23 – 28
BE	mmol/L (mEq/L)	(-30) – (+30)	(-2) – (+3)	(-2) – (+3)
Anion Gap/AnGap	mmol/L (mEq/L)	(-10) – (+99)	10 – 20	10 – 20
sO_2	%	0 – 100	95 – 98	

CARTRIDGE CONFIGURATIONS AND SAMPLE VOLUME

i-STAT EC8+ (65µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
pH
PCO_2
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Hematocrit (Hct)
TCO_2*
HCO_3*
BE*
Anion Gap* (Angap)
Hemoglobin* (Hb)

i-STAT 6+ (65µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT EC4+ (65µL)
Sodium (Na)
Potassium (K)
Glucose (Glu)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT E3+ (65µL)
Sodium (Na)
Potassium (K)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT G (65µL)
Glucose (Glu)

i-STAT CREA (65µL)
Creatinine (Crea)

i-STAT EG7+ (95µL)
Sodium (Na)
Potassium (K)
Ionized Calcium (iCa)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT EG6+ (95µL)
Sodium (Na)
Potassium (K)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT G3+ (95µL)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*

i-STAT CG4+ (95µL)
pH
PCO_2
PO_2
Lactate
TCO_2*
HCO_3*
BE*
sO_2*

i-STAT TOTAL ß-hCG (17µL)
Total Beta-Human Chorionic Gonadotropin

Calculated

i-STAT CG8+ (95µL)
Sodium (Na)
Potassium (K)
Ionized Calcium (iCa)
Glucose (Glu)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT CeliteACT (40µL)
Celite® ACT

i-STAT KAOLINACT (40µL)
Kaolin ACT

i-STAT PT/INR (20µL)
Prothrombin Time

i-STAT cTnI (17 µL)
Troponin I

i-STAT CK-MB (17µL)
Creatine Kinase MB

i-STAT BNP (17µL)
B-type Natriuretic Peptide

i-STAT CHEM8+ (95µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Creatinine (Crea)
Ionized Calcium (iCa)
TCO_2
Hematocrit (Hct)
Anion Gap* (Angap)
Hemoglobin* (Hb)

Celite is a registered trademark of Celite Corporation, Santa Barbara, CA, for its diatomaceous earth products.

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ABN: 38 113 072 755

18 March 2022

Examination report No. 1 for standard patent application

Griffith Hack
GPO Box 4164
Sydney NSW 2001
Australia

Your reference:	P108089.AU.1
Application number:	2021202622
Applicant name:	KURIN, INC.
Earliest priority date:	24 July 2015

Final date for acceptance:	**18 March 2023**
Date of this report:	18 March 2022
Examination request date:	6 July 2021

Dear Griffith Hack,

Your application has been examined under *section 45 of the Patents Act 1990*.

You have **12 months** from the date of this report to overcome all my objection(s) otherwise this application will lapse.

You will also need to pay any annual continuation fees that apply. Your next continuation fee is due on **22 July 2022**.

While the application is otherwise in order for acceptance, it cannot be accepted because there is a current postponement of acceptance in place.

You must respond to this report in order to gain acceptance. The Commissioner will only proceed to accept the application if you file a clear and unambiguous statement requesting the postponement be withdrawn with sufficient time for the request to be processed. If the application is not accepted by **18 March 2023**, your application will lapse.

Details of this patent application can be viewed on Auspat, our Australian patent search database.

Yours sincerely,

Kevin Sivieng
Section: MECH 4 - MEDICAL DEVICES
Phone: +61 2 6283 2609

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Report details

Basis of the report

In examining this application I have considered:

- the specification as filed.
- allowed and/or proposed amendment/s under S104 including amendment item number 1, filed on 4 May 2021.

Summary of novelty, inventive step and patentable subject matter

	Satisfy requirements?	*Claim numbers*
Novelty/inventive step	**Yes**	1-16
	No	NONE
Patentable subject matter	**Yes**	1-16
	No	NONE

Detailed objections on issues that have been identified

Documents cited or considered relevant

D1: WO 2011162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES LLC [US], et al) 29 December 2011 [1]
Category: A

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Category: A

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Category: A

D7: JP 2001000424 A (NISSHO KK) 9 January 2001, English translation retrieved from Espacenet [5]
Category: A

[1] Cited in the search/examination report of WO 2017/019552 A1

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[4] Cited in the search/examination report of JP 2018525191

[5] Cited in the search/examination report of JP 2020192333

Special categories of cited documents:

A: Document defining the general state of the art which is not considered to be of particular relevance.
&: Document member of the same patent family.

END OF REPORT

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Patentanwälte PartG mbB
Siebertstr. 6
81675 München
ALLEMAGNE

Date
28.10.2022

Reference	Application No./Patent No.
KUR-18996-P-EP	20781928.5 - 1122 / 3948211 PCT/US2020026276
Applicant/Proprietor	
Kurin, Inc.	

Communication

The extended European search report is enclosed.

The extended European search report includes, pursuant to Rule 62 EPC, the supplementary European search report (Art. 153(7) EPC) and the European search opinion.

Copies of documents cited in the European search report are attached.

☒ 0 additional set(s) of copies of such documents is (are) enclosed as well.

Refund of the search fee
If applicable under Article 9 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.

Should you wish to further prosecute this application in the examination phase, your attention is drawn to the provisions of Rule 70a EPC. An invitation to respond to the extended European search report will be issued shortly (R. 70(2) EPC).

Europäisches Patentamt • European Patent Office • Office européen des brevets

The examination is being carried out on the **following application documents**

Description, Pages

1-28 as published

Claims, Numbers

1-20 as published

Drawings, Sheets

1/16-16/16 as published

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 US 2018/271425 A1 (ROGERS BOBBY E [US] ET AL) 27 September 2018 (2018-09-27)

D2 EP 3 324 845 A1 (KURIN INC [US]) 30 May 2018 (2018-05-30)

D3 WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 5 December 2019 (2019-12-05)

D4 WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 21 March 2019 (2019-03-21)

1. The application does not meet the requirements of Article 84 EPC, because claims 1, 6 and 14 are not clear.

Claims 1, 6 and 14 have been drafted as separate independent claims.

Under Article 84 in combination with Rule 43(2) EPC, an application may contain more than one independent claim in a particular category only if the subject-matter claimed falls within one or more of the exceptional situations set out in paragraph (a), (b) or (c) of Rule 43(2) EPC. However, this is not the case in the present application.

2. The present application does not meet the requirements of Article 52(1) EPC because the subject-matter of claims 1, 6 and 14 is not new within the meaning of Article 54(1) and (2) EPC.

2.1 D1 discloses **a fluid sample optimization device** (see fig.23,24, par. [0141]-[0149]:"blood sample optimization system 2400") **for optimizing a fluid sample collected by a fluid collection device from a fluid source, a first portion of the fluid sample potentially having contaminants** (see par. [0141]:" a sampling channel 2308 that bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be sequestered"), **the fluid sample optimization device comprising:**

an inlet ("inlet port 2412") **configured to connect with the fluid source;**

an outlet ("outlet port 2414") **configured to connect with the fluid collection device;**

a sample path ("blood sample channel 2422") **connected between the inlet and the outlet; and**

a contaminant containment reservoir ("blood sequestration chamber 2418 ") **connected between the inlet and the outlet, the contaminant containment reservoir having an air permeable fluid resistor** ("air permeable blood barrier 2420") **proximate the outlet, the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet, a first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet, such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir, subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet** (see par. [0148]:"As the initial aliquot of blood flows into the blood sequestration chamber, it displaces air therein and eventually the blood contacts the blood barrier 2420, forcing the inner chamber housing to the second position.","Once in the second position, the initial aliquot of blood is sequestered in the blood sequestration chamber 2418 and the one or more apertures 2424 are opened to create a pathway from the inlet port 2412 to the blood sampling channel 2422, bypassing and/or flowing around the blood sequestration chamber 2418.".

The subject-matter of claim 1 is therefore not new (Article 54(1) and (2) EPC).

2.2 D1 discloses a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source (see fig.23,24, par. [0141]-[0149]:"blood sample optimization system 2400"), a first portion of the fluid sample potentially having contaminants (see par. [0141]:" a sampling channel 2308 that

bypasses the sequestration chamber 2306 once the sequestration chamber is filled to an initial aliquot of potentially contaminated blood to be sequestered"), the fluid sample optimization device comprising:

an inlet ("inlet port 2412") configured to connect with the fluid source;

an outlet ("outlet port 2414") configured to connect with the fluid collection device;

a sample path ("blood sample channel 2422") connected between the inlet and the outlet, the sample path further having a resistive plug ("apertures 2424") that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path (see par.[0141]:"the inner chamber housing 2419 is in the first position toward the inlet port 2412, such that the one or more apertures 2424 are closed, and the blood sequestration chamber 2418 is in a direct path from the patient needle."); and

a contaminant containment reservoir ("blood sequestration chamber 2418 ") connected between the inlet and the outlet, the contaminant containment reservoir further having an air permeable fluid resistor ("air permeable blood barrier 2420") proximate the outlet, the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet, the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet, such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir, subsequent portions of the fluid sample can be forced through the resistive plug and conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (see par.[0148]:"As the initial aliquot of blood flows into the blood sequestration chamber, it displaces air therein and eventually the blood contacts the blood barrier 2420, forcing the inner chamber housing to the second position.","Once in the second position, the initial aliquot of blood is sequestered in the blood sequestration chamber 2418 and the one or more apertures 2424 are opened to create a pathway from the inlet port 2412 to the blood sampling channel 2422, bypassing and/or flowing around the blood sequestration chamber 2418.").

The subject-matter of claim 6 is therefore not new (Article 54(1) and (2) EPC).

2.3 The subject-matter of claim 14, which comprises for essentially the same features as the subject matter of claim 1, is for essentially the same reasons as those given above (see point 2.1) also not new (Article 54(1) and (2) EPC).

2.4 Furthermore, the documents D2-D3 also disclose all the features of claim 1, 6 and 14. For further details, see the relevant parts thereof as cited in the Search Report.

3. The dependent claims 2 to 5, 7 to 13 and 15 to 20 and seem not to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC in respect of novelty and/or inventive step, defining either features already known from any of D1-D3 or straightforward possibilities from which the person skilled in the art would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

4. Independent claims are not in the two-part form in accordance with Rule 43(1) EPC, which in the present case would be appropriate, with those features known in combination from the prior art being placed in the preamble (Rule 43(1)(a) EPC) and the remaining features being included in the characterising part (Rule 43(1)(b) EPC).

5. The features of the claims should be provided with reference signs placed in parentheses to increase the intelligibility of the claims (Rule 43(7) EPC). This applies to both the preamble and characterising portion (see Guidelines F-IV, 4.18).

6. The applicant is invited to file new claims which take account of the above comments.

In order to comply with the requirements of Rule 137(4) EPC, the applicant should clearly identify the amendments made, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed on which these amendments are based (see Guidelines H III, 2.1).

If the applicant considers it appropriate, these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed or in documents with tracked changes.

When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and of any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

Information on Search Strategy - Pilot phase (see OJ 2015, A86)
The type of information contained in this sheet may change during the pilot for improving the usefulness of this new service.

Application Number
EP 20 78 1928

TITLE: NON-VENTING BODILY FLUID SAMPLE OPTIMIZATION DEVICE AND SYSTEM

APPLICANT: Kurin, Inc.

IPC CLASSIFICATION: G01N1/10, G01N1/02, A61B5/15, A61B5/154

EXAMINER: Coja, Michael

CONSULTED DATABASES: EPODOC, WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

IPC:

CPC: A61B5/15003, A61B5/150213, A61B5/150221, A61B5/150251

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

EPO FORM P04A42

Europäisches Patentamt
European Patent Office
Office européen des brevets

SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 20 78 1928

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 2018/271425 A1 (ROGERS BOBBY E [US] ET AL) 27 September 2018 (2018-09-27) * the whole document *	1-20	INV. G01N1/10 G01N1/02 A61B5/15
X	EP 3 324 845 A1 (KURIN INC [US]) 30 May 2018 (2018-05-30) * paragraph [0104]; figure 23 *	1-20	A61B5/154
X,P	WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 5 December 2019 (2019-12-05) * paragraphs [0074], [0099], [0120], [0141]; figures 1-14 *	1,6,14	
A	WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]) 21 March 2019 (2019-03-21) * paragraph [1179]; figures 35-37 *	1-20	

TECHNICAL FIELDS SEARCHED (IPC)

A61B

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
The Hague	20 October 2022	Coja, Michael

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

1

EPO FORM 1503 03.82 (P04C04)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 20 78 1928

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

20-10-2022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2018271425 A1	27-09-2018	US 2018271425 A1	27-09-2018
		US 2021145336 A1	20-05-2021
EP 3324845 A1	30-05-2018	AU 2016297849 A1	22-02-2018
		AU 2021202622 A1	27-05-2021
		CA 2993646 A1	02-02-2017
		EP 3324845 A1	30-05-2018
		EP 3622890 A1	18-03-2020
		IL 257137 A	29-03-2018
		IL 286030 A	31-10-2021
		JP 6643474 B2	12-02-2020
		JP 6734490 B2	05-08-2020
		JP 2018525191 A	06-09-2018
		JP 2020096843 A	25-06-2020
		JP 2020192333 A	03-12-2020
		US 2017020427 A1	26-01-2017
		US 2017020428 A1	26-01-2017
		US 2018289304 A1	11-10-2018
		US 2019159711 A1	30-05-2019
		US 2022079483 A1	17-03-2022
		WO 2017019552 A1	02-02-2017
WO 2019232196 A1	05-12-2019	CA 3101972 A1	05-12-2019
		EP 3801258 A1	14-04-2021
		JP 2021525862 A	27-09-2021
		US 2019365303 A1	05-12-2019
		US 2022151526 A1	19-05-2022
		US 2022151527 A1	19-05-2022
		US 2022304601 A1	29-09-2022
		WO 2019232196 A1	05-12-2019
WO 2019055487 A1	21-03-2019	AU 2018334138 A1	12-03-2020
		CA 3074105 A1	21-03-2019
		CN 111212597 A	29-05-2020
		EP 3681384 A1	22-07-2020
		IL 273025 A	30-04-2020
		JP 2020533045 A	19-11-2020
		US 2019076074 A1	14-03-2019
		US 2022175284 A1	09-06-2022
		WO 2019055487 A1	21-03-2019

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

Europäisches Patentamt
European Patent Office
Office européen des brevets

Application No.: 20781928.5

The search has started on 19.10.22 (see Notice from the European Patent Office dated 03/2013, OJ EPO 2013, 153).

