8638249

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

September 23, 2025

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: ***18/898,239***
FILING DATE: ***September 26, 2024***
PATENT NUMBER: ***12390137***
ISSUE DATE: ***August 19, 2025***

Certified by

DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Bobby E. Rogers	Nonprovisional Application Number (if known):	
Title of Invention:	BLOOD SAMPLE OPTIMIZATION DEVICE		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Ben Hudson/	Date 2024-09-26
Name (Print/Typed) Benjamin F. Hudson	Practitioner Registration Number 71,474

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☐ *Total of _____ forms are submitted.

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to 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)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES
PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/898,239	**09/26/2024 05:52:39 PM Z ET**	**069366-0581370_KUR2C07US**

Title of Invention

BLOOD SAMPLE OPTIMIZATION DEVICE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7801	FILED BY	Trent Tercenio
PATENT CENTER #	67342093	FILING DATE	-
CUSTOMER #	27500	FIRST NAMED INVENTOR	Bobby E. Rogers
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Benjamin Hudson

Documents

TOTAL DOCUMENTS: 5

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
069366-0581370_KUR2C07US-ADS.pdf	10	Application Data Sheet	2175 KB
069366-0581370_KUR2C07US-Track-One-Request.pdf	2	Track One Request	121 KB
069366-0581370_KUR2C07US-Specification-APP.TEXT.docx	37	Application body structured text document	62 KB

Warning: The margins of the attached document do not meet USPTO rules. This may cause processing errors or delays. All artifacts (SmartArt, Drawings, Charts, etc) have been replaced with images. Bookmarks were found and have been removed. The abstract contains more than one paragraph. Please review and revise if necessary.

Images have been detected in the abstract section. Please review. You may be missing a drawing heading.

069366-0581370_KUR2C07US-Drawings.pdf	50	Drawings-only black and white line drawings	876 KB
069366-0581370_KUR2C07US-Declarations.pdf	3	Oath or Declaration filed	780 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security,