Receiving Section

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US21/35294

A. CLASSIFICATION OF SUBJECT MATTER

IPC - G01N 1/10; G01N 1/02; A61B 5/15; A61B 5/00; A61M 39/00; A61M 39/06; B01L 3/00; G01N 1/18 (2021.01)

CPC - G01N 1/10; B01L 3/0203; A61B 5/15; G01N 1/02; A61B 5/15; A61B 5/150992; A61M 39/06; B01L 3/02; B01L 3/0289; B01L 3/0296; G01N 1/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGY INC) 05 December 2019; paragraphs [0021], [0036], [0148]-[0160]; figures 11-14	1-10, 14, 16-18 --- 11-13, 15, 19-20
Y	WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGY INC) 21 March 2019; paragraphs [1146], [1149]-[1150]; figures 23-24	11-13, 15, 19-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 August 2021 (04.08.2021)	SEP 28 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: James Scott Nolan
P.O. Box 371710
San Diego, CA 92110
United States Of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* SEP 28 2021

Applicant's or agent's file reference	FOR FURTHER ACTION
KURIN8PCT	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US21/35294	01 June 2021 (01.06.2021)	01 June 2020 (01.06.2020)

International Patent Classification (IPC) or both national classification and IPC

IPC - G01N 1/10; G01N 1/02; A61B 5/15; A61B 5/00; A61M 39/00; A61M 39/06; B01L 3/00; G01N 1/18 (2021.01)

CPC - G01N 1/10; B01L 3/0203; A61B 5/15; G01N 1/02; A61B 5/15; A61B 5/150992; A61M 39/06; B01L 3/02; B01L 3/0289; B01L 3/0296; G01N 1/18

Applicant Kurin, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	04 August 2021 (04.08.2021)	Shane Thomas PCT Help Desk Telephone No. 571-272-4300

Form PCT/ISA/237 (cover sheet) (revised January 2019)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US21/35294

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Form PCT/ISA/237 (Box No. I) (revised January 2019)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US21/35294

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	11-13, 15, 19-20	YES
	Claims	1-10, 14, 16-18	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-10, 14, 16-18 lack novelty under PCT Article 33(2) as being anticipated by (NAME). WO 2019/232196 A1 to Magnolia Medical Technologies, INC. (herein "Magnolia'196").

As to claim 1, Magnolia'196 discloses a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source (devices and methods for procuring bodily fluid samples with reduced contaminants; paragraphs [0007], [0021]), a first portion of the fluid sample potentially having contaminants (fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source; paragraphs [0007], [0021]), the fluid sample optimization device (similar devices 600 and 700; paragraphs [0149], [0158]; figures 11-14) comprising: an inlet configured to connect with the fluid source (device 600 includes an inlet 612 and comparable IN for device 700; paragraph [0148]; figures 11-14); an outlet configured to connect with the fluid collection device (an outlet 616 and comparable OUT for device 700; paragraph [0148]; figures 11-14); a sample path connected between the inlet and the outlet (fluid flow path 654 and 754 (sample path); paragraphs [0148], [0158]; figures 11-14); a contaminant containment reservoir connected between the inlet and the outlet (a sequestration chamber 614 with a comparable section shown in device 700, shown between inlet and the outlet; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir having an air permeable fluid resistor proximate the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet (negative pressure within the fluid flow path 654 is transferred and/or exerted through the flow restrictor 631 and is operable in drawing an initial flow of bodily fluid from the inlet 612, through at least a portion of the fluid flow path 613, and into the sequestration chamber 614; paragraph [0154], [0158]; figures 11-14), the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir (volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 615 and the flow controller 615 in its second or sealed state, the flow controller 615 substantially sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents a flow of fluid (e.g., gas and liquid) through the flow controller 615, thereby sequestering and/or fluidically isolating the sequestration chamber 614 from the fluid flow path 654, and comparable structures for device 700; paragraphs [0155], [0158]; figures 11-14), subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (when the flow controller 615 is placed in its second or sealed state, at least a portion of the negative pressure otherwise being exerted through the flow controller 615 is instead exerted on a concave side or surface of the diaphragm 676 or 776 and opens barriers 675 or 775 to define an opening which fluid can flow from inlet to outlet; paragraphs [0157]-[0158]; figures 11-14); and a displaceable plug between the inlet and the sample path that is displaced by the subsequent pressure differentials to allow the subsequent portions of the fluid to be conveyed through the sample path (barriers 675 and 775 are forced open when a negative pressure is generated within a portion of the device 700; paragraphs [0157]-[0158], [0160]; figures 11-14).

As to claim 2, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 1, and Magnolia'196 further discloses further comprising a housing that houses and defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (a fluid control device includes a housing, specifically first portion 624 and the second portion 625 can be collectively disposed in a housing; paragraphs [0021], [0149]).

As to claim 3, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 1, and Magnolia'196 further discloses wherein the air permeable fluid resistor includes a material that seals upon contact with the first portion of the fluid sample (flow controller 615 can be a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, or its first state is at a permeable state and is saturated to a sealed state; paragraphs [0148], [0155]).

As to claim 4, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 1, and Magnolia'196 further discloses wherein the contaminant containment reservoir includes a main basin and a channel connecting the main basin and the inlet (the inlet 612 via the fluid flow path 613 feeds into sequestration chamber 614, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14).

-***-Continued in Supplemental Box-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US21/35294

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
-***-Continued From Box V. 2: Citations and Explanations-***-

As to claim 5, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 1, and Magnolia'196 further discloses wherein each pressure differential is provided by a vacuum pressure from the fluid collection device (a fluid collection device configured to define or produce a vacuum, to produce negative pressures in device 600; paragraphs [0036], [0152]).

As to claim 6, Magnolia'196 discloses a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source (devices and methods for procuring bodily fluid samples with reduced contaminants; paragraphs [0007], [0021]), a first portion of the fluid sample potentially having contaminants (fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source; paragraphs [0007], [0021]), the fluid sample optimization device (similar devices 600 and 700; paragraphs [0149], [0158]; figures 11-14) comprising: an inlet configured to connect with the fluid source (device 600 includes an inlet 612 and comparable IN for device 700; paragraph [0148]; figures 11-14); an outlet configured to connect with the fluid collection device (an outlet 616 and comparable OUT for device 700; paragraph [0148]; figures 11-14); a sample path connected between the inlet and the outlet (fluid flow path 654 and 754 (sample path); paragraphs [0148], [0158]; figures 11-14), the sample path further having a displaceable plug that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path (barriers 675 or 775, in a first state, fluidically isolates at least a portion of the fluid flow path 654 from other portions of the device 600 or 700, causing contaminants to be sequestered; paragraphs [0153], [0157]-[0158], [0160]; figures 11-14); and a contaminant containment reservoir connected between the inlet and the outlet (a sequestration chamber 614 with a comparable section shown in device 700, shown between inlet and the outlet; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir further having an air permeable fluid resistor proximate the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet (negative pressure within the fluid flow path 654 is transferred and/or exerted through the flow restrictor 631 and is operable in drawing an initial flow of bodily fluid from the inlet 612, through at least a portion of the fluid flow path 613, and into the sequestration chamber 614; paragraph [0154], [0158]; figures 11-14), the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir (volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 615 and the flow controller 615 in its second or sealed state, the flow controller 615 substantially sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents a flow of fluid (e.g., gas and liquid) through the flow controller 615, thereby sequestering and/or fluidically isolating the sequestration chamber 614 from the fluid flow path 654, and comparable structures for device 700; paragraphs [0155], [0158]; figures 11-14), subsequent portions of the fluid sample displace the displaceable plug and are conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (when the flow controller 615 is placed in its second or sealed state, at least a portion of the negative pressure otherwise being exerted through the flow controller 615 is instead exerted on a concave side or surface of the diaphragm 676 or 776 and opens barriers 675 or 775 to define an opening which fluid can flow from inlet to outlet; paragraphs [0157]-[0158]; figures 11-14).

As to claim 7, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 6, and Magnolia'196 further discloses further comprising a housing that houses and defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (a fluid control device includes a housing, specifically first portion 624 and the second portion 625 can be collectively disposed in a housing; paragraphs [0021], [0149]).

As to claim 8, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 6, and Magnolia'196 further discloses wherein the air permeable fluid resistor includes a material that seals upon contact with the first portion of the fluid sample (flow controller 615 can be a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, or its first state is at a permeable state and is saturated to a sealed state; paragraphs [0148], [0155]).

As to claim 9 The fluid sample optimization device in accordance with claim 6, wherein the contaminant containment reservoir includes a tortuous path (the inlet 612 via the fluid flow path 613 (tortuous path) feeds into sequestration chamber 614, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14).

As to claim 10, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 6, and Magnolia'196 further discloses wherein each pressure differential is provided by a vacuum pressure provided by the fluid collection device (a fluid collection device configured to define or produce a vacuum, to produce negative pressures in device 600; paragraphs [0036], [0152]).

As to claim 14, Magnolia'196 discloses a fluid sample optimization device for optimizing a fluid sample (devices and methods for procuring bodily fluid samples with reduced contaminants; paragraphs [0007], [0021]), a first portion of the fluid sample potentially having contaminants (fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source; paragraphs [0007], [0021]), the fluid sample optimization device (similar devices 600 and 700; paragraphs [0149], [0158]; figures 11-14) comprising: an inlet (device 600 includes an inlet 612 and comparable IN for device 700; paragraph [0148]; figures 11-14); an outlet (an outlet 616 and comparable OUT for device 700; paragraph [0148]; figures 11-14); a contaminant containment reservoir connected between the inlet and the outlet (a sequestration chamber 614 with a comparable section shown in device 700, shown between inlet and the outlet; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir having an air permeable fluid resistor proximate the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), the contaminant containment reservoir being arranged to receive, when a pressure

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International application No.
PCT/US21/35294

Supplemental Box

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differential is applied between the inlet and the outlet (negative pressure within the fluid flow path 654 is transferred and/or exerted through the flow restrictor 631 and is operable in drawing an initial flow of bodily fluid from the inlet 612, through at least a portion of the fluid flow path 613, and into the sequestration chamber 614; paragraph [0154], [0158]; figures 11-14), a first portion of the fluid sample to displace air therein through the air permeable fluid resistor and the outlet (sequestration chamber 614 in fluid communication with flow controller 615, a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir (volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 615 and the flow controller 615 in its second or sealed state, the flow controller 615 substantially sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents a flow of fluid (e.g., gas and liquid) through the flow controller 615, thereby sequestering and/or fluidically isolating the sequestration chamber 614 from the fluid flow path 654, and comparable structures for device 700; paragraphs [0155], [0158]; figures 11-14); and a sample path connected between the inlet and the outlet (fluid flow path 654 and 754 (sample path); paragraphs [0148], [0158]; figures 11-14), the sample path further including a displaceable plug that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path during receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir (barriers 675 or 775, in a first state, fluidically isolates at least a portion of the fluid flow path 654 from other portions of the device 600 or 700, causing contaminants to be sequestered; paragraphs [0153], [0157]-[0158], [0160]; figures 11-14), wherein subsequent portions of the fluid sample are conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (when the flow controller 615 is placed in its second or sealed state, at least a portion of the negative pressure otherwise being exerted through the flow controller 615 is instead exerted on a concave side or surface of the diaphragm 676 or 776 and opens barriers 675 or 775 to define an opening which fluid can flow from inlet to outlet; paragraphs [0157]-[0158]; figures 11-14).

As to claim 16, Magnolia'196 discloses, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 14, and Magnolia'196 further discloses comprising a housing that houses and defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (a fluid control device includes a housing, specifically first portion 624 and the second portion 625 can be collectively disposed in a housing; paragraphs [0021], [0149]).

As to claim 17, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 14, and Magnolia'196 further discloses wherein the air permeable fluid resistor includes a material that seals upon contact with the first portion of the fluid sample (flow controller 615 can be a selectively permeable member configured to be selectively permeable to a gas (e.g., air) and substantially impermeable to a liquid, or its first state is at a permeable state and is saturated to a sealed state; paragraphs [0148], [0155]).

As to claim 18, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 14, and Magnolia'196 further discloses wherein the contaminant containment reservoir includes a main basin fluidically connected with the inlet by a conduit (the inlet 612 via the fluid flow path 613 feeds into sequestration chamber 614, with comparable structures shown in device 700; paragraphs [0148], [0158]; figures 11-14).

Claims 11-13, 15, and 19-20 lack an inventive step under PCT Article 33(3) as being obvious over Magnolia'196 in view of WO 2019/055487 A1 to Magnolia Medical Technologies, INC. (herein "Magnolia'487").