and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

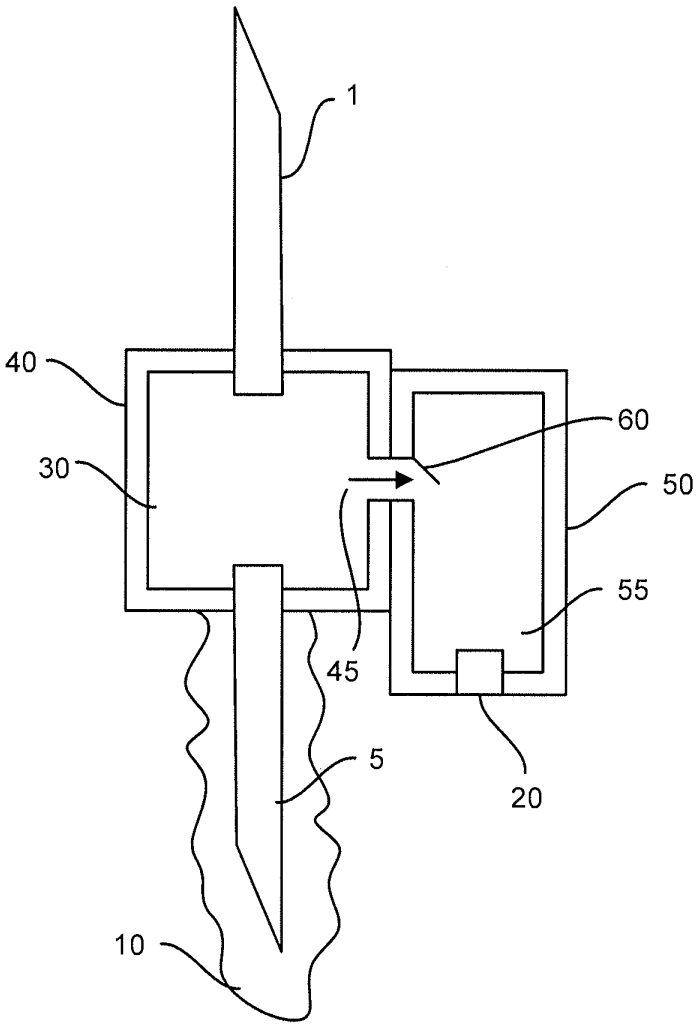


FIG. 1

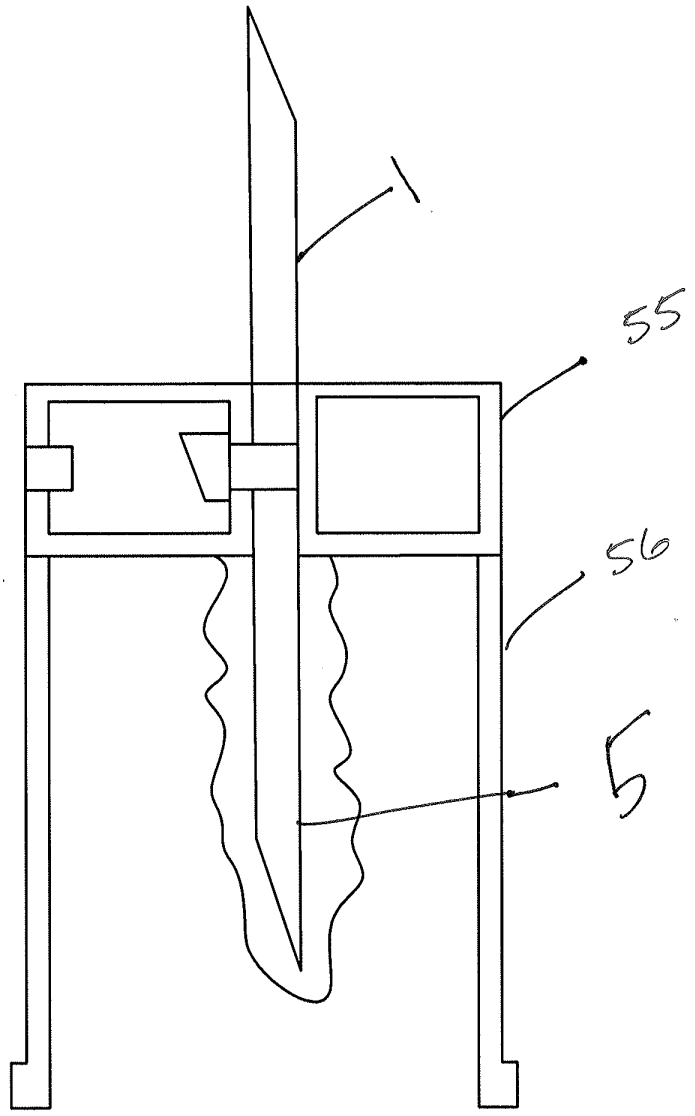


FIG. 2

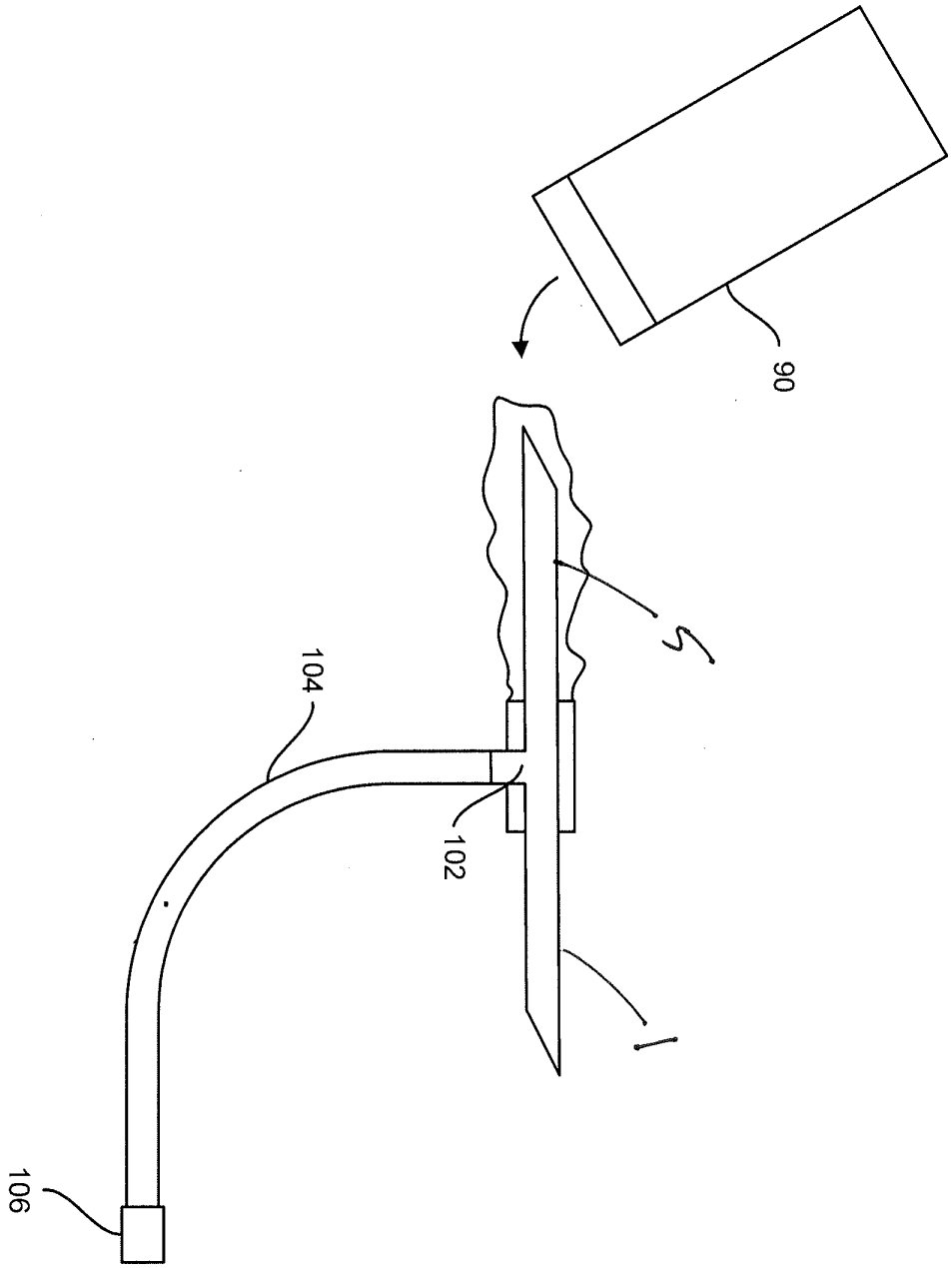


FIG. 3

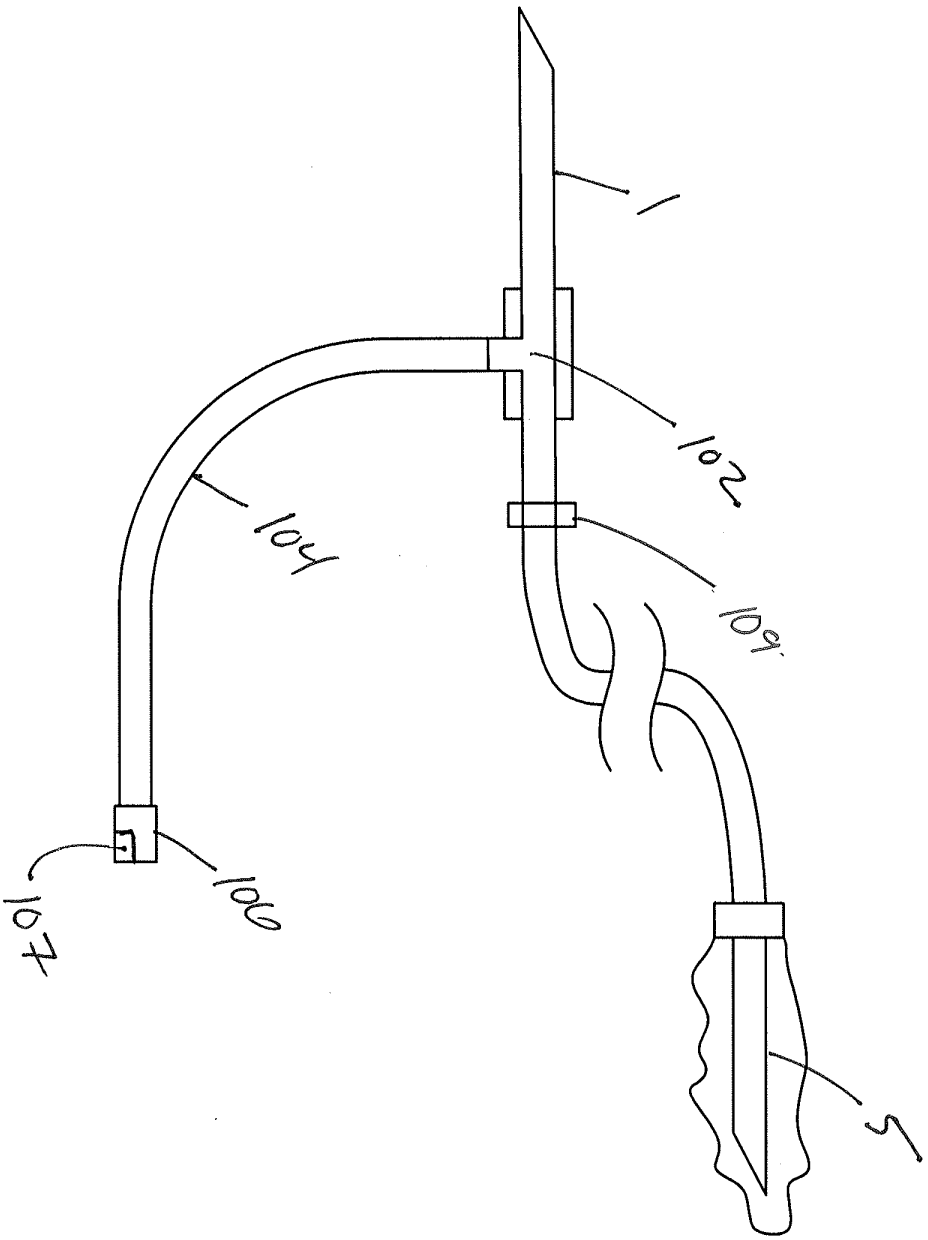


FIG. 4

FIG. 5

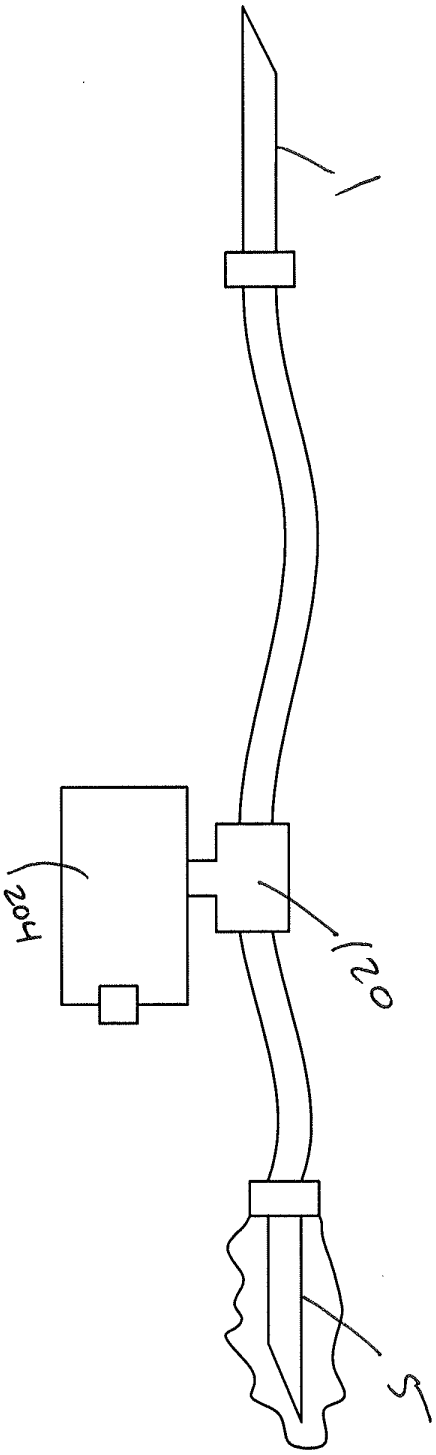
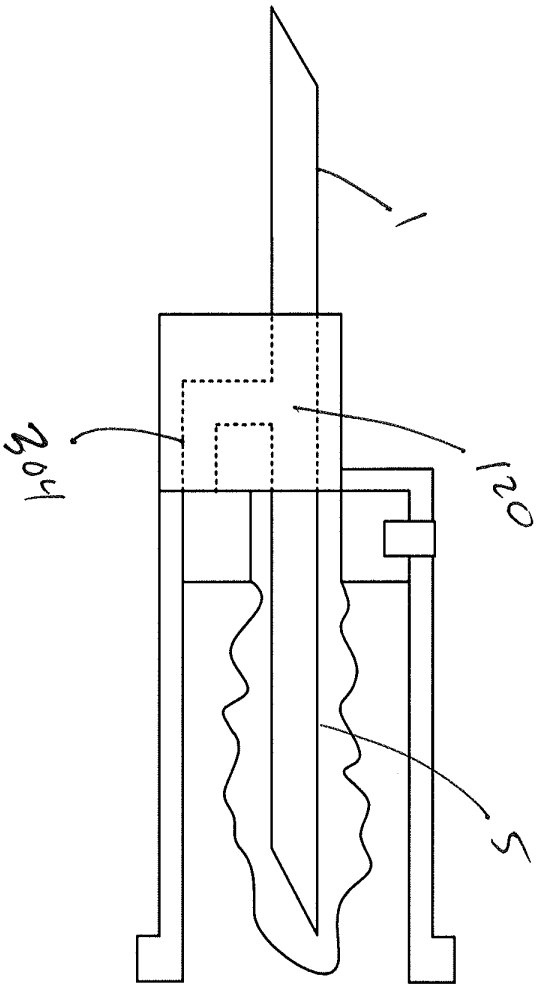


FIG. 6



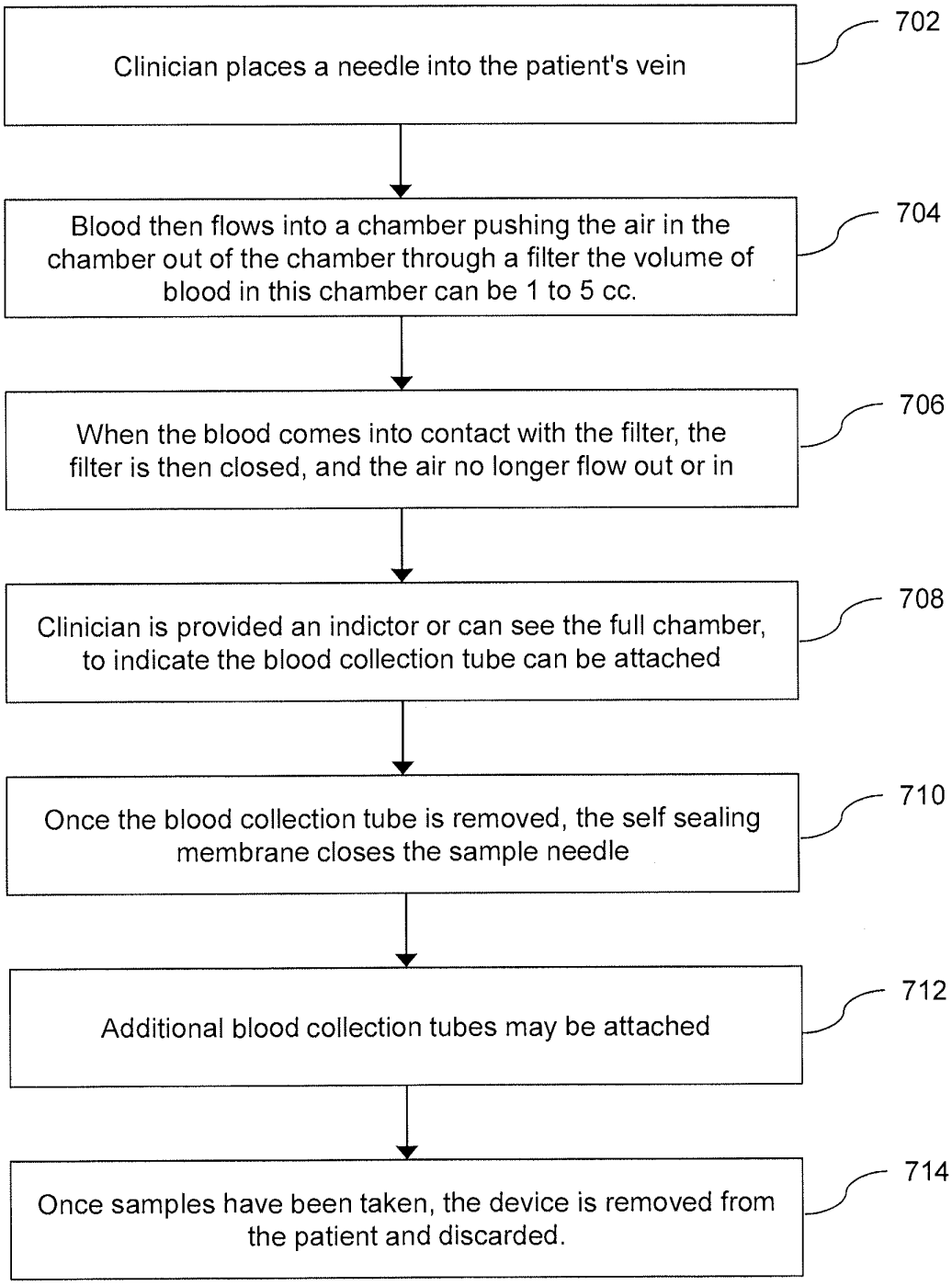
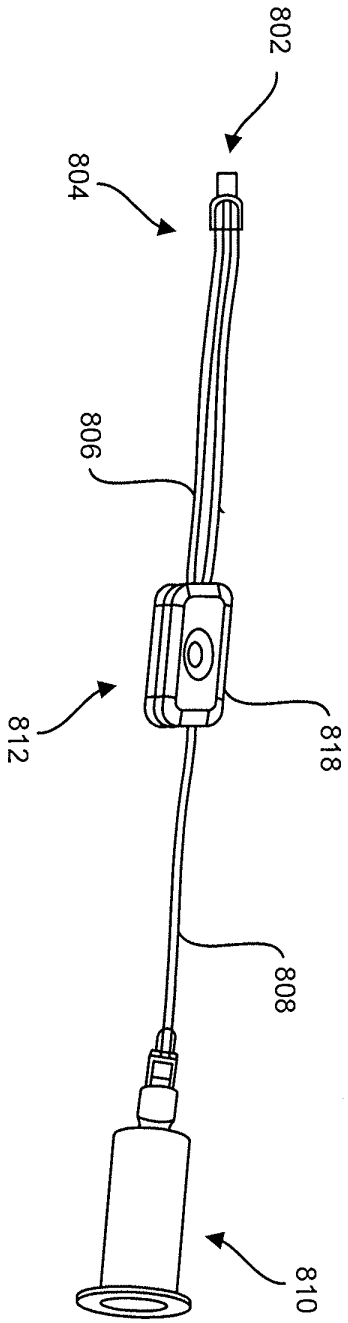

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter, the filter is then closed, and the air 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



800

FIG. 8A

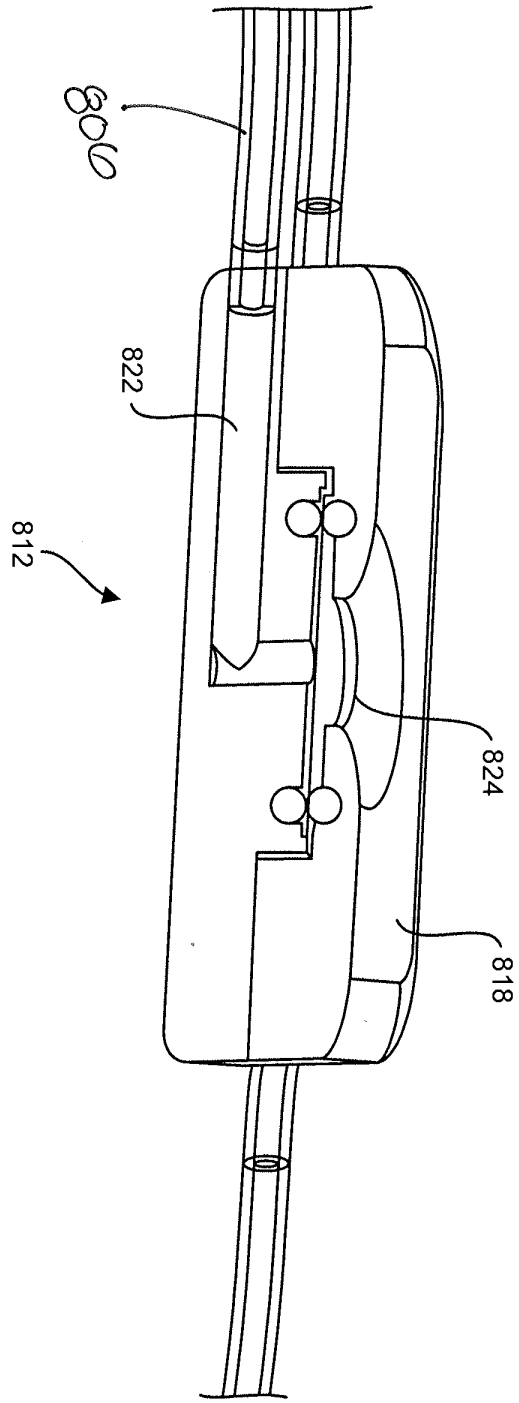


FIG. 8B

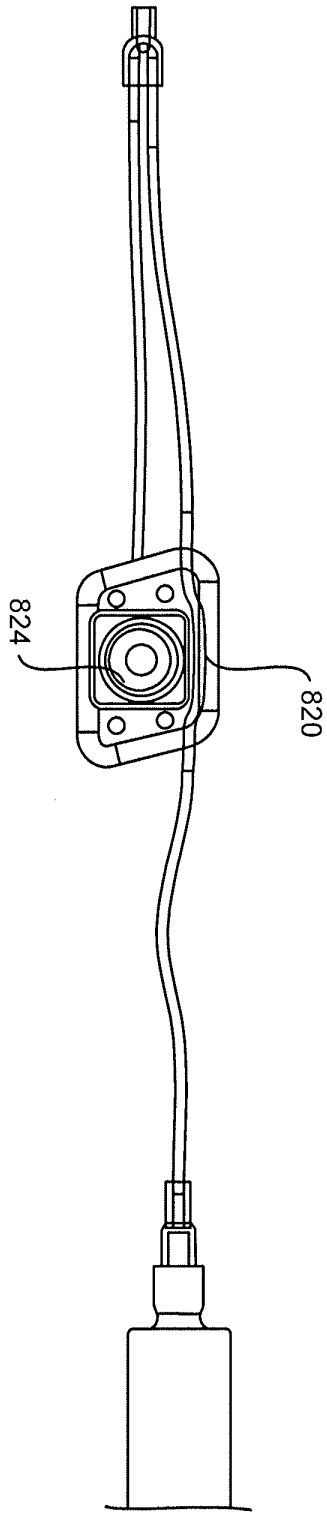
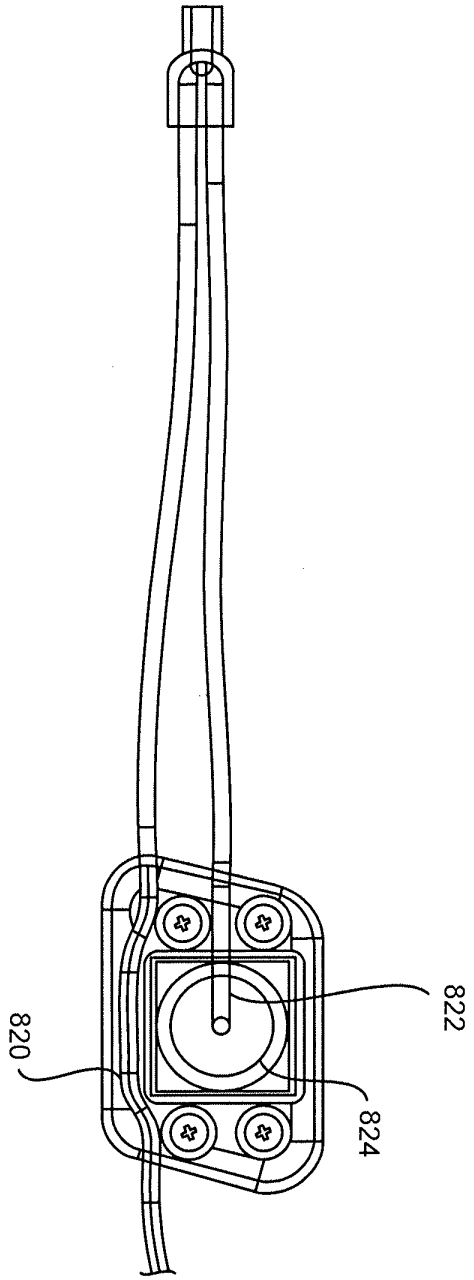


FIG. 8C

FIG. 8D



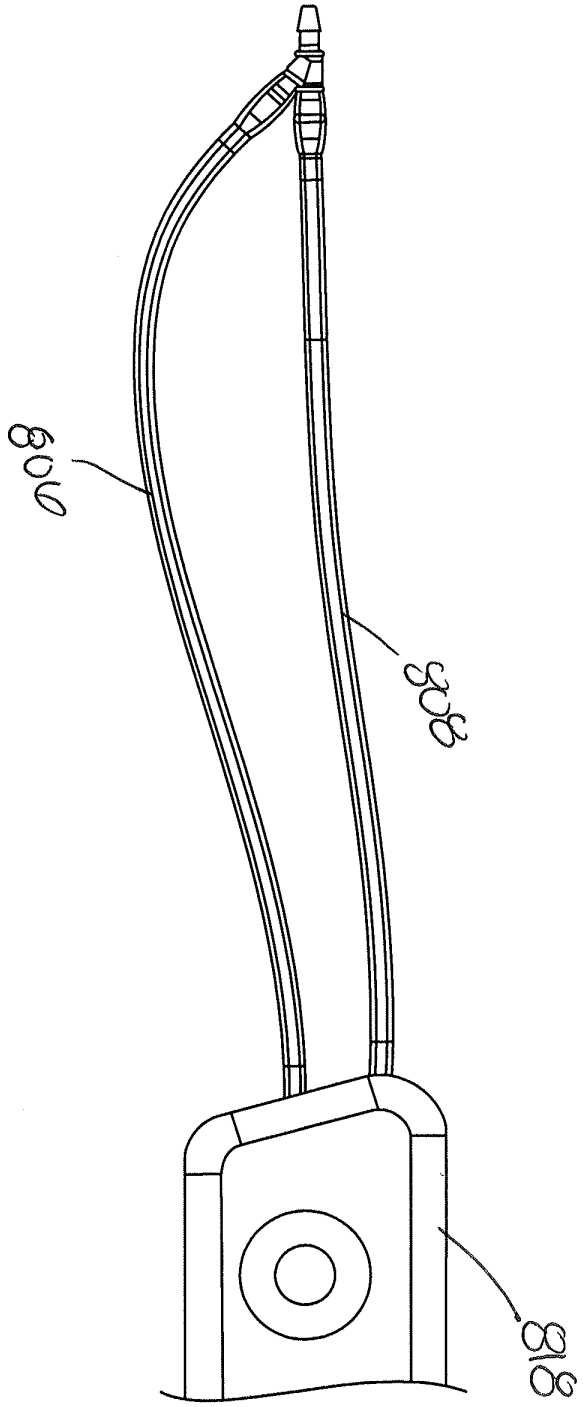
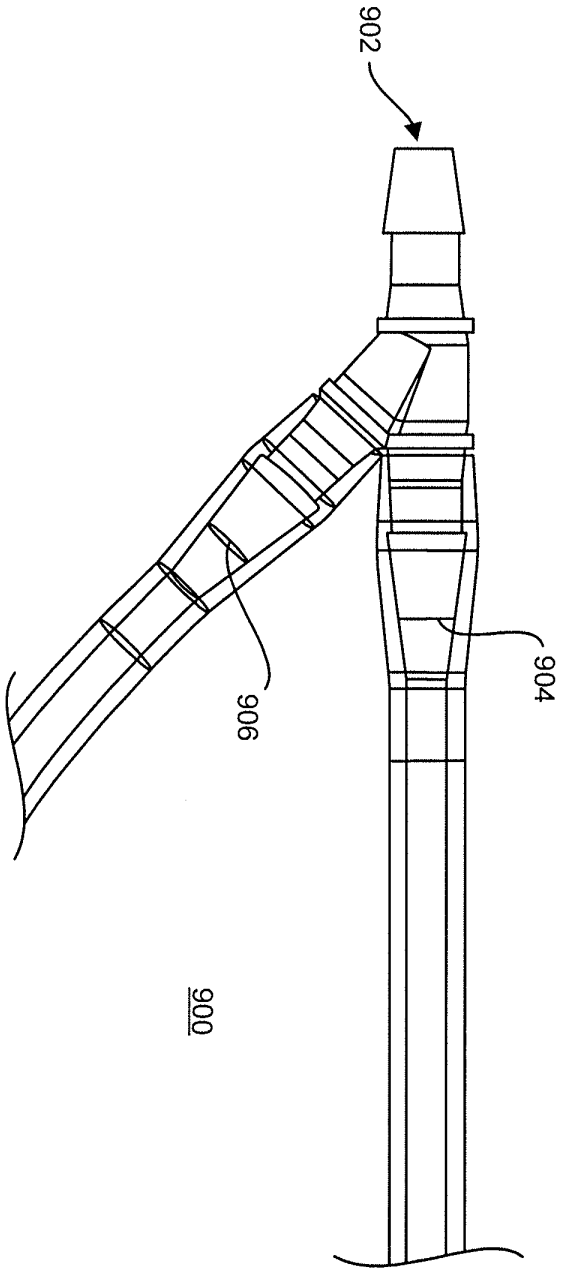