As to claim 11, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 6, and Magnolia'196 further discloses wherein the displaceable plug is fit into a portion of the sample path (barrier 775 provides a seal to the outlet flow path 754 and is moved linearly to provide flow, barrier is shown fit into a cavity of the device; paragraph [0159]-[0160]; figures 13-14). Magnolia'196 does not disclose a friction-fit. Magnolia'487 discloses a friction-fit (actuator rod 862, with ends 863 and 864 set into recesses in body 851 where the travel of the actuator is stopped by the recess (friction fit); paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide a friction-fit, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

As to claim 12, Magnolia'196 and Magnolia'487, in combination, disclose the fluid sample optimization device in accordance with claim 11, but Magnolia'196 does not disclose wherein the portion of the sample path in which the displaceable plug is friction-fit includes a seat. Magnolia'487 discloses a portion of the sample path in which the displaceable plug is friction-fit includes a seat (actuator rod 862, includes seals 865 that are shown as o-rings seated into the actuator; paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide wherein the portion of the sample path in which the displaceable plug is friction-fit includes a seat, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

As to claim 13, Magnolia'196 and Magnolia'487, in combination, disclose the fluid sample optimization device in accordance with claim 12, but Magnolia'196 does not disclose wherein the seat comprises an elastomeric O-ring. Magnolia'487 discloses the seat comprises an elastomeric O-ring (actuator rod 862, includes seals 865 that are shown as (elastomeric) o-rings seated into the actuator; paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide wherein the portion of the sample path in which the displaceable plug is friction-fit includes a seat, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

As to claim 15, Magnolia'196 discloses, Magnolia'196 discloses the fluid sample optimization device in accordance with claim 14, and Magnolia'196 further discloses wherein the displaceable plug is initially secured in the sample path proximate the inlet (barrier 775 provides a seal to the outlet flow path 754 and is moved linearly to provide flow, barrier is shown fit into a cavity of the device; paragraph

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International application No.
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Supplemental Box

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[0159]-[0160]; figures 13-14). Magnolia'196 does not disclose by an elastomeric seat. Magnolia'487 discloses an elastomeric seat (actuator rod 862, includes seals 865 that are shown as (elastomeric) o-rings seated into the actuator; paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide an elastomeric seat, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

As to claim 19, Magnolia'196 and Magnolia'487, in combination, disclose the fluid sample optimization device in accordance with claim 15, and Magnolia'196 discloses wherein the displaceable plug is fit into a portion of the sample path (barrier 775 provides a seal to the outlet flow path 754 and is moved linearly to provide flow, barrier is shown fit into a cavity of the device; paragraph [0159]-[0160]; figures 13-14). Magnolia'196 does not disclose a friction-fit. Magnolia'487 discloses a friction-fit (actuator rod 862, with ends 863 and 864 set into recesses in body 851 where the travel of the actuator is stopped by the recess (friction fit); paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide a friction-fit, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

As to claim 20, Magnolia'196 and Magnolia'487, in combination, disclose the fluid sample optimization device in accordance with claim 19, but Magnolia'196 does not disclose wherein the displaceable plug is formed of an elostomeric material. Magnolia'487 discloses a displaceable plug is formed of an elostomeric material (actuator rod 862, includes seals 865 that are shown as (elastomeric) o-rings seated into the actuator; paragraphs [1146], [1149]-[1150]; figures 23-24). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Magnolia'196 invention to provide wherein the displaceable plug is formed of an elostomeric material, as taught by Magnolia'487, in order to provide a path for the flow diverter (Magnolia'487: paragraph [1149]).

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Japanese Patent Application No. 2020-118498
Your Ref: KURIN2JP-DIV2
Our Ref: TS/KRN-C0137JP03
March 28, 2022

Translation of "Notice of Reasons for Rejection"

Patent Application Number: JP 2020-118498
Date of Delivery: February 15, 2022
Applied Provision: Patent Law Article 29(2)

The present application should be rejected for the following reasons. The applicant may present an argument against the reasons within three months from the date of delivery of this notice.

Reasons

1. The inventions of the following claims should not be granted a patent under Patent Law Article 29(2) as lacking inventive step over the documents listed below.

Remarks (See the Document List below)

- Reason 1 (Inventive step)
- Claims 1 to 10
- Documents D1 to D4

[Claim 1]

D1 ([0019]-[0055], Figs. 5-8) discloses

a blood sample optimization system (sample-procurement system; [0038], etc.) for optimizing a blood sample ([0020], etc.) collected by a blood collector (sample vessels 506; [0038], etc.), the system comprising:

a patient needle (first needle 508; [0038], etc.) configured for a venipuncture of a patient to access a sample of blood of a patient, the sample of blood including a first portion containing contaminants ([0021], etc.) and a second portion following the first portion;

a blood sampling pathway connected with the patient needle configured for conveying the sample of blood (see Fig. 5, etc.); and

a sample needle configured for receiving the blood collector to collect a second portion of the sample of blood(see suggestions in Fig. 5, etc.); and

a blood sequestration device connected on the blood sampling pathway between the patient needle and the sample needle, the blood sequestration device comprising;

an inlet port (sterile input tubing 514; [0039], etc.) configured for receiving the sample of blood;

a sequestration chamber (pre-sample reservoirs 504; [0038], etc.) connected with the inlet port, the sequestration chamber configured for receiving the first portion of the sample of blood to contain the contaminants in the first portion of the blood sample; and

a sampling channel (second sterile output tubing 518; [0038], Fig. 5, etc.) having a proximal end connected with the inlet port, configured for receiving the second portion of the

sample of blood,

the sequestration chamber, the sampling channel and the inlet port being configured to allow the second portion of the sample of blood to bypass the sequestration chamber and direct the second portion of the sample of blood toward an outlet port that is configured to output the second portion of the sample of blood to the blood collector ([0038], etc.).

As explained in the previous Notice of Reasons for Rejection, D2 ([0012]-[0013] etc.) discloses arts in a blood sample optimization system (blood sampling needle) of configuring a sequestration chamber having a vent comprising an air permeable blood barrier (air permeable blood impermeable member 23) to displace air in the sequestration chamber through the vent, and of configuring a housing (needle tube support 2) that houses and defines ports, the sequestration chamber and a channel.

In addition, newly cited D3 (see pages 5-6, FIG. 1, etc.) discloses arts in a blood sample optimization system (closed system blood sampling device) of configuring a sequestration chamber (blood disposal chamber 22) having a vent comprising an air permeable blood barrier (air permeable hydrophobic membrane 30) to displace air in the sequestration chamber through the vent, and of configuring a housing that houses and defines ports, the sequestration chamber and a channel (see FIG. 1, etc.).

Further, D4 ([0042], etc.) also discloses art of configuring a sequestration chamber having a vent comprising an air permeable blood barrier to displace air in the sequestration chamber through the vent.

And, as supported by the disclosure of D2 to D4 described above, in a blood sample optimization system, configuring a sequestration chamber having a vent comprising an air permeable blood barrier to displace air in the sequestration chamber through the vent, and configuring a housing that houses and defines ports, the sequestration chamber and a channel are both well-known arts.

The system disclosed in D1 and the well-known arts disclosed in D2 to D4 belong to the same technical field called the blood collection field.

Configuring the system disclosed in D1 to have an air permeable blood barrier and a housing similar to the invention of claim 1 of the present application with reference to the well-known arts disclosed in D2 to D4 is easy for those skilled in the art, or a matter that those skill in the art could have made as appropriate.

[Claims 2 and 4]

See [0012]-[0013] of D2.

[Claim 3]

Placing a seal on the sample needle can be said to be a design matter.

[Claim 5]

See [0011] of D2.

[Claim 6]

See Fig. 5 of D1.

[Claims 7-10]

See the above explanations including the descriptions of D1 to D4.

Document List

D1: US 2008/0145933A

D2: JP 2001-000424A

D3: JP H09-504726A (newly cited; document disclosing well-known art)

D4: US 2006/0009713A (newly cited; document disclosing well-known art)

Record of the Result of Prior Art Search

Technical field(s) searched	IPC A61B 5/00-5/398
Prior art document(s)	JP S58-025146A
	JP H02-224742A
	US 2011/0306899A

This record is not a component of the reasons for rejection.

Bibliographic data: WO2015150742 (A1) — 2015-10-08

FLUID DELIVERY

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Classification: **- international:** ***B01L3/00***
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Application number: WO2015GB50905 20150326 Global Dossier

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Abstract of WO2015150742 (A1)

Certain embodiments of the present invention relate to apparatus and methods for providing a target liquid at a desired location. In certain embodiments, the apparatus includes a piercing member locatable with respect to a sealing membrane of a respective blister pouch that has a tip region which is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing member in a further mode of operation for providing liquid from the blister pouch at a desired location. Also included in the present invention, inter alia, is a piercing plate comprising a piercing member, together with devices, for example, bio chips and microfluidic devices, which are for use in combination with the apparatus.

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(54) **Title**: FLUID DELIVERY

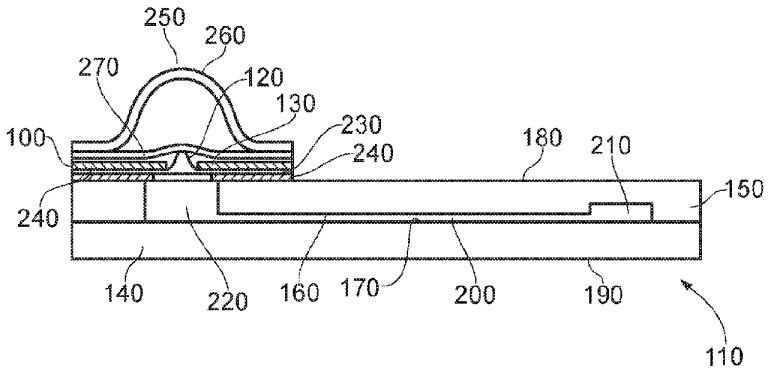


FIG. 1

(57) **Abstract**: Certain embodiments of the present invention relate to apparatus and methods for providing a target liquid at a desired location. In certain embodiments, the apparatus includes a piercing member locatable with respect to a sealing membrane of a respective blister pouch that has a tip region which is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing member in a further mode of operation for providing liquid from the blister pouch at a desired location. Also included in the present invention, *inter alia*, is a piercing plate comprising a piercing member, together with devices, for example, bio chips and microfluidic devices, which are for use in combination with the apparatus.

WO 2015/150742 A1

FLUID DELIVERY

Field of the Invention

Certain embodiments of the present invention relate to apparatus and methods for providing a target liquid at a desired location. In certain embodiments, the apparatus includes a piercing member locatable with respect to a sealing membrane of a respective blister pouch that has a tip region which is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing member in a further mode of operation for providing liquid from the blister pouch at a desired location. Also included in the present invention, *inter alia,* is a piercing plate comprising a piercing member, together with devices, for example, bio chips and microfluidic devices, which are for use in combination with the apparatus.

Background to the Invention

Microfluidic systems have recently emerged as powerful tools for bio-sensing, particularly in enriching and purifying molecules and cells in biological samples. Microfluidic technology has enabled the miniaturisation of normal sized equipment and has resulted in more readily portable devices and the sensing of increasingly small sample volumes and target analyte concentrations which have not been possible with previous technologies.

Microfluidic devices can be laboratory-based devices for use in genomics, sequencing, high-throughput screening and separations. Additionally, microfluidic devices provide the opportunity to integrate processes and measurement systems on a single technology platform leading to the concept of the “lab on a chip”. Thus, microfluidic devices are also sometimes known as "bio-chips" or lab-on-chip" systems. Microfluidic technology has found applications in chemical and system biology, point-of-care analysis, high-throughput biological screening. Advantages associated with lab-on-chip include consumption of small volumes of reagents and sample, and delivery of results in a short timescale.

Microfluidic devices often comprise a substrate together with microstructures such as micropumps, micromixers, ports, microchannels and the like.

The delivery of fluids plays an important role in fields such as chemistry, microbiology and biochemistry. These fluids may include liquids or gases and may provide reagents, buffers, solvents or reactants, to chemical and/or biological processes, including processes involving

microfluidic technology. A problem often associated with fluid delivery to microfluidic devices is the difficulty of delivering known volumes of reagents into the microfluidic flow system in a controlled manner at a steady rate.

Existing technology often relies upon pipetting of reagents and/or samples into wells or chambers of the device. As a result, whilst microfluidic technology may have resulted in portable devices being developed, there still remains the problem of how to easily transport and deliver reagents and/or samples outside a laboratory environment.

One way of storing and delivering fluids such as reagents and/or samples that has been developed is by way of a "blister pouch". Blister pouches include individually sealed units which store fluids or solids prior to delivery and have been used to store and subsequently deliver fluids to microfluidic devices. In order to deliver the fluid or solid to a target location, a user breaks the seal of the unit. The seal may be broken by a user manually applying a force to the seal or by way of an actuator applying pressure. Often, when the seal is broken, the release of the stored fluid is not always controlled and thus at least some of the stored fluid is not directed to the target location. Also there is a risk of fluid "surging" from the blister.

One way of automatically providing the right reagents in the correct volume is to package the reagents into blister packages and allow the blister to release the reagents once the sample is on the chip. However, most conventional blister popper constructs lead to the blisters rupturing in the wrong place and the reagent splashing outside of the chip. This results in a waste of reagent and can lead to a reduction in accuracy if a precise amount of the fluid is required. In addition, on occasion there is a failure of the sealed unit to burst.

Certain embodiments of the present invention aim to at least partially mitigate the problems associated with the prior art.

Summary of Certain Embodiments of the Invention

Certain embodiments of the present invention aim to provide a device and/or method which delivers a fluid, e.g. a liquid, in a controlled manner to a target location.

It is an aim of certain embodiments of the present invention to provide a mechanism that can selectively burst a blister pouch when desired and in a controlled way but which doesn't pose a risk (in terms of causing an undesired breach) at other times.

In a first aspect of the present invention, there is provided apparatus for providing a target liquid at a desired location, comprising at least one piercing member upstanding from a support surface at a height of about around 300 to 1200 microns and locatable with respect to a sealing membrane of a respective blister pouch; wherein a tip region of the piercing member is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing membrane in a further mode of operation for providing liquid from the blister pouch at a desired location.

In one embodiment, the piercing member is upstanding from a support surface at a height of about around 300 to 1200 microns e.g. 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150 or 1200 microns.

In one embodiment, the piercing member has a height of from about 300 to 1200 microns.

Aptly, in the first mode of operation the piercing member is locatable to deform but not pierce the sealing membrane. In one embodiment, in the first mode of operation, the piercing member does not pierce the sealing membrane when an abutment force of up to about around 1N is applied by the piercing member to the sealing membrane. In one embodiment, in the first mode of operation, the piercing member does not pierce the sealing membrane when an abutment force of up to about around 1N, e.g. 0.80, 0.85, 0.9, 0.95 or 1.0N, is applied by the piercing member to the sealing membrane.

In one embodiment, the tip region comprises a rounded nose region having a generally arcuate shape with a radius of curvature of about around 50 to 1000 microns. Aptly, the radius of curvature is about around 100 to 500 microns. In one embodiment, the radius of curvature of the rounded nose region of the piercing member is approximately 100, 150, 200, 250, 300, 350, 400, 450 or 500 microns.