FIG. 8E

FIG. 9



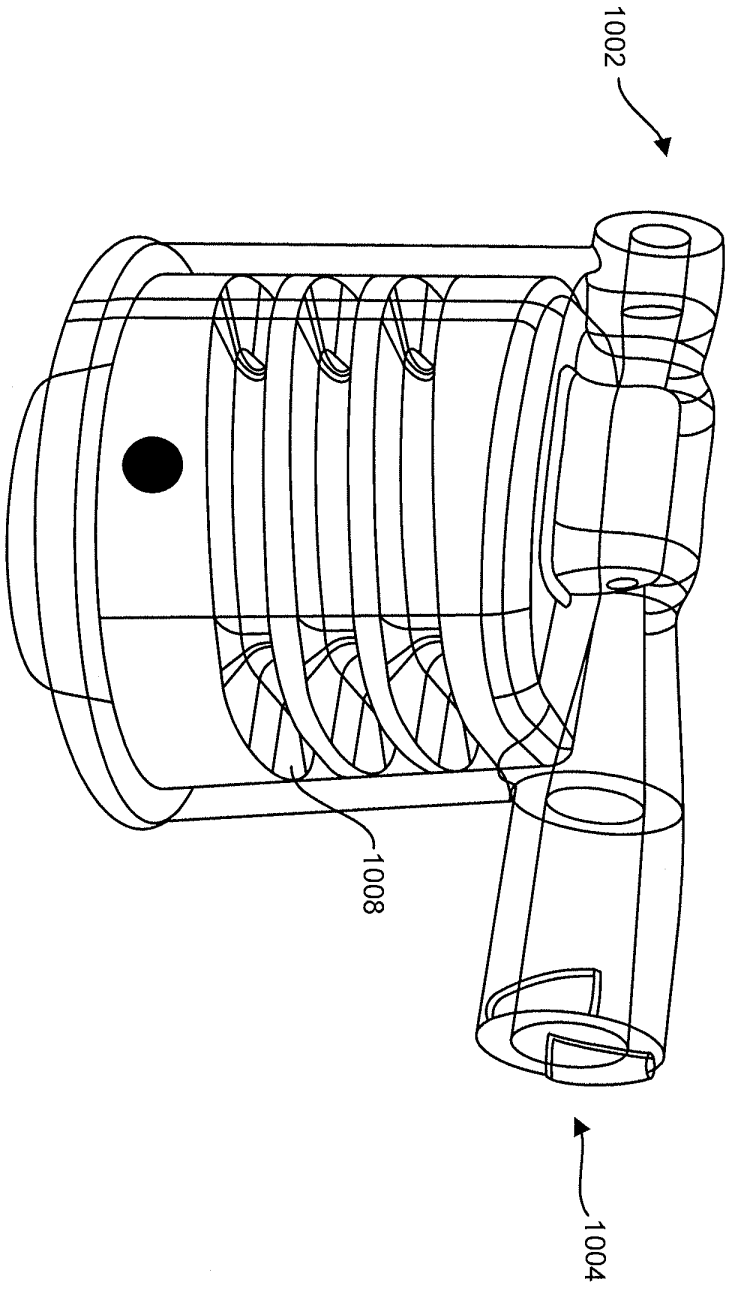


FIG. 10A

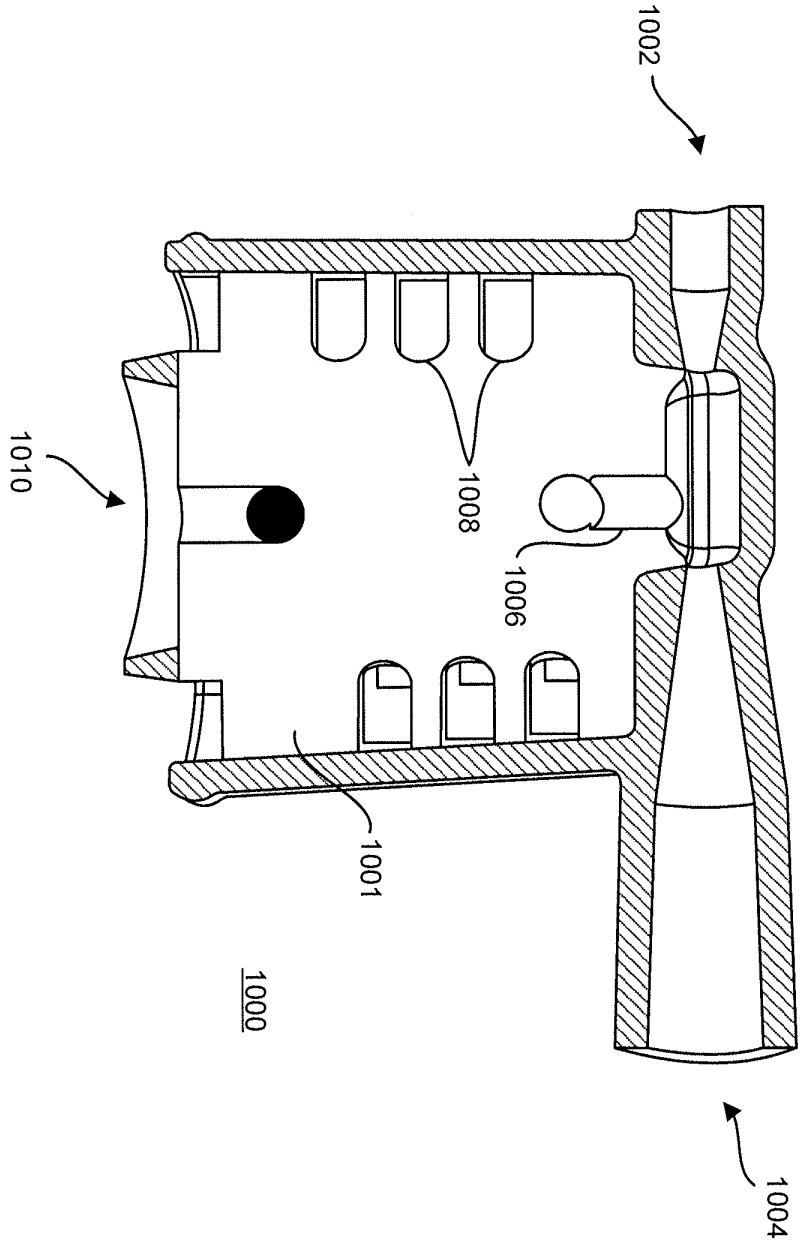


FIG. 10B

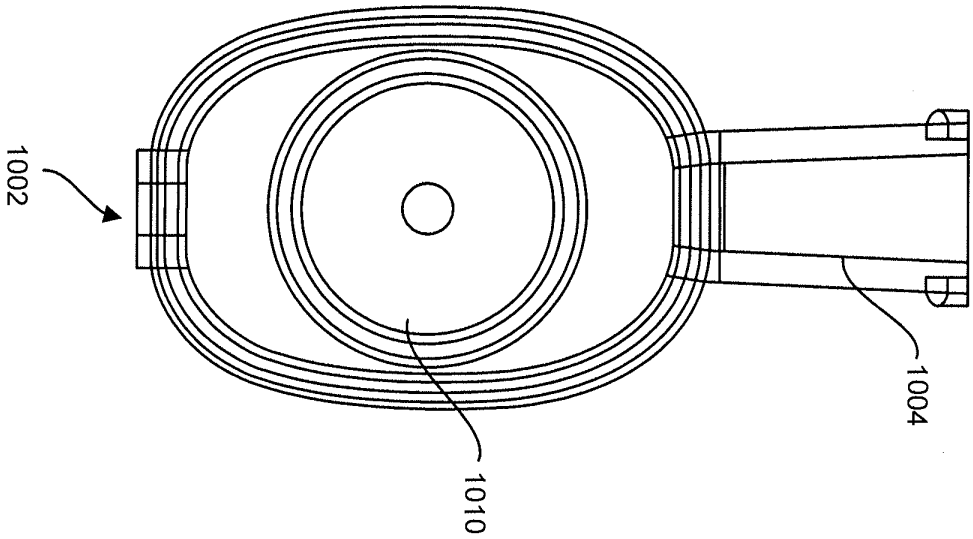
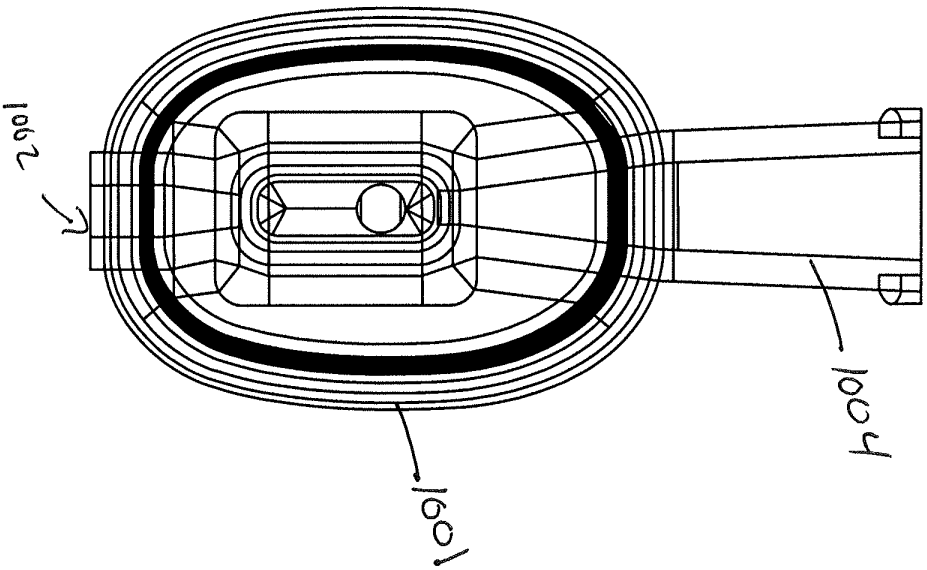