Thus, in certain embodiments of the present invention the piercing member has a comparatively blunt nose region, which is used to pierce the sealing membrane of the blister pouch when desired. As a result of the "blunt" nose region, when the sealing membrane is

pierced, substantially all of the fluid held in the blister pouch flows over and through the piercing member, rather than, as is the case with many prior art fluid delivery systems, the fluid is released in an uncontrolled manner leading to a portion of the liquid not being directed into the chamber.

In one embodiment, the piercing member further comprises a plurality of abutment wall regions extending from the support surface to the tip region at a predetermined angle so that each wall region forms a tangent with an arc of a rounded nose region at an end of the tip region. Aptly, each abutment wall region meets the nose region at an angle of about around 45 degrees. In one embodiment, each abutment wall region meets the nose region at an angle of approximately 45 degrees e.g. 40, 41, 42, 43, 44, 45, 46 or 47 degrees. Aptly, each abutment wall region meets the nose region at substantially the same angle. Alternatively, each abutment wall region meets the nose region at a different angle to each other abutment wall region.

In one embodiment, the piercing member provides a plurality of fluid communication passageways proximate to the tip region that each communicate liquid urged from a pierced blister pouch to at least one collection chamber under the support surface. In one embodiment, the piercing member comprises two or more fluid communication passageways proximate to the tip region, e.g. 2, 3, 4 or more. In one embodiment, the piercing member comprises four fluid communication passageways.

In an embodiment, the piercing member comprises a plurality of arms extending upwards and in an inclined manner from the support surface. Aptly, the fluid communication passageways are provided by openings in the support surface in notched regions between adjacent arms. In one embodiment, the piercing member comprises two or more upwardly extending arms e.g. 2, 3, 4, or more. In one embodiment, the piercing member comprises four upwardly extending arms.

Certain embodiments of the present invention provide the advantage of a piercing member which provides openings through which the fluid, e.g. a liquid, released from the blister pouch may flow. The liquid may subsequently flow into a chamber e.g. a collection chamber as described herein below. As a result, the likelihood of the reagent being spilt and not collected in the chamber is reduced. Blister pouches are often pre-filled with a required volume of liquid and thus it follows that certain embodiments of the present invention may

provide a more accurate result in a method which is based on calculations involving the known volume of the liquid in the blister pouch.

Certain embodiments of the present invention provide a piercing member which comprises a plurality of openings which allow fluid released from the blister pouch to flow into a chamber situated beneath the piercing member. The plurality of openings results in the fluid flowing downwardly in a plurality of flow streams which should enable the flow of fluid to be controlled more effectively.

Aptly, the first mode of operation comprises a transportation mode during which a blister pouch is transportable in an abutting relationship with the piercing member without risk of puncture.

Certain embodiments of the present invention provide the advantage that the piercing member is capable of piercing a sealing membrane of a blister pouch when a predetermined level of force is applied to either the piercing member or the blister pouch but does not pierce the sealing member when simply in an abutting relationship with the sealing membrane. Thus, certain embodiments of the present invention provide an apparatus which is capable of being transported in an abutting relationship with a sealed blister pouch pre-filled with a reagent for example without the blister pouch being pierced and its contents released.

In one embodiment, in the further mode of operation in which the blister pouch is urged against the piercing member, the piercing member is disposed to rupture the sealing membrane at a rupture force of about around 3 to 12N. Aptly, the piercing member is disposed to rupture the sealing membrane at a force of about 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 N.

In one embodiment, each piercing member is manufactured from a material selected from a group comprising glass, polycarbonate or polymethyl methacrylate (PMMA), cyclic olefin copolymer (COC), polystyrene (PS), polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE) and polypropylene (PP).

In a further aspect of the present invention, there is provided a piercing plate, securable to at least one blister pouch, comprising an apparatus for providing a target liquid at a desired location comprising at least one piercing member upstanding from a support surface at a

height of about around 300 to 1200 microns and locatable with respect to a sealing membrane of a respective blister pouch; wherein a tip region of the piercing member is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing member in a further mode of operation for providing liquid from the blister pouch at a desired location. Aptly, the apparatus is as further described herein.

In one embodiment, the piercing plate further comprises a planar upper surface, comprising the support surface, and a planar lower surface that is securable to an upper surface of a bio chip. Aptly the piercing plate further comprises an adhesive layer on the lower surface.

In one embodiment, the piercing plate further comprises at least one alignment element that locates the piercing plate at a desired position with respect to each blister pouch. Aptly, the alignment element comprises at least one edge of the piercing plate. In one embodiment, the alignment element comprises at least one locating lug or recess that mates with a complimentary alignment element of the blister pouch.

Aptly, the piercing plate further comprises one further alignment element that locates the piercing plate at a desired position with respect to a bio chip. In one embodiment, each further alignment element comprises at least one edge of the piercing plate.

Aptly, each further alignment element comprises at least one locating lug or recess that mates with a complimentary alignment element of the bio chip. In one embodiment, the piercing plate further comprises a cavity under each piercing member that is locatable in fluid communication with a collection chamber of a bio chip.

Aptly, the piercing plate has a thickness of about around 200 to 1000 microns.

In one embodiment, the piercing plate is manufactured from a material selected from glass, polycarbonate and PMMA.

In one embodiment, the plate and each piercing member are integrally formed. In one embodiment, the plate and the apparatus are integrally formed.

In one embodiment, the plate is retrofittable to an underside of a blister package comprising one or more blister pouches sealed with a sealing membrane.

In a further aspect of the present invention, there is provided a blister pack, comprising a plurality of blister pouches secured together via a web and a common sealing membrane; and at least one piercing plate as described herein secured to a lower surface of the sealing membrane. In one embodiment, the blister pack may be fabricated using vacuum thermoforming of polymer films, for example.

In one embodiment, the blister pack comprises a plurality of frangible lines or perforation lines in the web. In one embodiment, the frangible lines or perforation lines are provided between each blister pouch so as to enable a single blister pouch to be removed from the blister pack.

In a further aspect of the present invention, there is provided a bio chip comprising an apparatus according to the first aspect of the invention as described herein.

As used herein, the term "bio chip" refers to a device which can be used to analyse samples having a volume of from about 10nl and 10ml. The terms "microfluidic device", "microfluidic assembly", "microfluidic systems" and the like may also be used herein to indicate devices, assembly and systems wherein samples for the processing and/or analysis of samples having a volume of from about 10 nl to about 10 ml. In one embodiment, the bio chip is used to analyse samples having a volume of between about 100µl and 2000µl. In one embodiment, the bio-chip is a microfluidic device.

In one embodiment, the bio chip comprises an upper chip layer comprising one or more piercing member as an integral unit. In one embodiment, the bio chip comprises an upper chip layer comprising each piercing member as an integral unit.

In an embodiment, the bio chip further comprises an upper chip layer having an upper surface on which at least one piercing plate comprising said at least one piercing member is secured.

In one embodiment, the bio chip comprises a lower surface of the upper chip layer and wherein the lower surface of the upper chip layer comprises a collection chamber located

beneath each piercing member and at least one channel connecting a collection chamber to a respective sample chamber. Aptly, the channel comprises a channel region that provides a serpentine pathway. Aptly, the channel comprises an inlet end and an outlet end.

In one embodiment, the bio chip comprises a plurality of channels.

In one embodiment, the bio chip comprises a plurality of piercing members and a corresponding plurality of collection chambers. Aptly, a collection chamber is located beneath the piercing element. Aptly, the bio chip comprises a first collection chamber and at least one further collection chamber. In one embodiment, the first collection chamber and the further collection chamber are in fluid communication via a channel region. Aptly, the channel region comprises a T-junction region and/or a Y-junction region.

Certain embodiments of the present invention provide a bio-chip which incorporates at least one blister pouch which is integrally formed with the bio-chip. Certain embodiments of the present invention provide an advantage that fluids may be stored on the bio-chip and delivered using the piercing member when required. Thus, certain embodiments of the present invention may result in a reduction of gas exchange with stored solutions and reagent waste, as well as cost reduction. Certain embodiments of the present invention provide a portable bio-chip device, e.g. a microfluidic device, which incorporates a blister pouch pre-filled with one or more reagents.

Certain embodiments of the present invention provide the advantage that precise location of the piercing member relative to the sealed unit of the blister pouch is not required providing that the piercing member contacts at least a portion of the blister pouch.

In one embodiment, the bio chip is formed from a material selected from glass, polycarbonate, polymethyl methacrylate (PMMA), cyclic olefin copolymer (COC), polystyrene (PS), polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE) and polypropylene (PP).

In one embodiment, the bio chip may be fabricated from a metal. Aptly, the chip may be formed from a metal which could be readily formed into the required shapes using a range of fabrication techniques. Aptly, the chip may be formed a technique selected from die casting, injection moulding and subtractive milling.

In one embodiment, the bio chip is fabricated from a ceramic material. Aptly, the bio chip is produced using an injection moulding technique. In one embodiment, the bio chip is formed from a polymer. Aptly, the polymer is an injection moulded polymer.

Aptly, the bio chip further comprises one or more further elements. In one embodiment, the bio chip comprises one or more of the following elements: one or more micropumps, one or more microvalves, a power source e.g. a battery, and/or a sensor.

In a further aspect of the present invention, there is provided a method of delivering a target fluid to a desired location, comprising locating an apparatus as described herein such that the piercing member of the apparatus abuts a sealing membrane of a respective blister pouch; wherein the fluid is located in the blister pouch; and applying a predetermined force to the sealing membrane such that the sealing membrane is pierced by the piercing member. Aptly, the method comprises applying a force of between about 3N and about 12N to the sealing membrane.

In one embodiment, the method comprises: locating a biochip comprising a collection chamber as described herein underneath the piercing member prior to the piercing of the sealing membrane; and collecting the fluid from the blister pouch in the collection chamber.

Aptly, the method further comprises locating the apparatus in an abutting relationship with the sealing membrane prior to application of a predetermined force.

Further details of certain embodiments are provided below.

Detailed Description of Embodiments of the Invention

Certain embodiments of the present invention will now be described hereinafter, by way of example only, with reference to the accompanying drawings in which:

Figure 1 illustrates a bio chip and blister pouch according to certain embodiments of the present invention;

Figure 2 illustrates a bio chip according to certain embodiments of the present invention;

Figure 3A illustrates an apparatus according to certain embodiments of the present invention which comprises a piercing member;

Figure 3B illustrates an apparatus according to certain embodiments of the present invention which comprises a piercing member;

Figure 3C illustrates an apparatus according to certain embodiments of the present invention which comprises two piercing members;

Figure 4 illustrates a cross-sectional view of a blister pouch located above a piercing member according to certain embodiments of the present invention;

Figure 5 illustrates a cross-sectional view of a blister pouch located above a piercing member according to certain embodiments of the present invention;

Figure 6 illustrates a side view of an apparatus comprising a piercing member according to certain embodiments of the present invention;

Figure 7 illustrates a cross sectional view of section A-A as shown in Figure 6 of an apparatus comprising a piercing member according to certain embodiments of the present invention;

Figure 8 illustrates a top view of an apparatus comprising a piercing member according to certain embodiments of the present invention;

Figure 9 illustrates a bottom view of an apparatus comprising a piercing member according to certain embodiments of the present invention;

Figure 10 illustrates an exploded view of a blister pack and a piercing plate comprising a piercing member according to certain embodiments of the present invention;

Figure 11 illustrates a blister pouch located above a piercing member according to certain embodiments of the present invention; and

Figure 12 illustrates a cross-sectional side view of a blister pouch located above a piercing member according to certain embodiments of the present invention;

Figure 1 illustrates an apparatus 100 for providing a target liquid at a desired location according to certain embodiments of the present invention. In certain embodiments, the desired location is situated on a device e.g. a bio-chip 110. The apparatus may be a distinct element from the bio-chip 110 or may be an integrally formed portion of the bio-chip. Further details of the bio chip which are not shown in the Figures are provided below.

The bio-chip may comprise a number of other elements e.g. one or more of sensing regions, micropumps, valves, heaters, microchannels and other elements known in the art (not shown).

In one embodiment, the bio chip comprises one or more elements for controlling fluid flow thereon e.g. electroosmotic flow, vacuum pumps, electrokinetic pumps, membrane actuated pumps, centrifugal force, gas bubbles, ferrofluidic plugs, capillary action, electrohydrodynamic pumps, and/or magnetohydrodynamic pumps. Aptly, pumps for microfluidics may be governed by electrokinetic principles or by the mechanism of differential pressure.

The bio chip can be used for automating a variety of bioassay protocols, such as absorption, fluorescence, ELISA, enzyme immunoassay (EIA), light scattering, electrochemical measurement assays and chemiluminescence for testing a variety of analytes. Such analytes include for example proteins, nucleic acids, cells, receptors, and the like. The biochip can be configured and designed for whole blood, tears, sweat, serum, plasma, urine, and other biological fluid applications. In one embodiment, the bio-chip is adapted to perform DNA hybridization assays, expression analysis of mRNA, certain forms of DNA detection and/or DNA sequencing. Aptly, the bio chip may be used in one or more of the techniques described in Sensors (Basel). 2012; 12(8): 10713–10741, incorporated herein by reference in its entirety.

Aptly, the bio chip is made of elastomers or polymers such as for example, PDMS, PMMA, polyurethane, PFPE, SIFEL and parylene. In one embodiment, the bio-chip is formed from a material selected from for example plastic, glass, silicon, polycarbonate, polycarbonate, polydimethylsiloxane, polymethyl methacrylate (PMMA), cyclic olefin copolymer (COC),

polystyrene (PS), polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE) and polypropylene (PP).

The bio-chip may comprise a sample region. As used herein, the term "sample region" refers to any portion of a bio-chip that provides storage, analysis, separation or that provides, conducts or is otherwise involved in any processing step on or with the sample liquid. In one embodiment, the sample region is involved in the analysis of a sample liquid or components therein, and the sample region is considered a sensor (or sensor region), for example a sensor surface.

In one embodiment, the sample is taken from a plant, e.g. a tree, a shrub and/or a flowering plant. In one embodiment, the sample is selected from a human and/or animal sample. In one embodiment, the sample is whole blood, serum and/or plasma. Aptly the sample is urine sample, a sample taken from a swab e.g. a nasal swab, a pharyngeal swab, a vaginal swab or a rectal swab. In one embodiment, the sample is taken from tears and/ or sweat. Aptly, multiple analytes or multiple samples may be detected in a very small quantity.

In one embodiment, the bio-chip comprises a sensor (not shown). As used herein, the term "sensor" refers to a device that detects a change in at least one physical property and produces a signal, or induces a change in a signal, in response to the detectable change. The manner in which the sensor detects a change may include, for example, acousto-mechanical changes, electrochemical changes, optical changes and/or electro-optical changes. For example, acousto-mechanical sensors can utilise resonant frequency, phase-shifts, piezoelectric properties. Aptly, electrochemical sensors utilise potentiometric and amperometric measurements. Aptly, optical sensors may utilise absorbance, fluorescence, luminescence and/or evanescent waves.

In one embodiment, the sensor is a biosensor and comprises at least one detection moiety attached thereto. In one embodiment, the detection moiety is selected from one or more of: an antibody; a nucleic acid, e.g. DNA, RNA, or PNA; a protein; a peptide; an aptamer; a cell; a charged molecule; a membrane; a vesicle; a chemical and/or electrochemical receptor.

The detection moiety may be immobilised directly to a surface of the bio-chip. In certain embodiments the detection moiety may be immobilised on a solid support e.g. latex beads or magnetic beads using techniques known in the art. The detection moiety may comprise a

label for detection. Alternatively, the detection moiety may be directly detectable via a label free detection method.

The bio-chip of certain embodiments of the present invention may be used to detect for example the presence or absence of a target protein, a target DNA molecule and/or a target RNA molecule. The target molecule for detection may be for example a hormone, a cell surface molecule, a cardiac protein, a tumour marker and/or a small molecule. In one embodiment, the target molecule is a drug of abuse. In one embodiment, the target molecule may be a plurality of target molecules and the bio-chip is for the detection of the presence and/or absence of one or more target molecules.

Turning to Figure 1 again, the apparatus 100 comprises a piercing member 120 located on a support surface 130. The piercing member 120 is described in more detail below and illustrated in Figures 6 to 9. In one embodiment, the apparatus 100 may comprise a plurality of spaced apart piercing members 120.

The bio chip 110 comprises a lower chip sealing plate 140. The lower chip sealing plate 140 may be rectangular for example in shape. The chip sealing plate may have dimensions of for example a length of about 120mm and a width of about 60mm, although it will be appreciated that bio-chips of other dimensions are encompassed by certain embodiments of the present invention. The lower chip sealing plate 140 may comprise a rectangular glass plate. Other materials which may be suitable to fabricate the bio chip plates are described herein.

The bio chip also comprises a chip top layer 150. The lower surface 160 of the chip top layer 150 can be bonded to the upper surface 170 of the lower chip sealing plate 140 by a suitable known method e.g. thermal bonding. The upper surface 180 of the chip top layer 150 forms an upper external surface of the bio chip and the lower surface 190 of the lower chip sealing plate 140 forms a lower external surface of the bio chip 110. By way of example, the chip top layer 150 may have a thickness of for example about 3mm and the lower chip sealing plate may have a thickness of 1mm.

The bio chip 110 further comprises one or more channels. Figure 1 illustrates that the chip top layer comprises one or more channels 200. The chip top layer also comprises a sample chamber 210 which is in fluid communication with at least one channel. The chip top layer

150 further comprises a collection chamber 220. The collection chamber may be considered a fluid introduction chamber. In use, the collection chamber 220 is situated beneath a piercing member as described herein. The collection chamber is in fluid communication with at least one channel 200 and may provide an inlet for the channel 200.

The dimensions of the channels may differ between devices. In one embodiment, the channels may have a cross-sectional width of between about 0.1 mm and 5mm. The channels may have a depth of e.g. 20 microns and 1mm.

As shown in Figure 1, in certain embodiments the piercing member 120 is provided on a piercing plate 230. The piercing plate 230 is secured to the chip top layer 150 by a layer of adhesive 240. Prior to application of the layer of adhesive, the piercing plate is positioned such that the piercing member is located above the collection chamber 220. The piercing plate may be about around 200 to 1000 microns thick and/or manufactured from a material e.g. glass, polycarbonate or PMMA.

Figure 1 illustrates a blister pouch 250 located above the piercing member 120. The blister pouch 250 is formed from a blister forming material. The blister pouch comprises a reservoir 260 which may be filled with a predetermined volume of liquid e.g. a reagent. The reservoir is sealed by a blister sealing membrane 270. The liquid may be a reagent such as for example a buffer, a liquid comprising one or more detection molecule and/ or a liquid comprising a sample material. The nature of the liquid may depend on the reaction being carried out on the bio chip.

The blister sealing membrane 270 is formed from a blister sealing material. The blister sealing material is capable of being pierced by the piercing member 120 when brought into contact with the piercing member with a predetermined level of force. Aptly, the piercing member does not pierce the blister sealing membrane when it is located abutting the blister membrane at a level of force which is less than about 1N.

When the reagent or other liquid stored in the blister pouch is required, force may be applied manually by a user pressing the blister pouch on a surface opposing the blister sealing material. Alternatively, force may be applied by an automated actuator. The force is aptly greater than about 3N.

Figure 2 illustrates an embodiment in which two piercing members 120a, 120b are located in a bio chip 110. The illustrated bio chip may be generally square in shape as shown in Figure 2. In other embodiments, the bio chip may be alternative shapes e.g. rectangular, circular, hexagonal or pentagonal.

The piercing members 120a, 120b are each provided above a respective collection chamber 220a, 220b. During use, the collection chamber holds the liquid released from the blister pouch when the sealing membrane 270 is pierced by the corresponding piercing member. Thus, the collecting chamber helps to prevent liquid being released from the blister pouch over the surface of the bio-chip and thus away from the target location i.e. the channels of the bio-chip.

The bio chip 110 of Figure 2 includes a channel 200a which is generally linear and extends between a first piercing member 120a and a second piercing member 120b. The channel 200a includes a T-junction intersection with a further portion of the channel 200b. The further portion of the channel is serpentine and is connected to a sample chamber 210.

Figure 3 illustrates alternative embodiments of a bio chip 110. Figure 3A illustrates a bio chip 110 which comprises a linear channel 200. The linear channel is in fluid communication with the collection chamber 220 and the sample chamber 210. The linear channel 200 connects the collection chamber 220 and the sample chamber 210. The piercing member 120 located above the collection chamber 220 and is either integrally formed with the upper surface of the biochip or within a piercing plate.

Figure 3B illustrates an alternative embodiment of a bio chip according to certain embodiments of the present invention. The bio chip comprises a channel 200 which follows a serpentine path between the collection chamber 220 and the sample chamber 210. The piercing member 120 is located above the collection chamber 220 and can be either integrally formed with the bio chip 110 or within a separate piercing plate 230 as described herein.

Figure 3C illustrates a further alternative embodiment of a bio-chip 110 according to certain embodiments of the present invention. Two piercing members 120a and 120b are located above two separate collection chambers 220a and 220b. One or both piercing members

120a and 120b are either integrally formed with the upper surface of the biochip or within a piercing plate 230.

The collection chambers 220a, 220b are linked by a linear channel 200a. The channel 200a is intersected by and in fluid communication with a further portion of the channel 200b at an intersection point 300. The further portion of the channel 200b is in fluid communication with the sample chamber 210. The channel has a linear portion 310 extending from the intersection point 300, a middle serpentine section 320 and an end linear section 330 which is connected to the sample chamber 210.

Figure 4 illustrates a cut through of a piercing member 120 provided on a piercing plate 230 and located above a collection chamber 220 located in a bio chip. As described above, the collection chamber 220 is provided in an upper chip plate 150 of the bio chip 110. The piercing plate 230 is secured to the upper surface of the upper chip plate by a layer of adhesive 240.

A blister pouch 250 is located above the piercing member 120. The blister membrane 270 of the blister pouch 250 is in contact with the piercing member 120 but since the force applied to the blister sealing membrane by the piercing member does not exceed about 1N, the blister sealing material of the blister membrane is not punctured by the piercing member. As a result, the fluid is retained in the blister pouch 250 shown in Figure 4.

Figure 5 is an alternative view of the blister pouch 250, piercing plate 230 and bio chip shown in Figure 4.

The piercing member 120 is shown in more detail in Figures 6 to 9. The piercing member illustrated in Figures 6 to 9 may be comprised in a piercing plate or a bio chip as described herein.

Figure 6 illustrates a cross sectional view of a piercing member 120. The piercing member 120 is located upstanding from a support surface 130 at a height of about around 300 to 1200 microns. As noted herein, the support surface 130 may be provided as an integral surface of the bio chip. Alternatively, the support surface 130 may be provided on a piercing plate or as an integral part of the piercing plate. The piercing member 120 comprises a tip region 600 which has a rounded nose region 610. In use, the upper surface of the rounded

nose region 610 is locatable in an abutting relationship with the sealing membrane of the blister pouch and is capable of piercing the blister sealing membrane when a force is applied. Aptly, the force required to pierce the blister membrane is about 3N or more.

As illustrated in Figure 6, Figure 8 and Figure 9, the piercing member 120 also comprises a plurality of abutment wall regions or angled struts 620, 630, 640 and 650 which extend upwardly from the support surface to the tip region 600. Each strut extends from the support surface 130 to the tip region at a predetermined angle so that each wall region or strut forms a tangent with an arc of the rounded nose region 610 at an end of the tip region. In the illustrated embodiment, the piercing member comprises four angled struts, however, in alternative embodiments the piercing member may comprise a different number of angled struts e.g. two, three or five.

The abutment wall regions 620, 630, 640, 650 form a cross when viewed from above with the centre of the cross being the rounded nose region 610. The abutment wall regions extend upwardly from the support surface at an angle of approximately 90°, as shown in Figure 6. The rounded nose region of the piercing member allows the piercing member to abut a blister sealing membrane without piercing it. This embodiment has the advantage that a blister pouch may be stored and e.g. transported in an abutting relationship with a piercing member which may be an integral part of a microfluidic device e.g. a bio-chip. Thus, certain embodiments of the present invention may have utility in systems which need to be easily transported e.g. lab-on-chip portable devices.

Thus, between each abutment wall region and an adjacent abutment wall region is a passageway 660, 670, 680, 690 through which fluid stored in the blister pouch can flow once the blister sealing membrane is punctured by the piercing member. The fluid can then flow into the collection chamber 220 located beneath the passageways formed by adjacent abutment wall regions. The passageways are sized such that liquid may pass through the passageway and do not pool on top of the piercing member and therefore the bio-chip. As a result, substantially all of the liquid stored in the blister pouch passes into the biochip which means that the amount of liquid used in the process taking place on the bio-chip can be accurately determined.

Figure 7 is a cross sectional view of section A-A of Figure 6 and shows the collection chamber 220 located underneath the rounded nose region 610 of the piercing member 120.

Figure 9 is a bottom view of the apparatus 100 showing a lower surface 900 of for example a piercing plate or a bio chip.

Figure 10 is an exploded view illustrating a blister pack 710 which comprises two blister pouches 250a, 250b which protrude from and are supported by a backing web 720. It will be appreciated that a blister pack 710 may comprise a plurality of blister pouches 250. Figure 10 also illustrates a piercing plate 230 which comprises two piercing members 120a, 120b.

Each blister pouch may be filled with the same type of fluid or a different type of fluid. The backing web 720 includes one or more interconnecting regions 730 between the blister pouches. The backing web 720 may be provided with frangible lines or perforations (not shown) in the interconnecting regions between blister pouches to enable a section comprising one or more blister pouches to be "snapped-off" or removed from the blister pack.

The backing web may be formed from the same material as the blister forming material. In one embodiment, the backing web is formed from a plastic, a composite material, a film material or a combination of such materials.

The blister pack 710 may also include a sealing membrane (not shown) which extends across the backing web 720 and the otherwise open entrance of a plurality of blister pouches 250, thus sealing a plurality of blister pouches. The sealing membrane may comprise one or more perforations (not shown) which coincide with an outer perimeter surrounding an individual blister pouch. In embodiments in which the backing web comprises frangible lines or perforations, the sealing membrane may comprise corresponding frangible lines or perforations. The blister pouch may be sealed by a heat-sealing method. Alternatively, the blister pouch may be sealed by way of a cold-sealing method.

Alternatively, the blister pack may comprise a plurality of sealing membranes, each sealing membrane extending across an otherwise open blister pouch thus sealing a single blister pouch. The sealing membrane may be heat sealed to an upper surface of the backing web.

In one embodiment, the blister pouch 250 is filled with a pre-determined amount of a fluid e.g. a reagent. The blister pouch may be filled with the fluid using an automated filling

process. Alternatively, or in addition, the blister pouch may be filled with a liquid manually or using a semi-automated process.

Figure 10 also illustrates a layer of adhesive or adhesive material 740 which secures the blister pack to a piercing plate or to a biochip which comprises the piercing member. The embodiment illustrated in Figure 10 shows the piercing members being composed in a piercing plate.

The adhesive material 740 comprises one or more apertures 750a, 750b which are located to correspond to the location of the piercing members 120a, 120b respectively. The apertures 750a, 750b also provide a through passageway for fluid stored in the blister pouch to flow through the piercing member once the blister sealing membrane is pierced.

In the embodiment illustrated in Figure 10, the piercing member 120 is an integrally formed portion of a piercing plate 230. A piercing plate 230 can be used in conjunction with microfluidic devices of differing types. The piercing plate may be secured to a bio chip 110 by an adhesive element e.g. a layer of adhesive 240. Prior to being secured to the bio chip, the piercing plate will be aligned to the bio chip such that each piercing member is positioned above a collection chamber. The piercing plate can be used in combination with a variety of bio chips providing that the bio chip comprises at least one collection chamber in a position which corresponds to the positioning of at least one piercing member of the piercing plate.

Aptly, the piercing member 120 when comprised in the piercing plate 230 is upstanding from the upper surface of the piercing plate to a height of between about 300 to 1200 microns. Aptly, the piercing member 120 when comprised in the bio chip is upstanding from the upper surface of the piercing plate to a height of between about 300 to 1200 microns.