FIG. 10C

FIG. 10D



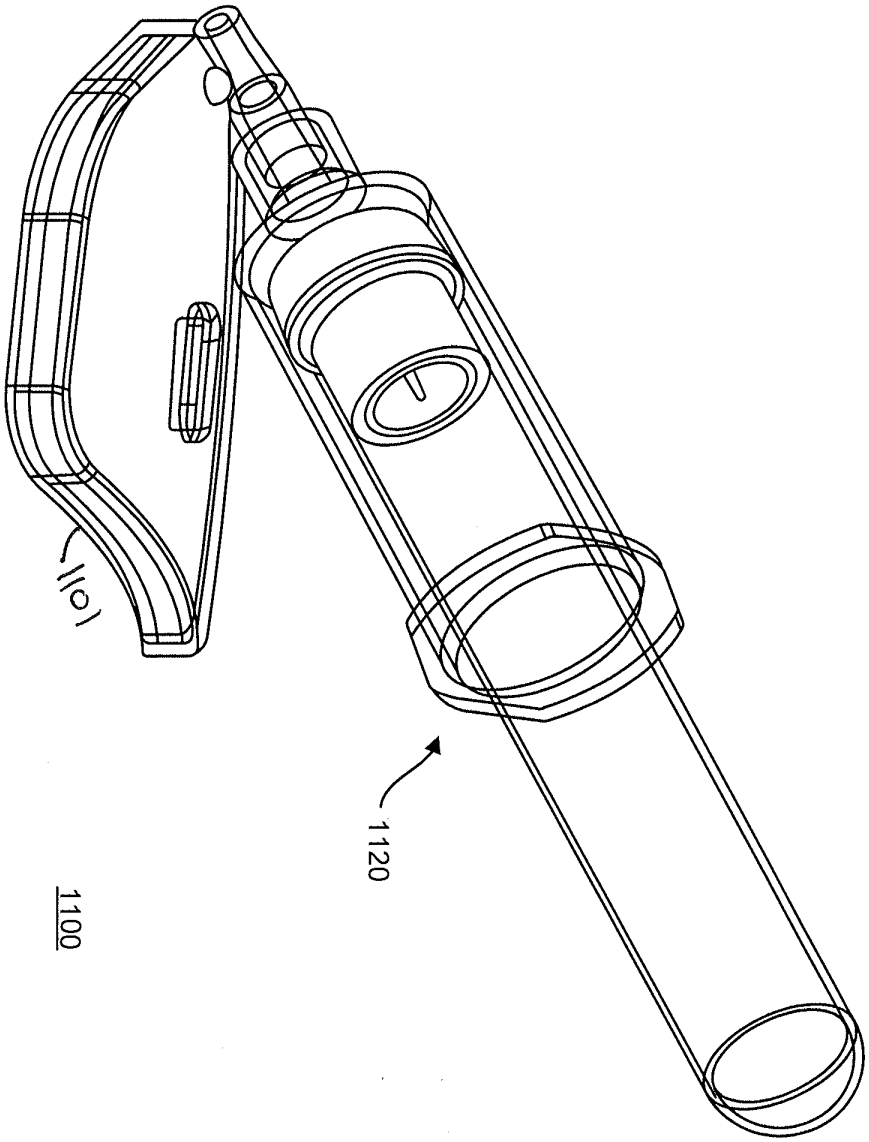


FIG. 11A

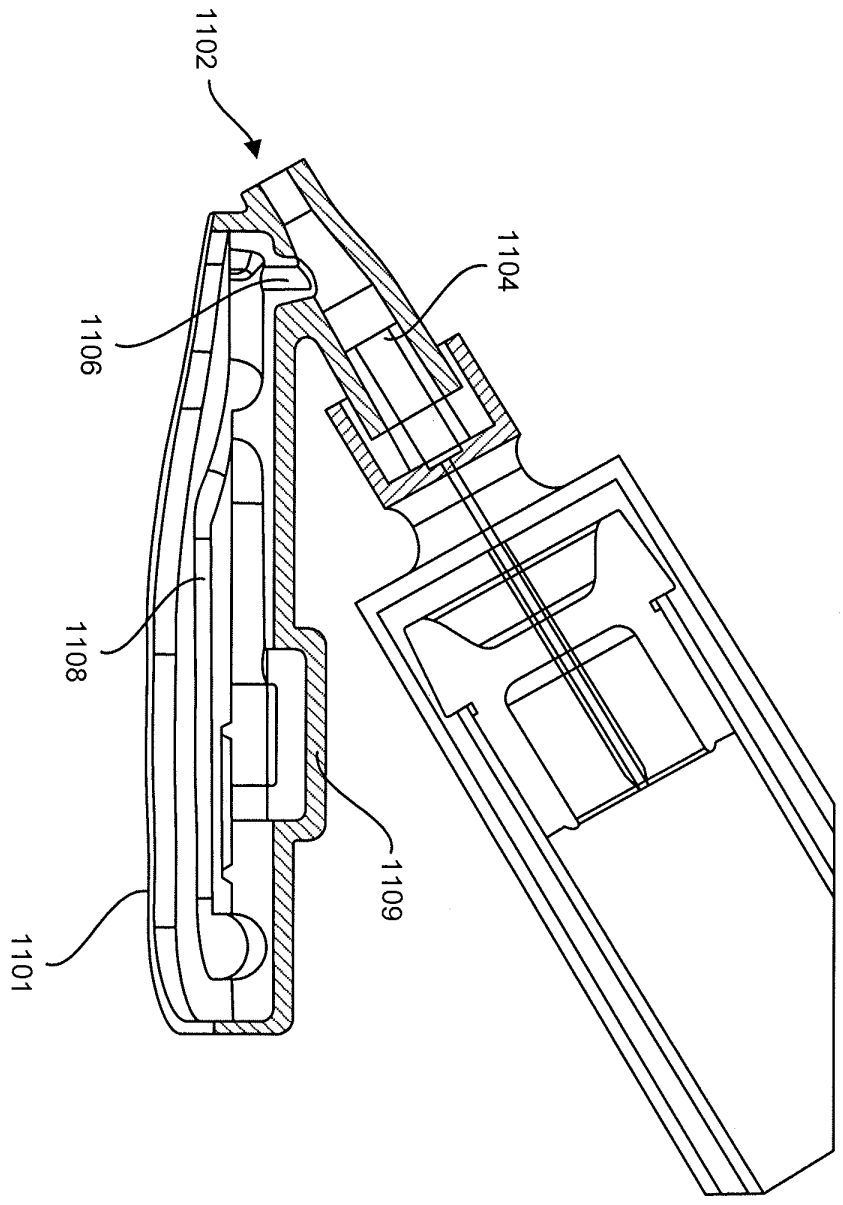


FIG. 11B

FIG. 11C

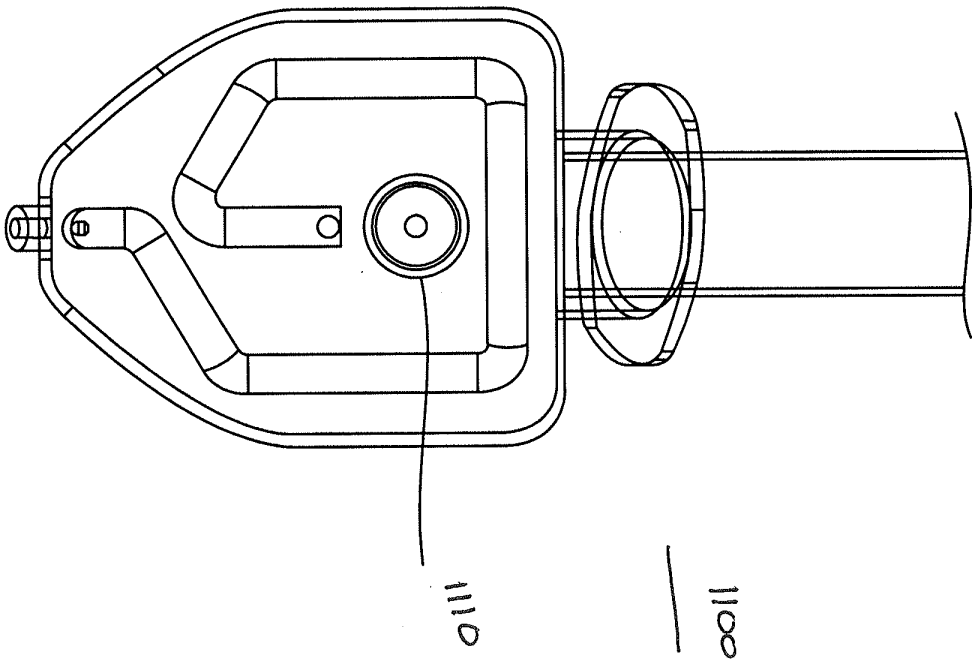


FIG. 11D

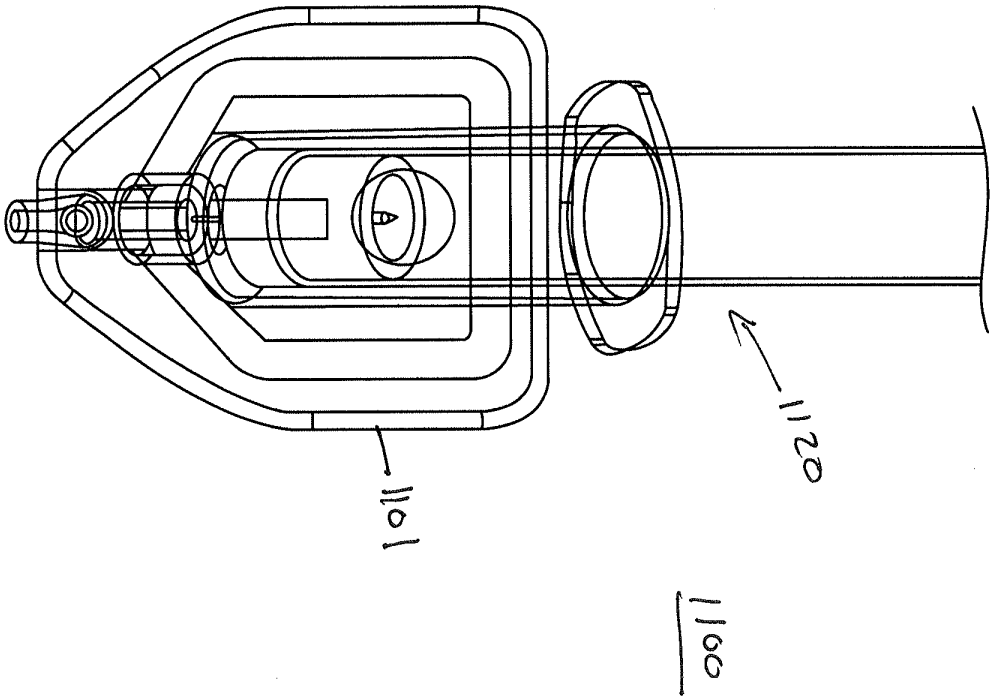
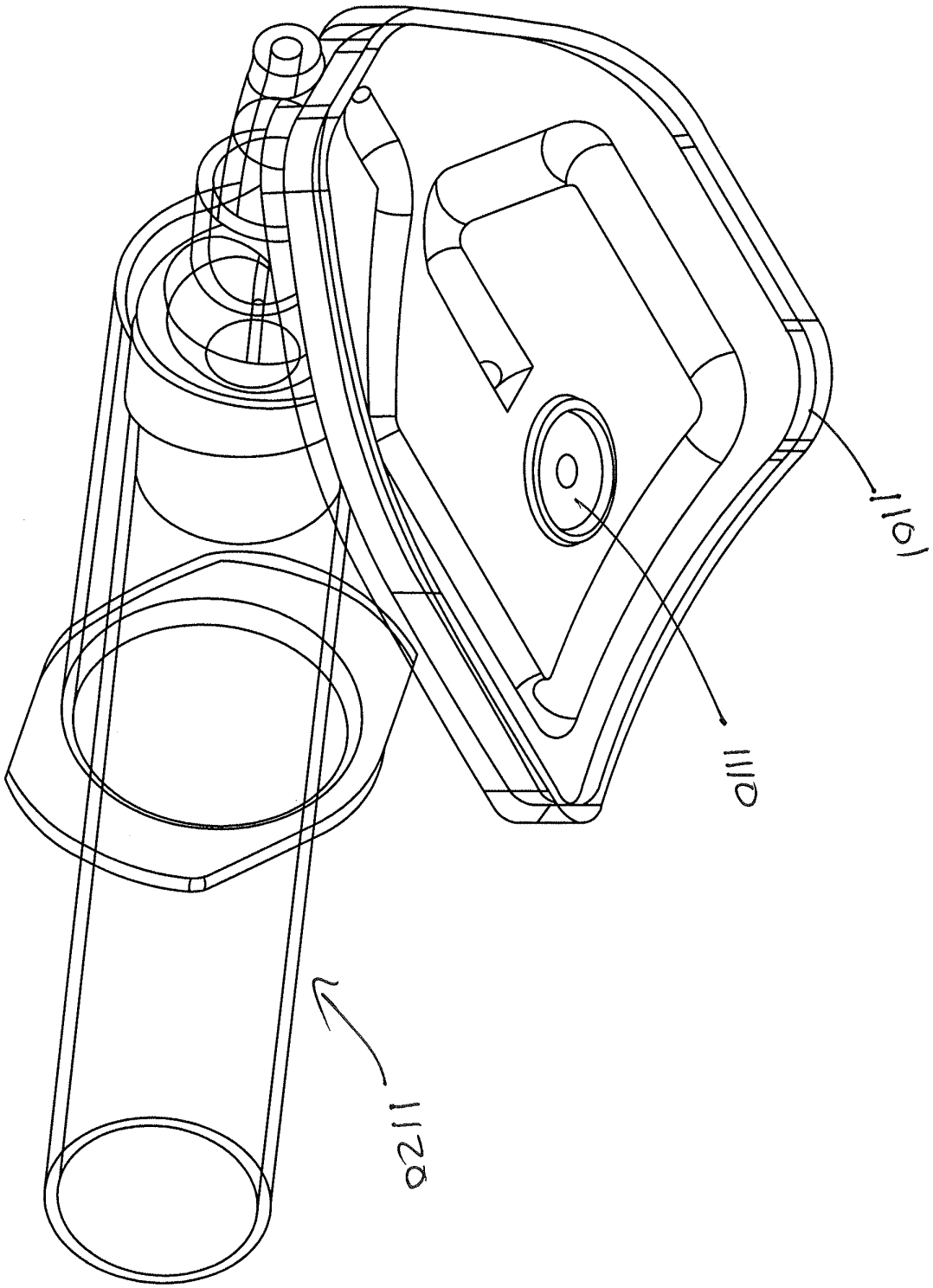


FIG. 11E



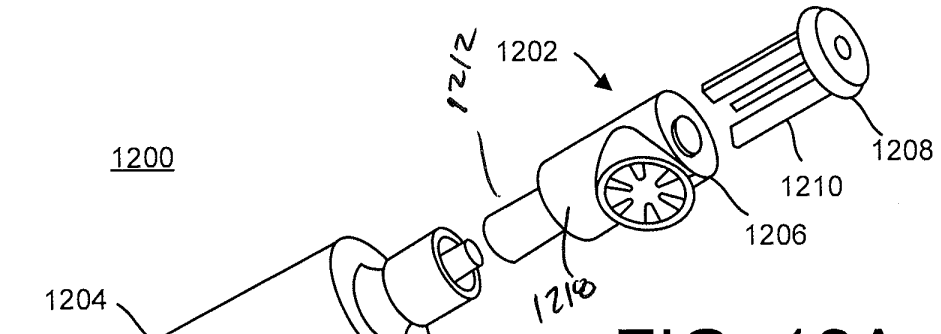


FIG. 12A

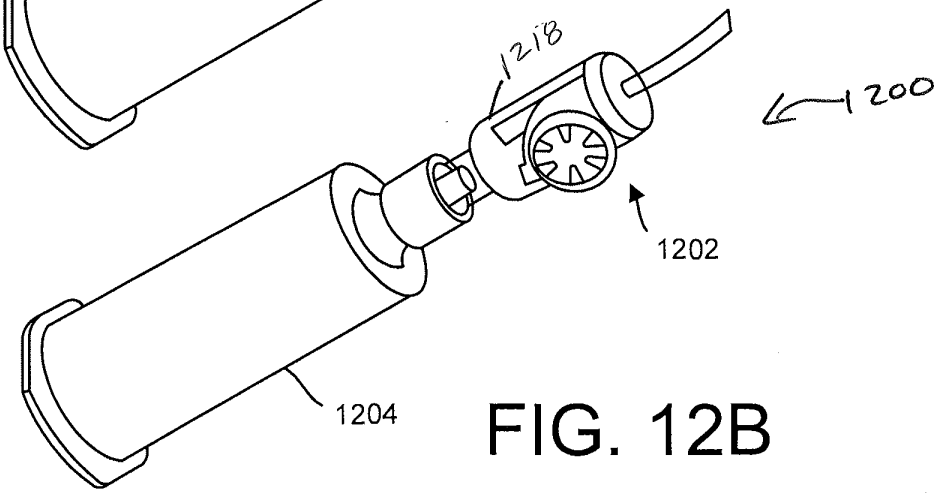


FIG. 12B

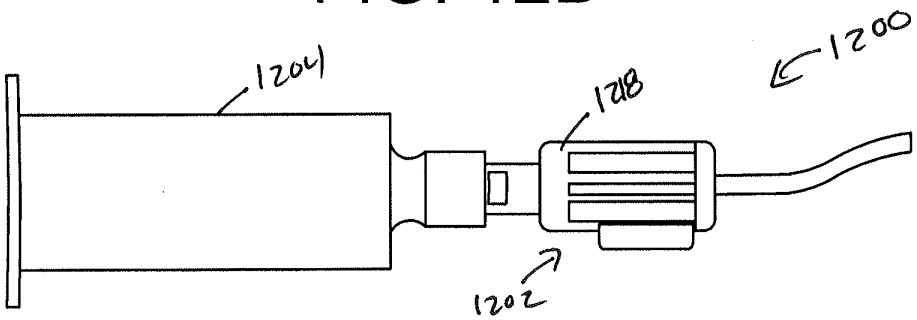


FIG. 12C

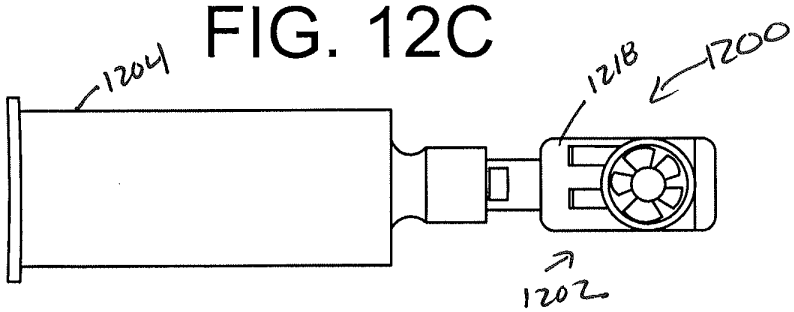


FIG. 12D