In certain embodiments, the piercing plate comprising one or more piercing members may be supplied in combination with a blister pack. The blister pack may be supplied with the piercing member abutting but not piercing the sealing membrane of a blister pouch comprised in the blister pack. The piercing member may pierce the blister sealing membrane only when a predetermined force is applied e.g. about 3N or greater.

Additionally or alternatively, the piercing plate may include at least one alignment element (not shown) which locates the piercing plate at a desired position with respect to each blister

pouch. Aptly, the alignment element comprises at least one edge of the piercing plate. Alternatively, the alignment element comprises at least one locating lug or recess which mates with a complimentary alignment element of the blister pouch.

Figure 11 illustrates an alternative view of an individual blister pouch 250. The blister pouch 250 comprises a continuous curved exterior wall 1100 which define a cavity in which fluids are introduced and stored prior to use. If individual blister pouches are used, which are not an integral part of a blister pack, the blister pouch may comprise a lip region 1110 which a user can grip to handle the blister pouch.

Figure 12 illustrates a side view of a blister pouch 250 positioned over a piercing member 120 which is in turn located above a collection chamber of a device e.g. a bio chip as described herein. The piercing member abuts the blister sealing membrane at an abutment point 1200 and deforms the membrane but since there is insufficient force applied the sealing membrane is not pierced. In certain embodiments, the apparatus comprising the piercing member may be stored and/or transported packaged such that the piercing member abuts but does not pierce the sealing membrane.

In use, a blister pouch 250 is prefilled with a predetermined volume of a liquid. As noted herein, the liquid may be any reagent for use in a process taking place on a microfluidic device e.g. a bio chip 110 as defined herein. An open mouth of the blister pouch is subsequently sealed by a sealing membrane 270. As described herein, the blister pouch may be one of a plurality of blister pouches in a blister pack. Alternatively, the blister pouch may be supplied as an individual pouch.

Aptly, the blister pouch is sealed in an air tight manner and as such may be suitable for long term storage of the liquid. Additionally, the blister pouch can be stored at low temperatures, e.g. in a refrigerator, if the liquid needs to be stored in this way. The provision of reagents in blister pouches in this way enable different liquids to be stored in their optimum conditions ready for use in a process carried out on a microfluidic device.

As discussed herein, a piercing member 120 is provided in an apparatus 100. The piercing member may be an integral element of a piercing plate 230 or an integral feature of a bio chip 110. The piercing member may be provided in an abutting relationship with the sealing membrane of the blister pouch such that it deforms but does not break the sealing

membrane in a first mode of operation. Aptly, the piercing member deforms but does not pierce the sealing membrane when a force of up to about 1N is applied.

In a second mode of operation, a predetermined amount of force is applied to the blister pouch and/or the piercing member such that the sealing membrane is punctured by the piercing member. Aptly, when the blister pouch is urged against the piercing member, the piercing member is disposed to rupture the membrane when a force of about around 3 to 12N is applied to the membrane.

The force may be applied to the blister pouch or the piercing member manually by a user or by an actuator. In one embodiment, the actuator may be adapted to apply a pressure at a predetermined rate. The actuator may further comprise a control element adapted to instruct the actuator to apply a force to a plurality of blister pouches at substantially the same time or at predetermined time intervals.

Once the blister sealing membrane has been broken by the piercing member, the liquid stored in the blister pouch is released in a controlled manner and substantially all of the liquid flows over the piercing member and through the openings formed between the abutment wall regions. The liquid then collects underneath the piercing member e.g. in a collection chamber comprised in a biochip. The liquid can then be used in a process on the bio-chip.

Throughout the description and claims of this specification, the words "comprise" and "contain" and variations of them mean "including but not limited to" and they are not intended to (and do not) exclude other moieties, additives, components, integers or steps. Throughout the description and claims of this specification, the singular encompasses the plural unless the context otherwise requires. In particular, where the indefinite article is used, the specification is to be understood as contemplating plurality as well as singularity, unless the context requires otherwise.

Features, integers, characteristics or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may

be combined in any combination, except combinations where at least some of the features and/or steps are mutually exclusive. The invention is not restricted to any details of any foregoing embodiments. The invention extends to any novel one, or novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

CLAIMS:

1. Apparatus for providing a target liquid at a desired location, comprising:

at least one piercing member upstanding from a support surface at a height of about around 300 to 1200 microns and locatable with respect to a sealing membrane of a respective blister pouch; wherein

a tip region of the piercing member is locatable in an abutting relationship with the sealing membrane in a first mode of operation and through the sealing membrane in a further mode of operation for providing liquid from the blister pouch at a desired location.

2. The apparatus as claimed in claim 1, further comprising:

in the first mode of operation the piercing member is locatable to deform but not pierce the sealing membrane.

3. The apparatus as claimed in claim 2, further comprising:

in the first mode of operation the piercing member does not pierce the sealing membrane when an abutment force of up to about around 1N is applied by the piercing member to the sealing membrane.

4. The apparatus as claimed in any preceding claim, further comprising:

said tip region comprises a rounded nose region having a generally arcuate shape with a radius of curvature of about around 50 to 1000 microns.

5. The apparatus as claimed in claim 4 wherein the radius of curvature is about around 100 to 500 microns.

6. The apparatus as claimed in any preceding claim, further comprising:

said piercing member further comprises a plurality of abutment wall regions extending from the support surface to the tip region at a predetermined angle so that each wall region forms a tangent with an arc of a rounded nose region at an end of the tip region.

7. The apparatus as claimed in claim 6, further comprising:

each abutment wall region meets the nose region at an angle of about around 45 degrees.

8. The apparatus as claimed in any preceding claim, further comprising:

the piercing member provides a plurality of fluid communication passageways proximate to the tip region that each communicate liquid urged from a pierced blister pouch to at least one collection chamber under the support surface.

9. The apparatus as claimed in claim 8 wherein the piercing member comprises a plurality of arms extending upwards and in an inclined manner from the support surface and the fluid communication passageways are provided by openings in the support surface in notched regions between adjacent arms.

10. The apparatus as claimed in any preceding claim wherein the first mode of operation comprises a transportation mode during which a blister pouch is transportable in an abutting relationship with said piercing member without risk of puncture.

11. The apparatus as claimed in any preceding claim wherein in the further mode of operation in which the blister pouch is urged against the piercing member the piercing member is disposed to rupture the membrane at a rupture force of about around 3 to 12N.

12. The apparatus as claimed in any preceding claim wherein each piercing member is manufactured from a material selected from a group comprising glass, polycarbonate, polymethyl methacrylate (PMMA), cyclic olefin copolymer (COC), polystyrene (PS), polyether ether ketone (PEEK), polytetrafluoroethylene (PTFE) and polypropylene (PP).

13. A piercing plate, securable to at least one blister pouch, comprising the apparatus as claimed in any preceding claim.

14. The piercing plate as claimed in claim 13, further comprising:

a planar upper surface, comprising said support surface, and a planar lower surface that is securable to an upper surface of a bio chip.

15. The piercing plate as claimed in claim 14 further comprising an adhesive layer on the lower surface.

16. The piercing plate as claimed in any one of claims 13 to 15, further comprising:

at least one alignment element that locates the piercing plate at a desired position with respect to each blister pouch.

17. The piercing plate as claimed in claim 16 wherein said alignment element comprises at least one edge of the piercing plate.

18. The piercing plate as claimed in claim 16 wherein said alignment element comprises at least one locating lug or recess that mates with a complimentary alignment element of the blister pouch.

19. The piercing plate as claimed in any one of claims 13 to 18 further comprising at least one further alignment element that locates the piercing plate at a desired position with respect to a bio chip.

20. The piercing plate as claimed in claim 19 wherein each further alignment element comprises at least one edge of the piercing plate.

21. The piercing plate as claimed in claim 19 wherein said further alignment element comprises at least one locating lug or recess that mates with a complimentary alignment element of the bio chip.

22. The piercing plate as claimed in any one of claims 13 to 21, further comprising:

a cavity under each piercing member that is locatable in fluid communication with a collection chamber of a bio chip.

23. The piercing plate as claimed in any one of claims 13 to 22, further comprising:

the plate is about around 200 to 1000 microns thick.

24. The piercing plate as claimed in any one of claims 13 to 23 wherein the plate is manufactured from a material selected from the list of glass, polycarbonate and PMMA.

25. The piercing plate as claimed in any one of claims 13 to 24 wherein the plate and each piercing member are integrally formed.

26. The piercing plate as claimed in any one of claims 13 to 25 wherein the plate is retrofittable to an underside of a blister package comprising one or more blister pouches sealed with a sealing membrane.

27. A blister pack, comprising:

a plurality of blister pouches secured together via a web and a common sealing membrane; and

at least one piercing plate as claimed in any one of claims 13 to 26 secured to a lower surface of the sealing membrane.

28. The blister pack as claimed in claim 27, further comprising:

a plurality of frangible lines or perforation lines in the web.

29. A bio chip, comprising the apparatus as claimed in any one of claims 1 to 9.

30. The bio chip as claimed in claim 29, further comprising:

an upper chip layer comprising each piercing member as an integral unit.

31. The bio chip as claimed in claim 29, further comprising:

an upper chip layer having an upper surface on which at least one piercing plate comprising said at least one piercing member is secured.

32. The bio chip as claimed in claim 30 or claim 31 wherein a lower surface of the upper chip layer includes a collection chamber located beneath each piercing member and at least one channel connecting a collection chamber to a respective sample chamber.

33. The bio chip as claimed in claim 32 wherein said channel comprises a channel region that provides a serpentine pathway.

34. Apparatus constructed and arranged substantially as hereinbefore described with reference to the accompanying drawings.

35. A piercing plate constructed and arranged substantially as hereinbefore described with reference to the accompanying drawings.

36. A bio chip constructed and arranged substantially as hereinbefore described with reference to the accompanying drawings.