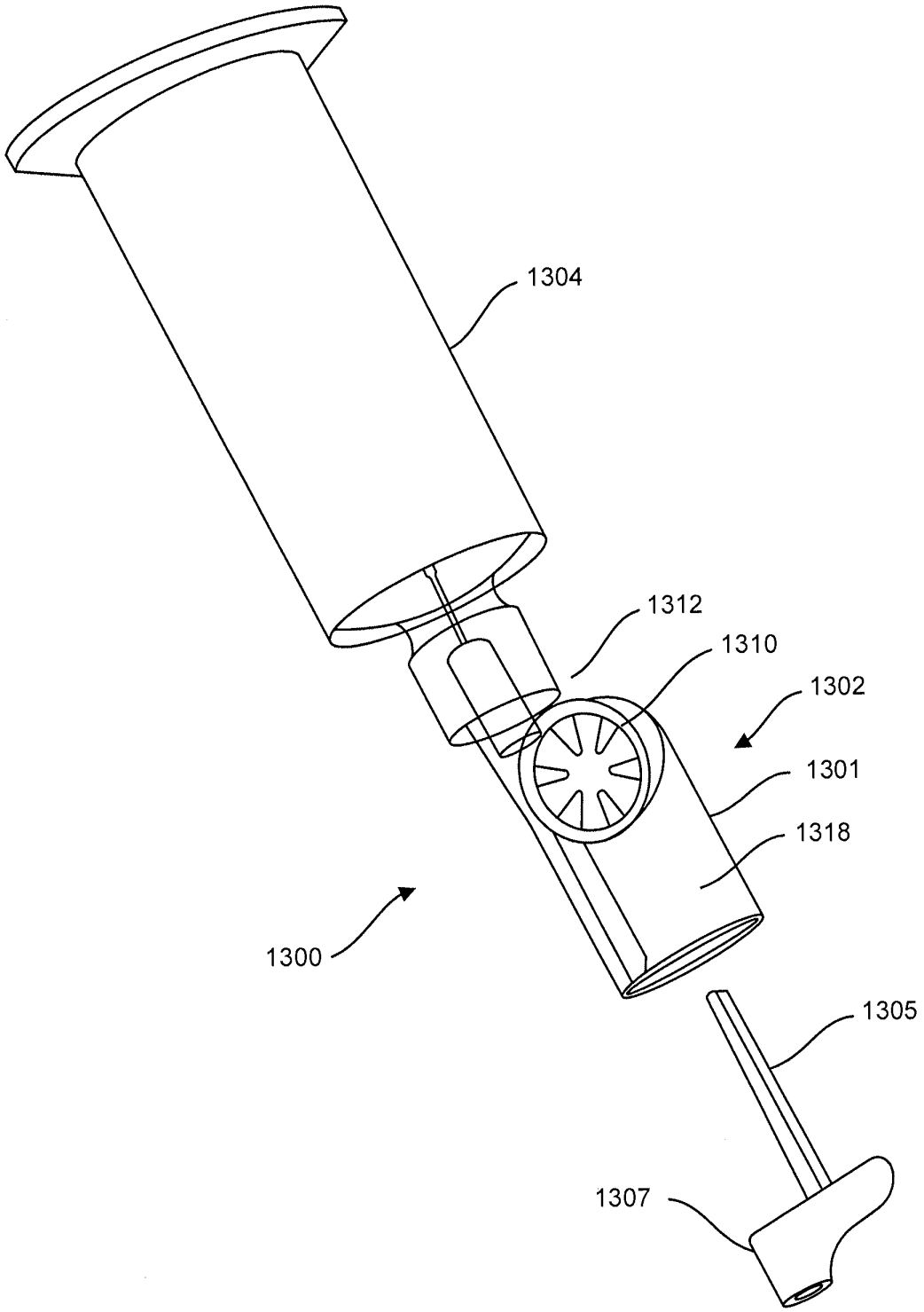


FIG. 13A

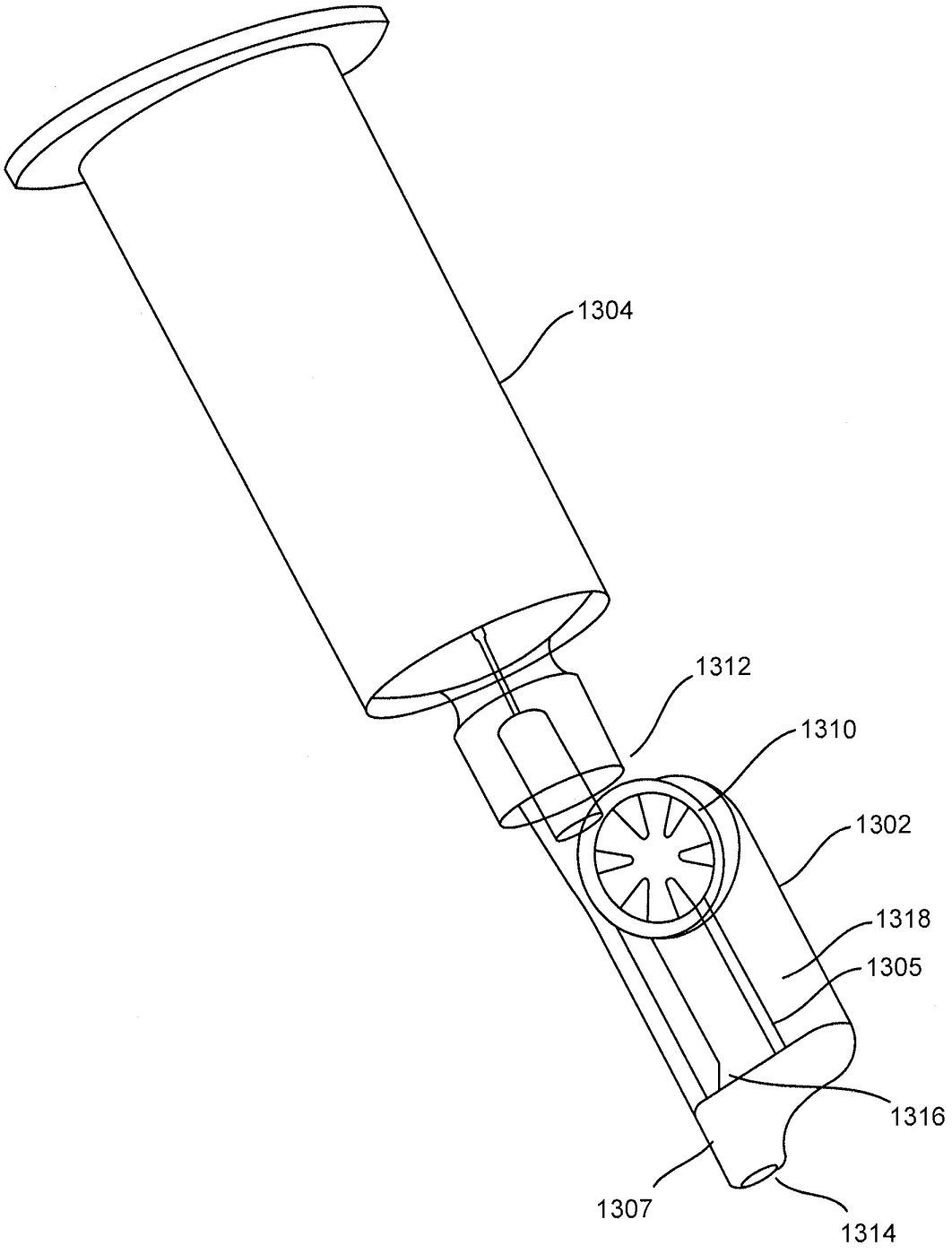


FIG. 13B

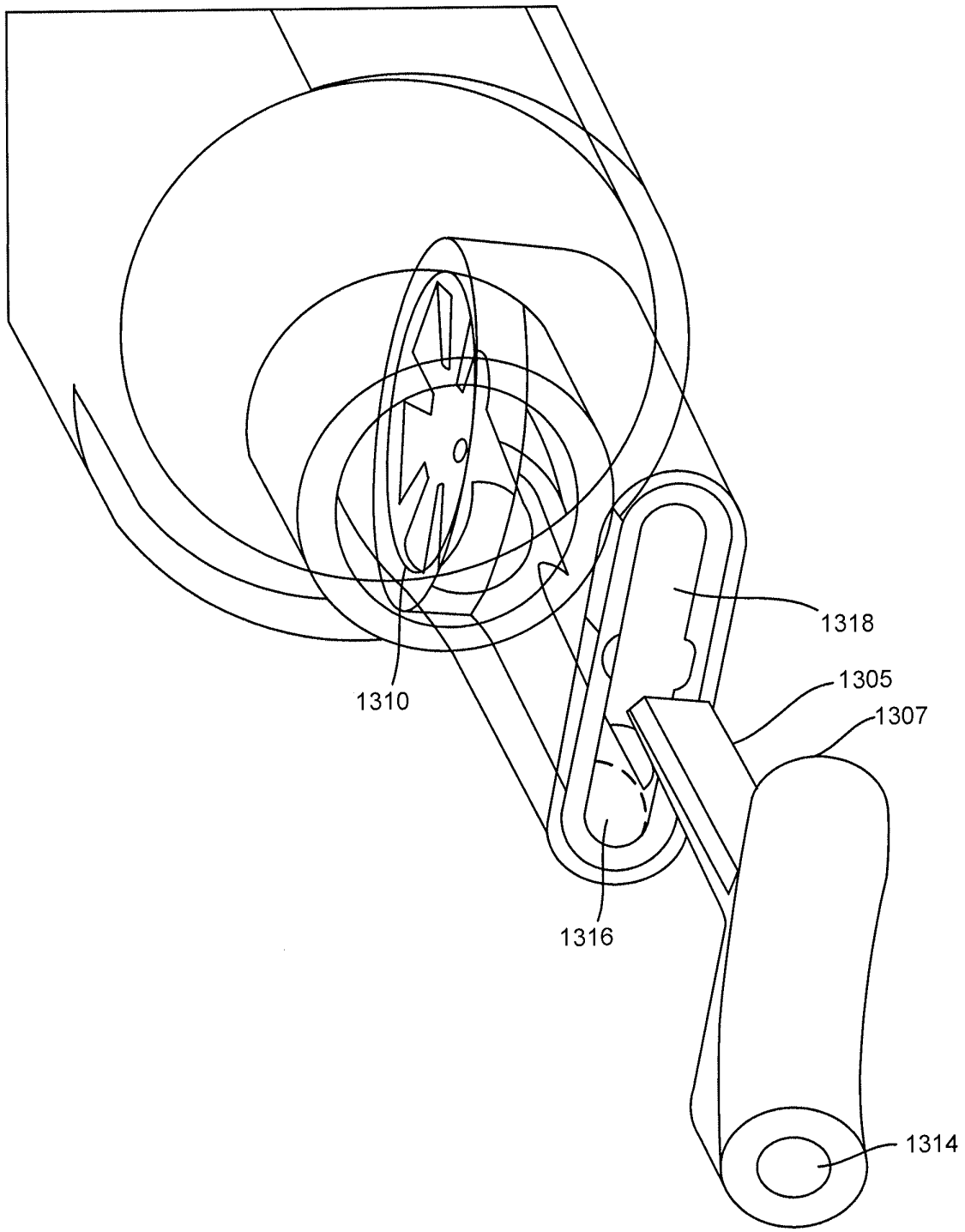


FIG. 13C

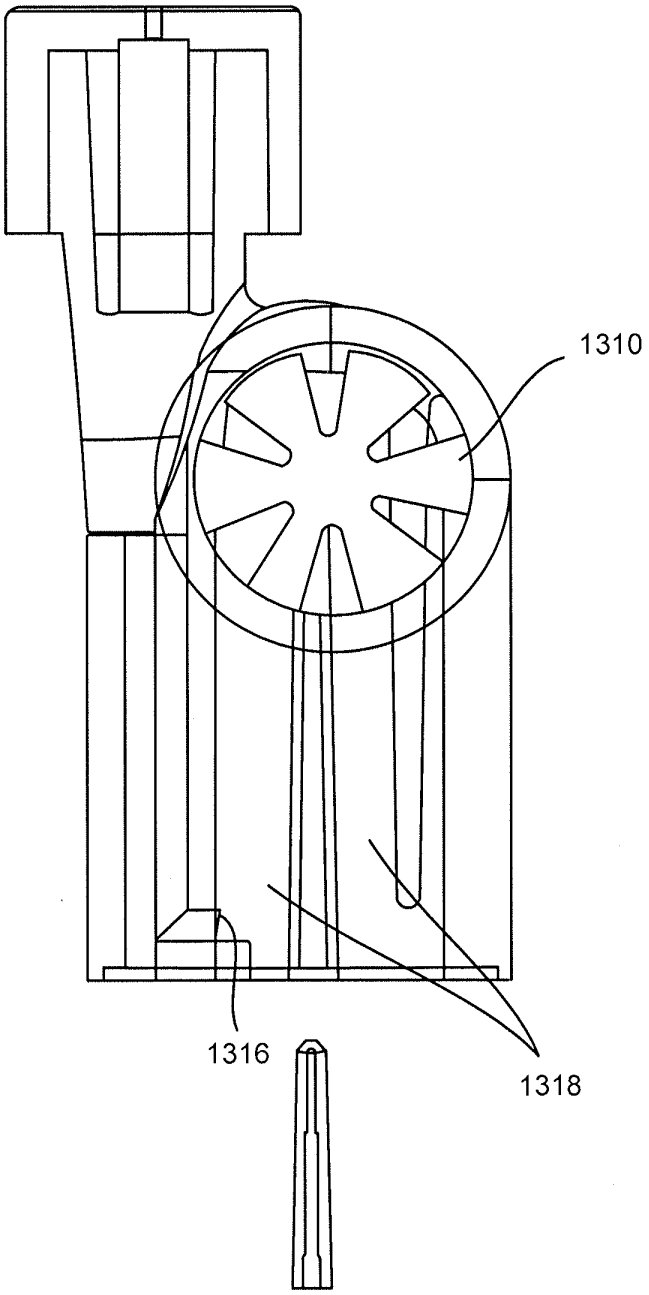


FIG. 13D

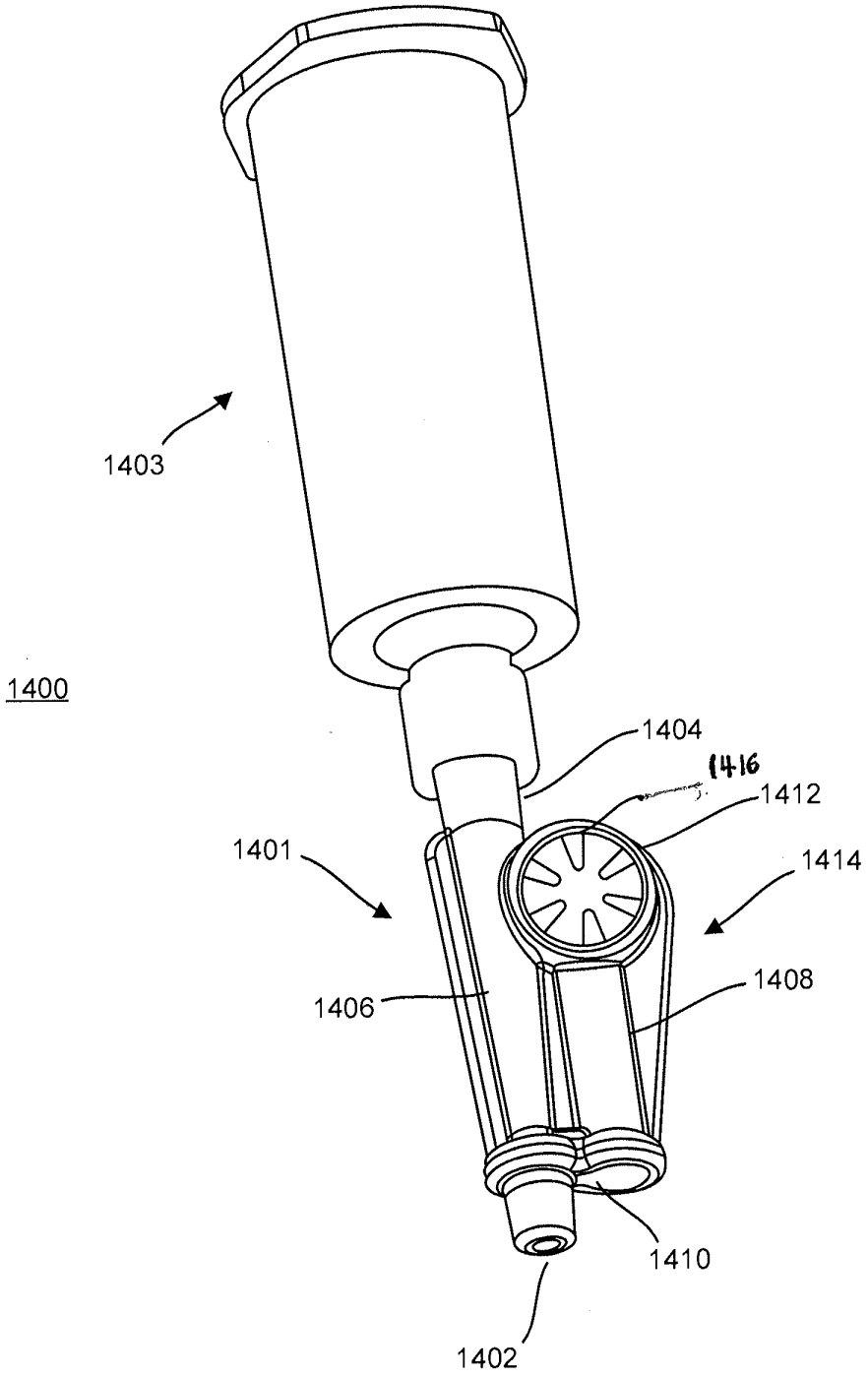