37. A method substantially as hereinbefore described with reference to the accompanying drawings.

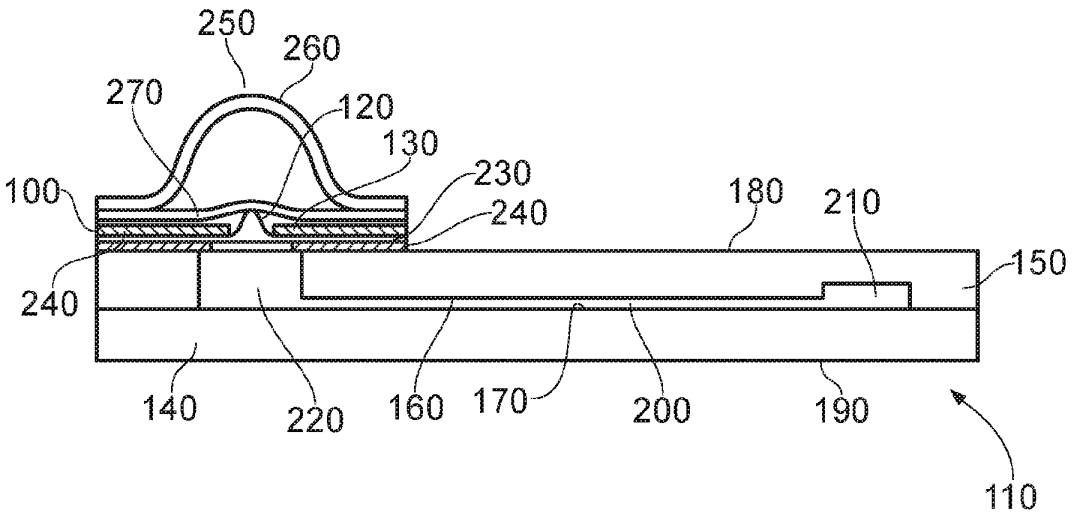

250
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FIG. 1

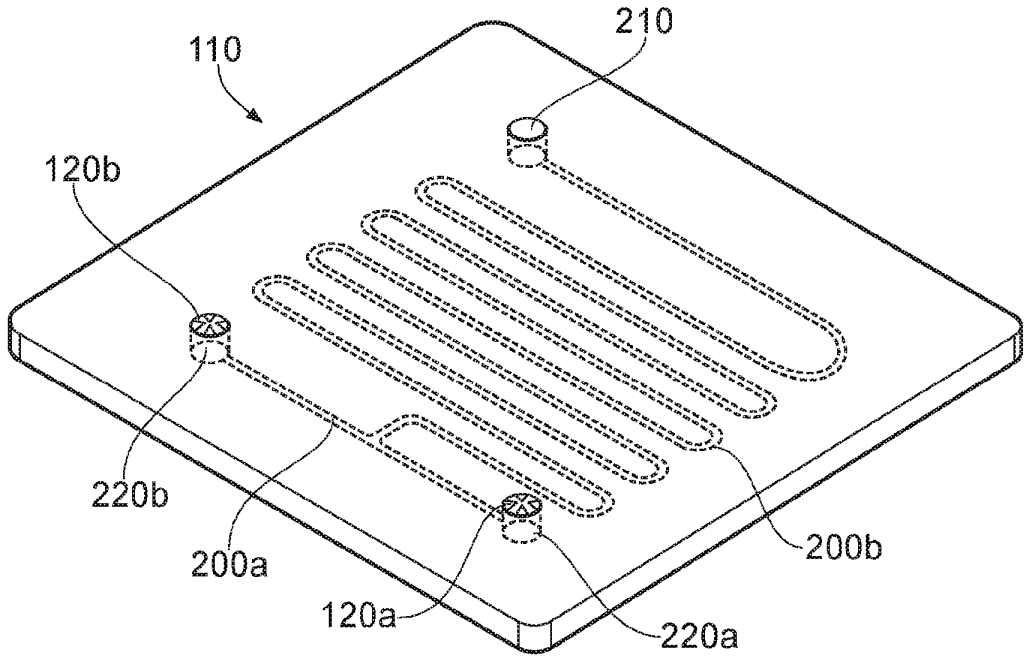


FIG. 2

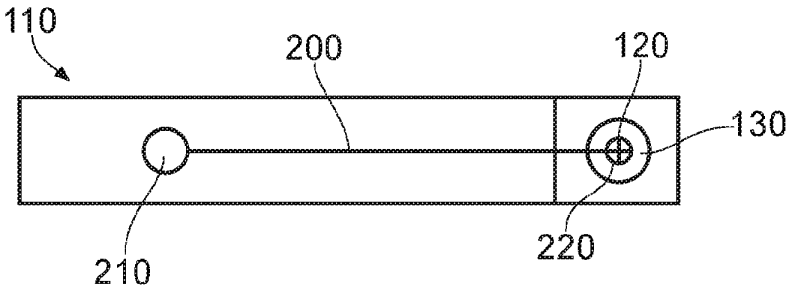


FIG. 3A

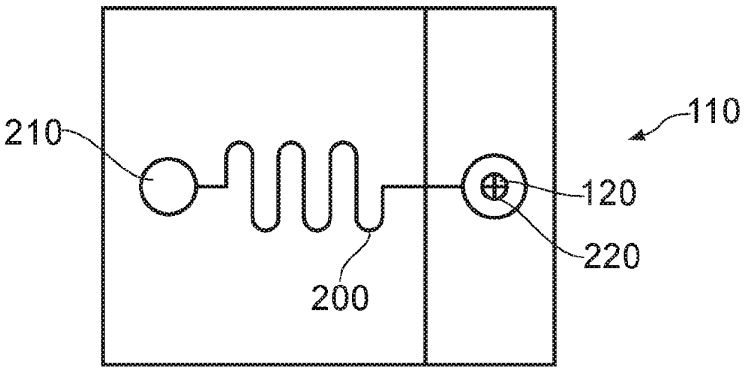


FIG. 3B

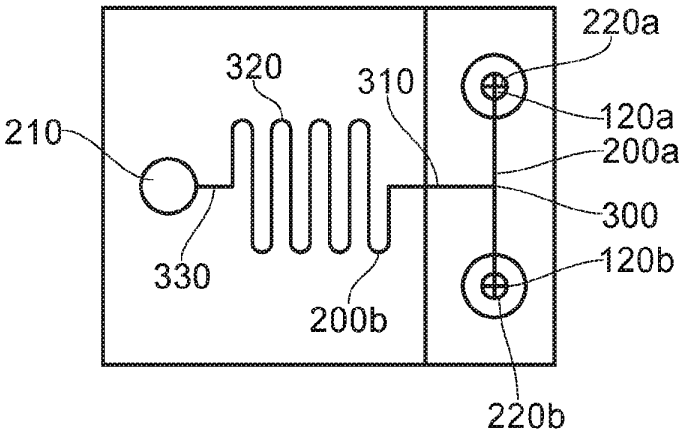


FIG. 3C

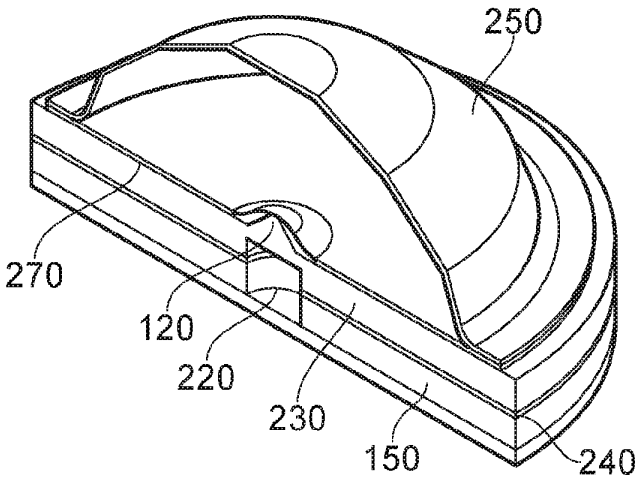


FIG. 4

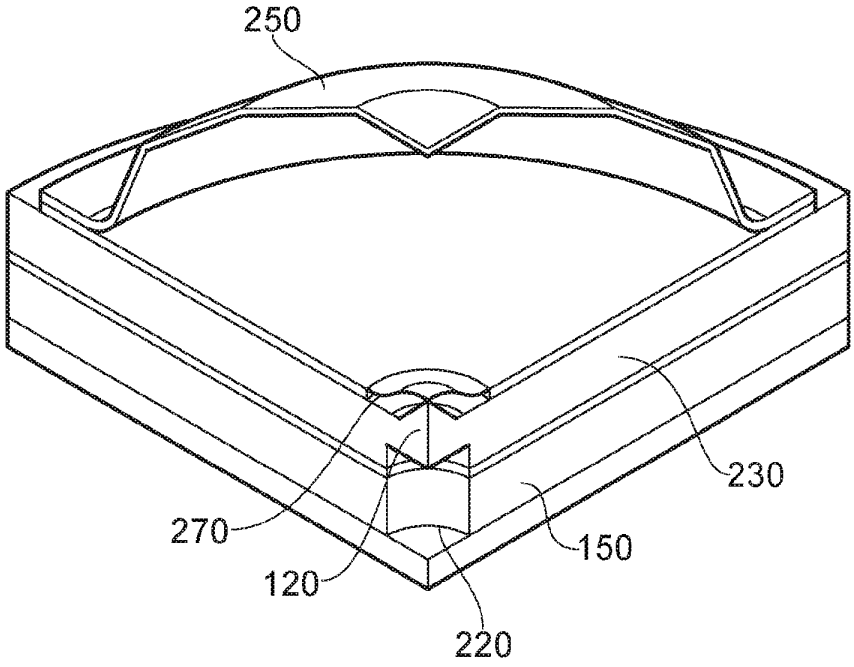


FIG. 5

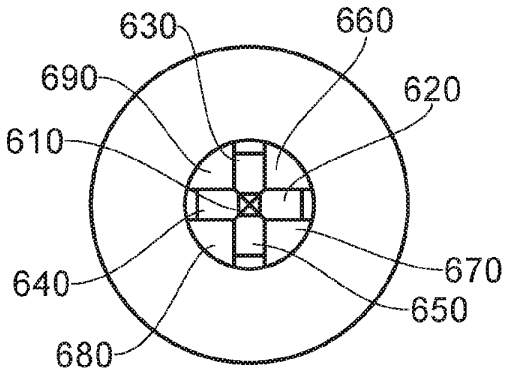


FIG. 8

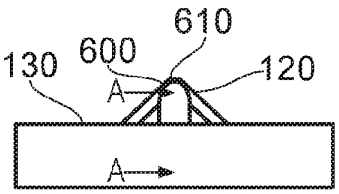
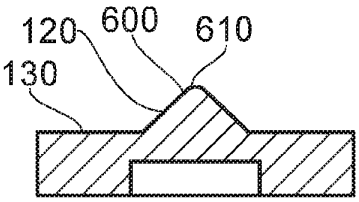


FIG. 6



SECTION A - A

FIG. 7

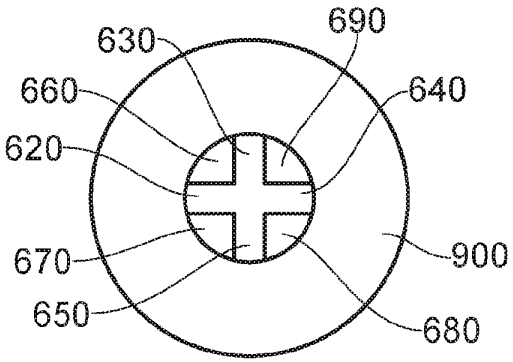


FIG. 9

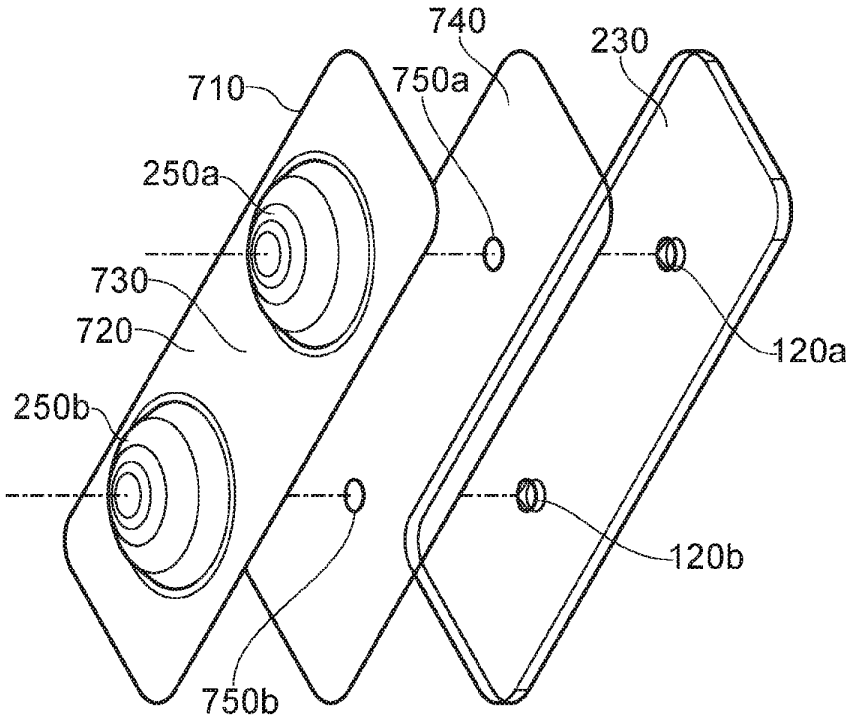


FIG. 10

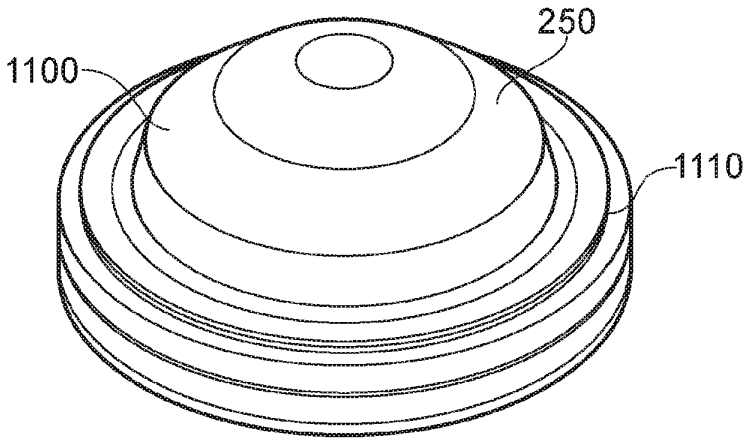


FIG. 11

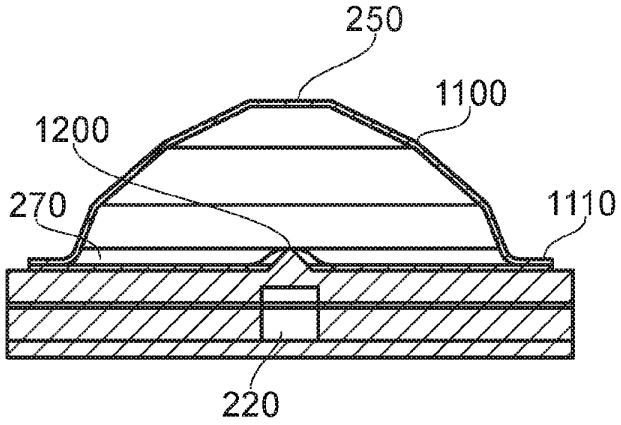


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050905

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01L3/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/057744 A2 (INVERNESS MEDICAL SWITZERLAND [CH]; PANESAR SATWINDER SINGH [GB]; HANN) 24 May 2007 (2007-05-24) page 10, line 5 - page 12, line 10 page 14, line 18 - line 25 figures 6A, 6B, 7A, 7B, 7C, 8	1-37
A	US 5 096 669 A (LAUKS IMANTS R [US] ET AL) 17 March 1992 (1992-03-17) the whole document	1-37
A	US 2010/291588 A1 (MCDEVITT JOHN T [US] ET AL) 18 November 2010 (2010-11-18) the whole document	1-37
A	US 2006/183216 A1 (HANDIQUE KALYAN [US] ET AL) 17 August 2006 (2006-08-17) the whole document	1-37

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2015	29/06/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bischoff, Laura

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/050905

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/304986 A1 (CHEN ZONGYUAN [US] ET AL) 2 December 2010 (2010-12-02) the whole document	1-37

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Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/050905

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007057744 A2	24-05-2007	NONE	
US 5096669 A	17-03-1992	AT 130092 T	15-11-1995
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		DE 68924782 D1	14-12-1995
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US 2010291588 A1	18-11-2010	AU 2006261953 A1	04-01-2007
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		WO 2007002480 A2	04-01-2007
US 2006183216 A1	17-08-2006	NONE	
US 2010304986 A1	02-12-2010	US 2010304986 A1	02-12-2010
		WO 2008076395 A2	26-06-2008

Form PCT/ISA/210 (patent family annex) (April 2005)

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REGISTRY OF MEDICAL TECHNOLOGISTS
Vol. 33, No. 2, February, 1963, pp. 29-31

THE STANDARD CLOTTING TIME

A METHOD BASED ON THE USE OF WHOLE VENOUS BLOOD IN CAPILLARY TUBES

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Rhode Island Hospital, Providence, Rhode Island, and Tufts University School of Medicine, Boston, Massachusetts

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In 1955, Mayer[1] described a method for testing the coagulation time of whole blood that was later referred to as the *standard clotting time*.[2] The method was reported to be reliable and to reveal a rather narrow range of normal values, as compared with the more widely used Lee-White technic for clotting time, and with the now almost abandoned capillary method for clotting time. In the course of investigating possible clotting abnormalities in patients with prostatic cancer,[5] we re-evaluated the method, particularly because its claimed normal range of 11.9 ± 0.9 min. was based merely on values obtained from 40 healthy, fasting men, in the age group of 25 to 35 years.

MATERIALS AND METHODS

Because Mayer's procedure as outlined in 1957 was followed in detail,[2] it will not be described fully. It is necessary to note, however, that the No. 19 gage stainless steel needle was replaced by the Becton, Dickinson and Company No. 20 sterile disposable needle. With this method, venous blood is drawn and diverted by a special adapter to 3 capillary tubes, which are maintained at a temperature of 21 C. in a water bath. The end point is obtained by means of breaking off each capillary tube in succession and observing a fibrin clot. The average value determined from the 3 tubes represents the standard clotting time. It differs considerably from the ordinarily performed capillary clotting time because of the use of venous blood, with minimal admixture of tissue thromboplastin, and because the temperature is controlled. The test is readily performed by 1 technologist, and it is possible to examine 2 patients at the same time. Although it is of necessity performed at the bedside and requires minutes rather than seconds, the total time of performance is comparable to that of other coagulation tests if preparation of blood samples and reagents is considered. The following groups of persons, who were generally in a postprandial state, were examined:

1. Fifty-three women in the age group of 17 to 60 years.
2. Fifteen healthy men, 25 to 50 years of age.
3. Thirty healthy employees in the age group of 60 to 80 years, to serve as controls for patients with prostatic cancer.
4. Twenty-two men with cancer of the prostate gland, in the age group of 60 to 80 years.
5. Twelve persons on 2 different occasions, 1 to 12 months apart, in order to determine the standard deviation of the test.
6. Thirty-six outpatients maintained on anticoagulants (Coumadin) over a period of 1 year, for comparison of the standard clotting time with Quick's 1-stage prothrombin time.[4]
7. Twenty-five persons with miscellaneous cases who were investigated because of a history of a suspected bleeding tendency, for comparison with the clotting time (Lee-White) for whole blood, and a battery of other screening tests for blood coagulation.[4]

Received, July 2, 1962; revision received, September 14; accepted for publication November 14.

Dr. Meissner is Associate Pathologist at the Rhode Island Hospital, and Assistant Professor at Tufts University Medical School. Mrs. Moehring is Medical Technologist at the Rhode Island Hospital.

KUR-MAG-DE005545

Page 4046 of 5977

RESULTS

1. Fifty-three healthy women (17 to 60 years) manifested a normal value of 11.2, with a standard deviation from the mean of ±1.1 min.

2. Fifteen healthy men (25 to 50 years) manifested normal values of 11.1 ± 1.1 min.

3. Thirty healthy male employees (60 to 80 years of age), with 42 determinations manifested normal values of 10.1 ± 1.3 min.

4. Twenty-two men (44 determinations) with cancer of the prostate gland manifested an average value of 10.5 ± 1.5 min. These men were also in the age group of 60 to 80 years.

5. Twelve controls taken on 2 different occasions (1 to 12 months apart) revealed a standard deviation from the mean of ±1.0 min.

6. One hundred thirty-nine determinations of the standard clotting time and also the prothrombin time on 36 patients being treated with anticoagulants revealed a poor correlation between these 2 tests. For the prothrombin activity in the so-called therapeutic range of from 20 to 30 per cent, the values in the standard clotting time ranged from 10.2 to 21.0 min. (Fig. 1). Prothrombin activity of less than 20 per cent revealed a range in the standard clotting time of 11.5 to 23.5 min.; values of prothrombin activity of more than 30 per cent manifested in the standard clotting time a range of 10.5 to 18.4 min. If, conversely, the therapeutic range of the standard clotting time is considered, which, according to Mayer and Connell[3] is between 15 and 20 min., the corresponding prothrombin activities revealed a range of 16 to 49 per cent (Fig. 1); taking values of the standard clotting time of less than 15 min., the range of the corresponding prothrombin activity varied from 15 to 70 per cent, and similarly, in values above 20 min., the variation of prothrombin activity was between 15 and 24 per cent.

7. Comparison of the standard clotting time with the clotting time for whole blood, and other screening tests, revealed that the standard clotting time was within the normal range whenever the clotting time for whole blood (Lee-White) was less than 20 min., with the following exceptions: 3 instances of patients treated with salicylates in whom the clotting time for whole blood was normal and the standard clotting time moderately prolonged (less than 20 min.); 3 other persons with a history of minor bleeding dif-

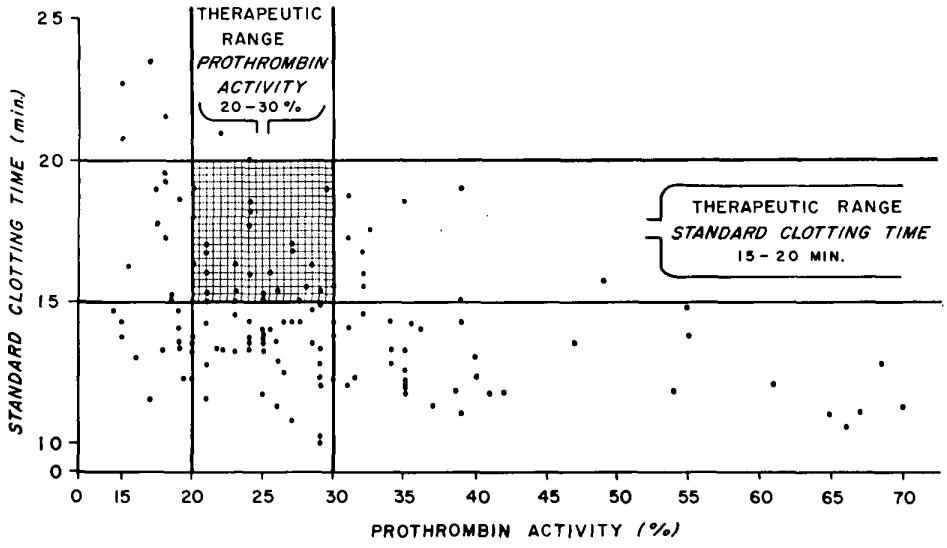


FIG. 1. A scattergram of the standard clotting time (min.) and prothrombin activity (per cent) of 139 determinations on 36 patients being treated with anticoagulants. Except for the *cross-hatched area*, there is no consistent correlation between the 2 tests.

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ficulty in whom the standard clotting time revealed a slight prolongation, in the range of from 15 to 20 min., whereas tests for other phases in blood coagulation, including the thromboplastin generation test, were normal. In addition, a patient with hemophilia A manifested a great prolongation of the standard clotting time, as well as the clotting time of the whole blood. There were 2 patients in whom, for unexplained reasons, the clotting time was less than normal, 9:00 and 7:33 min. One of these, a 34-year-old woman, had pulmonary coccidioidomycosis with multiple segmental pulmonary resections; her only other abnormality was a slightly positive tourniquet and petechiometer test. The other person, a 68-year-old man, is a patient with probable cirrhosis of the liver.

COMMENTS

We have found the standard clotting time a reliable and reproducible test for coagulation of whole blood. The normal range of values corresponds well with the figures reported by Mayer and Connell, except in the older age group, for whom the values are slightly less (approximately 1 min.).

The observation made by Mayer and Connell that there is poor correlation between the standard clotting time and the 1-stage prothrombin time is confirmed. The controversy[7] concerning which of the 2 tests more adequately represents a response to anticoagulation therapy is not resolved by our study; its resolution would require a very close clinical follow-up over a long period of time, which is not feasible for a study based on outpatients. According to Rapaport and Ames,[6] a Factor IX deficiency that is not measured by the prothrombin time does not seem to be the explanation. The standard clotting time may prove valuable whenever a discrepancy is encountered between 1 type of test, such as the 1-stage prothrombin time, and the clinical manifestations in anticoagulated patients. We also found that it may be a helpful procedure in evaluating a "borderline" prolonged clotting time, although it is by no means a substitute for detailed investigation of the patient with a history of definite bleeding. We have not determined whether or not values lower than normal (excluding faulty venipuncture) indicate a state of hypercoagulability. The greatest value of the test results from the fact that the normal range is rather narrow, as stated by Mayer and Connell.

SUMMARY

A re-evaluation of the standard clotting time, using several control groups, demonstrates that it is a reproducible test for coagulation of whole blood. It may be regarded as an additional useful test in the evaluation of an abnormal clotting time for whole blood, of patients with bleeding problems, and of patients being treated with anticoagulants.

SUMMARIO IN INTERLINGUA

Un re-evaluation del tempore standard de coagulation, utilisante plure gruppos de controlo, demonstra que illo es un reproducibile test pro le coagulation de sanguine total. Illo pote esser reguardate como un test additional de utilitate in le evalutation de anormal tempores de coagulation in sanguines total ab patientes con problemas hemorrhagic e ab patientes sub tractamento con anticoagulantes.

REFERENCES

1. Mayer, G. A.: Method for reliable determination of clotting time in whole blood. Canad. M. A. J., **72:** 927–929, 1955.
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4. McMillan, C. W.: Manual of the Coagulation Laboratory of Children's Medical Center. Boston, 1960.
5. Meissner, G. F., and Moehring, C. M.: Synthetic estrogens in treatment of atherosclerosis. (A study of prostatic cancer patients.) Arch. Int. Med., **110:** 467–471, 1962
6. Rapaport, S. I., and Ames, S. A.: Relation between levels of plasma thromboplastin component (PTC) and prothrombin times by the P & P and Quick methods in patients receiving Warfarin. New England J. Med., **267:** 125–130, 1962.
7. Roberts, L. N., and Mason, G. P.: A clinical assessment of anticoagulant control. Canad. M. A. J., **85:** 831–835, 1961.

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NOTICE OF ALLOWANCE AND FEE(S) DUE

27500 7590 01/17/2024

PILLSBURY WINTHROP SHAW PITTMAN LLP (CV)
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

EXAMINER	
ABOUELELA, MAY A	
ART UNIT	**PAPER NUMBER**
3791	

DATE MAILED: 01/17/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/538,990	11/30/2021	Bobby E. ROGERS	069366-0572201_KUR2C03US	3420

TITLE OF INVENTION: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/17/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

27500 7590 01/17/2024
PILLSBURY WINTHROP SHAW PITTMAN LLP (CV)
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/538,990	11/30/2021	Bobby E. ROGERS	069366-0572201_KUR2C03US	3420

TITLE OF INVENTION: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	04/17/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
ABOUELELA, MAY A	3791	600-573000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/538,990	11/30/2021	Bobby E. ROGERS	069366-0572201_KUR2C03US	3420

27500 7590 01/17/2024

PILLSBURY WINTHROP SHAW PITTMAN LLP (CV)
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

EXAMINER	
ABOUELELA, MAY A	

ART UNIT	PAPER NUMBER
3791	

DATE MAILED: 01/17/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 17/538,990	Applicant(s) ROGERS et al.	
	Examiner MAY A ABOUELELA	Art Unit 3791	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 12/20/2023.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-20 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. 10/08/2024.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/MAY A ABOUELELA/
Primary Examiner, Art Unit 3791

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 12/20/2023. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Terminal Disclaimer

3. The terminal disclaimer filed on 12/20/2023 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S Patent Applications No. 9820682, 10143412 and 11185266 has been reviewed and is accepted. The terminal disclaimer has been recorded.

EXAMINER'S AMENDMENT

4. Authorization for this examiner's amendment was given in an interview with BEN HUDSON on 01/08/2024.

Claim 5 should be amended as follow:

5. (Currently Amended) The blood sample control device in accordance with claim **3** ~~2~~, wherein the housing comprises a bottom member mated with a top member, each of the

bottom member and the top member defining a part of each of the inlet, the outlet, the chamber, and the sampling channel.

Claim 10 should be amended as follow:

10. (**Currently Amended**) The bodily fluid control device in accordance with claim 6, wherein the air permeable blood barrier includes an air permeable material that at least partially seals upon contact with **the bodily fluid** ~~blood~~.

Claim 13 should be amended as follow:

13. (Currently Amended) A bodily fluid control device comprising;

an inlet;

a junction connected with the inlet;

an outlet;

a chamber connected with the inlet via the junction, the chamber having a vent that includes an air permeable bodily fluid barrier that at least partially seals upon contact with a first portion of bodily fluid;

a housing that houses and defines the inlet, the outlet, and the chamber; and

wherein the chamber and the junction **are** ~~being~~ configured to direct the first portion of the bodily fluid from the inlet into the chamber toward the air permeable bodily fluid barrier and to displace air in the chamber, whereupon at least partially sealing of the air permeable bodily fluid barrier enables at least temporary containment of the first portion of the bodily fluid in the chamber, and enables a second portion of the bodily fluid from the inlet to bypass the chamber via the junction and be directed toward the outlet.

Allowable Subject Matter

5. Claims 1-20 are allowed.

6. The following is an examiner's statement of reasons for allowance: the most pertinent prior art Eldridge et al (U.S 4,207,870) teaches a blood sample device for sampling blood conveyed from a patient, the blood device comprising; an inlet port configured to receive the blood conveyed from the patient; an outlet port; a chamber; and a sampling channel having a distal end connected with the outlet port; a junction connected between the inlet port, the chamber and the sampling channel, the junction being sized and configured such that a first portion of blood conveyed from the patient flows into the chamber to displace air therein through the air permeable blood barrier and to be sequestered in the chamber.

The prior art does not teach, disclose and/or fairly suggest the chamber having a vent that includes an air permeable blood barrier, and wherein the junction is configured to allow a second portion of blood to bypass the chamber and the first portion of blood sequestered therein to be directed into the sampling channel toward the outlet port.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAY A ABOUELELA whose telephone number is (571)270-7917. The examiner can normally be reached 8-5.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JACQUELINE CHENG can be reached on 5712725596. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MAY A ABOUELELA/
Primary Examiner, Art Unit 3791

Examiner-Initiated Interview Summary	**Application No.** 17/538,990	**Applicant(s)** ROGERS et al.		
	Examiner MAY A ABOUELELA	**Art Unit** 3791	**AIA (First Inventor to File) Status** Yes	**Page** 1 of 1

All Participants (applicant, applicants representative, PTO personnel)	**Title**	**Type**
MAY A ABOUELELA	Primary Examiner	Telephonic
BEN HUDSON	Attorney of Record	

Date of Interview: 08 January 2024

Issues Discussed:

35 U.S.C. 112

Applicant and Examiner discussed the claims set mailed on 12/20/2023. Applicant and Examiner discussed the claim language with respect to the applied prior art and the disclosure. Applicant and Examiner discussed proposed claim amendments represented by the Examiner to overcome 112 rejection for claims 5, 10 and 13. The Applicant has authorized the Examiner to amend the claims.

/MAY A ABOUELELA/ Primary Examiner, Art Unit 3791	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.