FIG. 14A

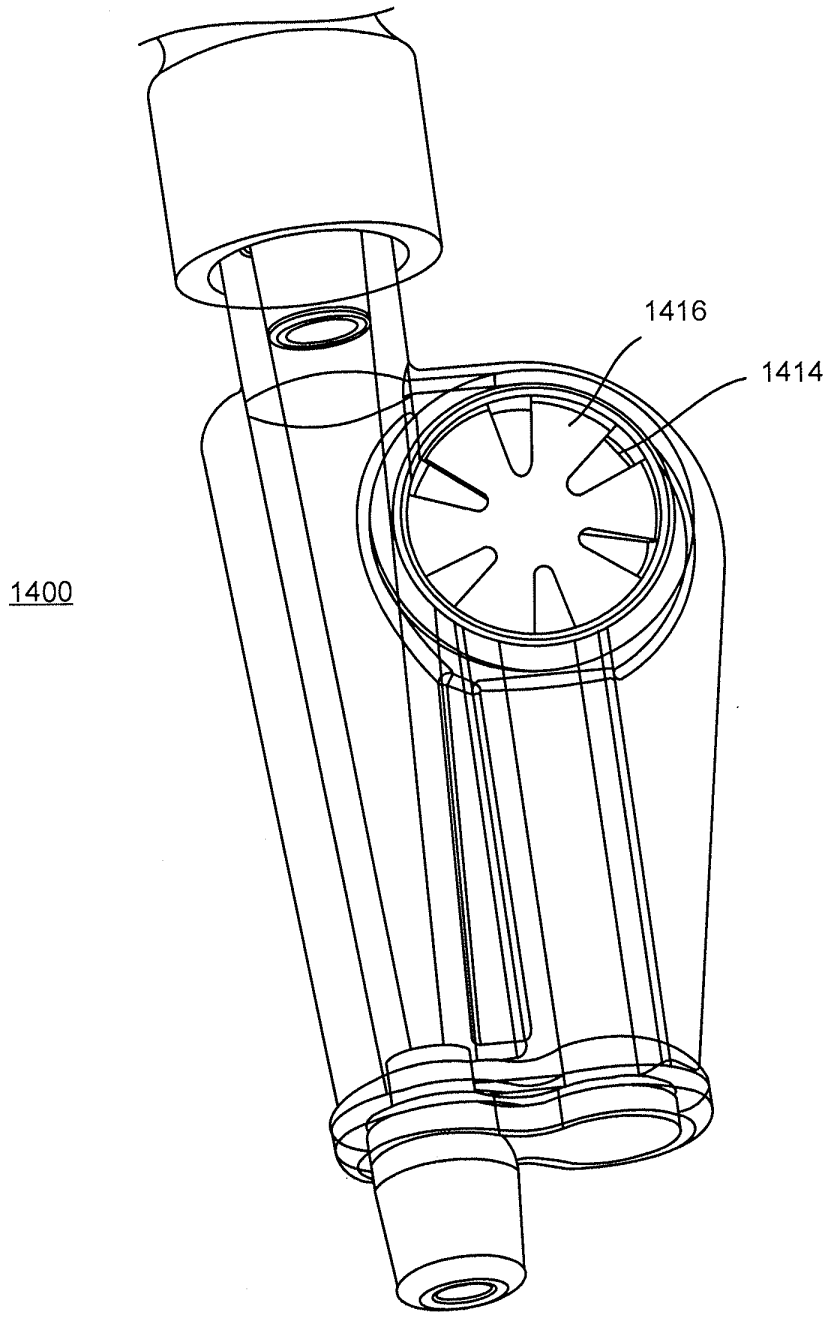


FIG. 14B

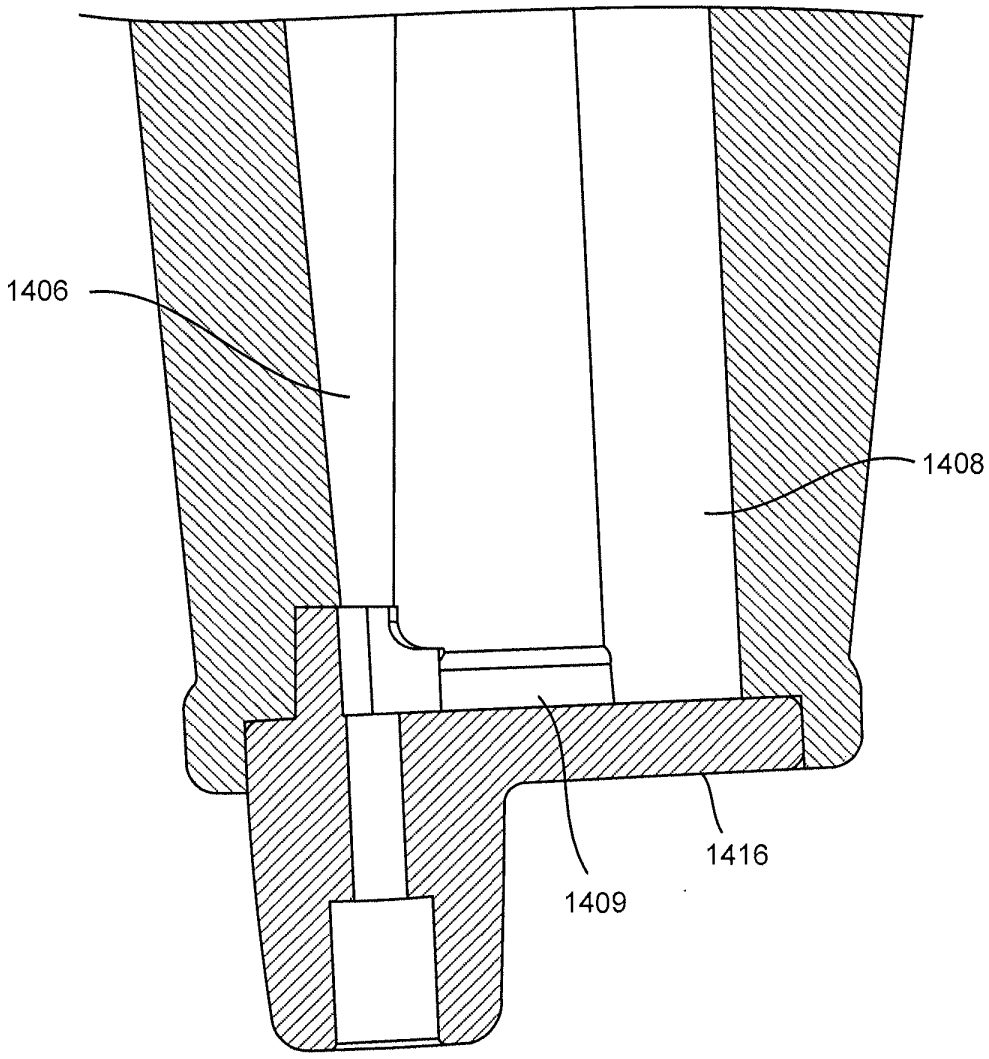


FIG. 14C

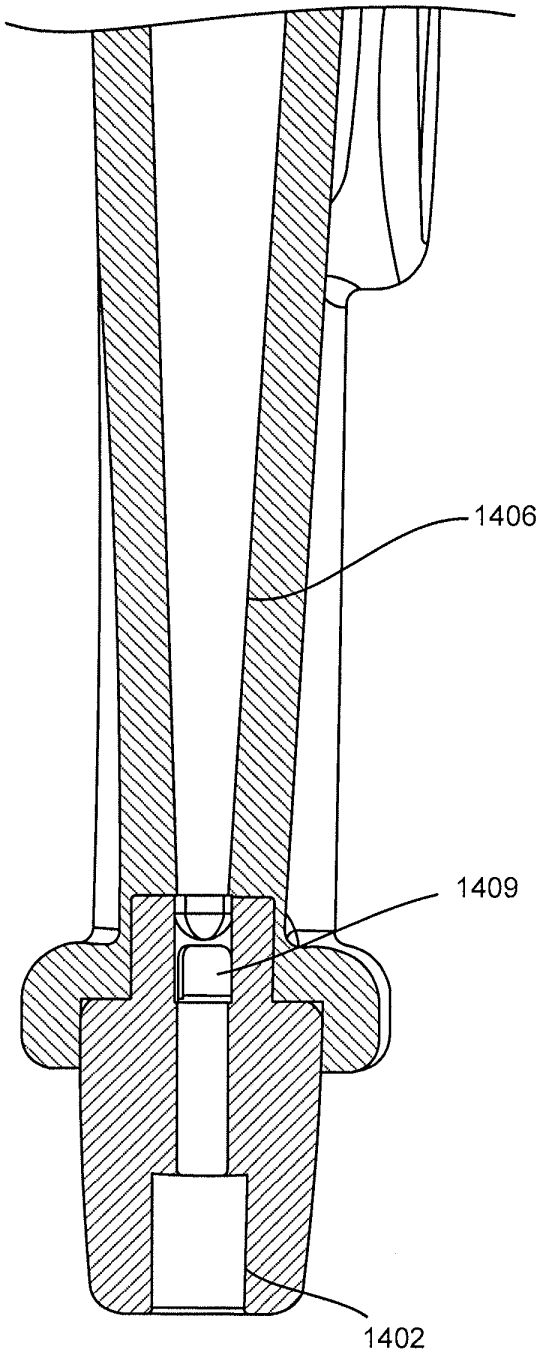


FIG. 14D

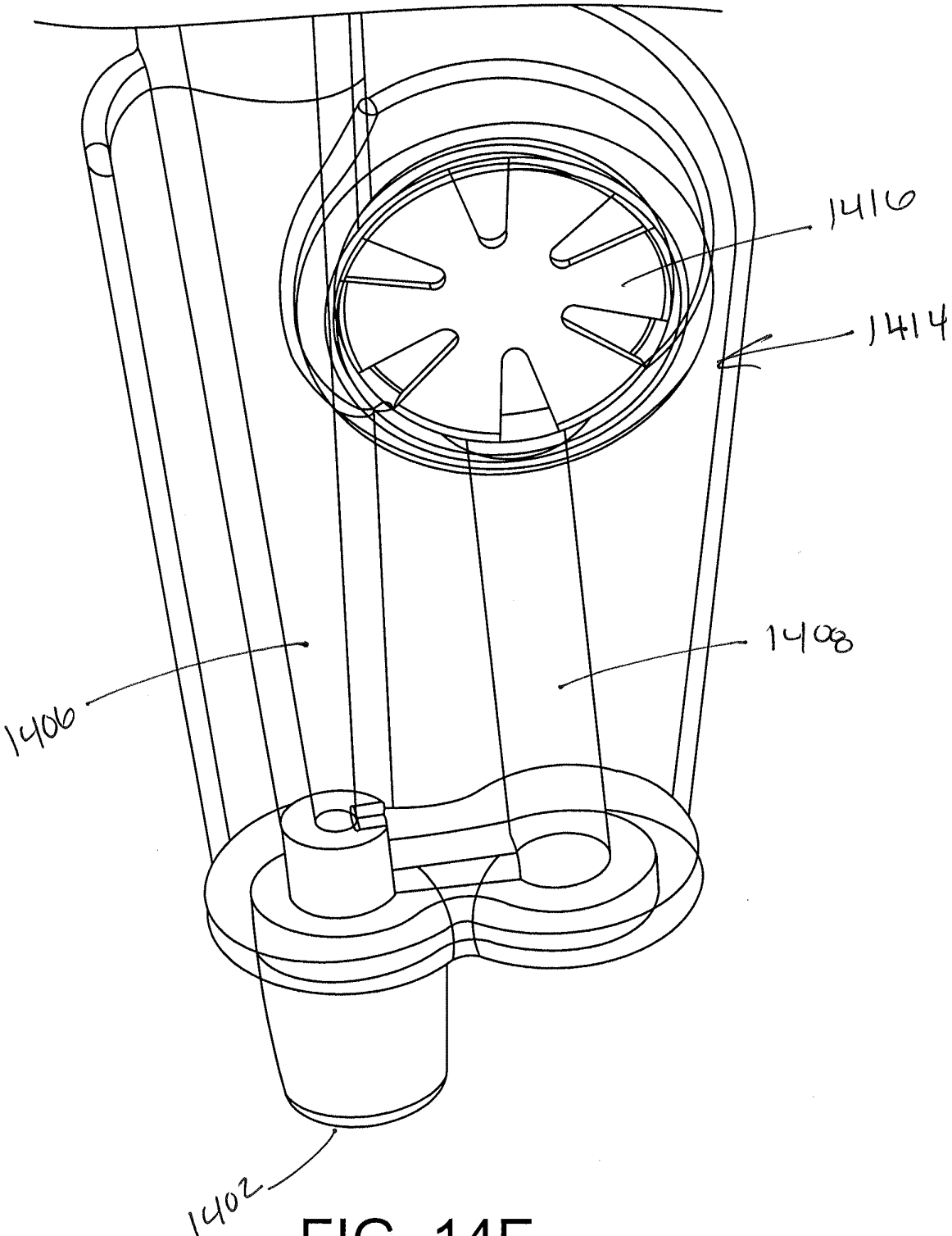


FIG. 14E

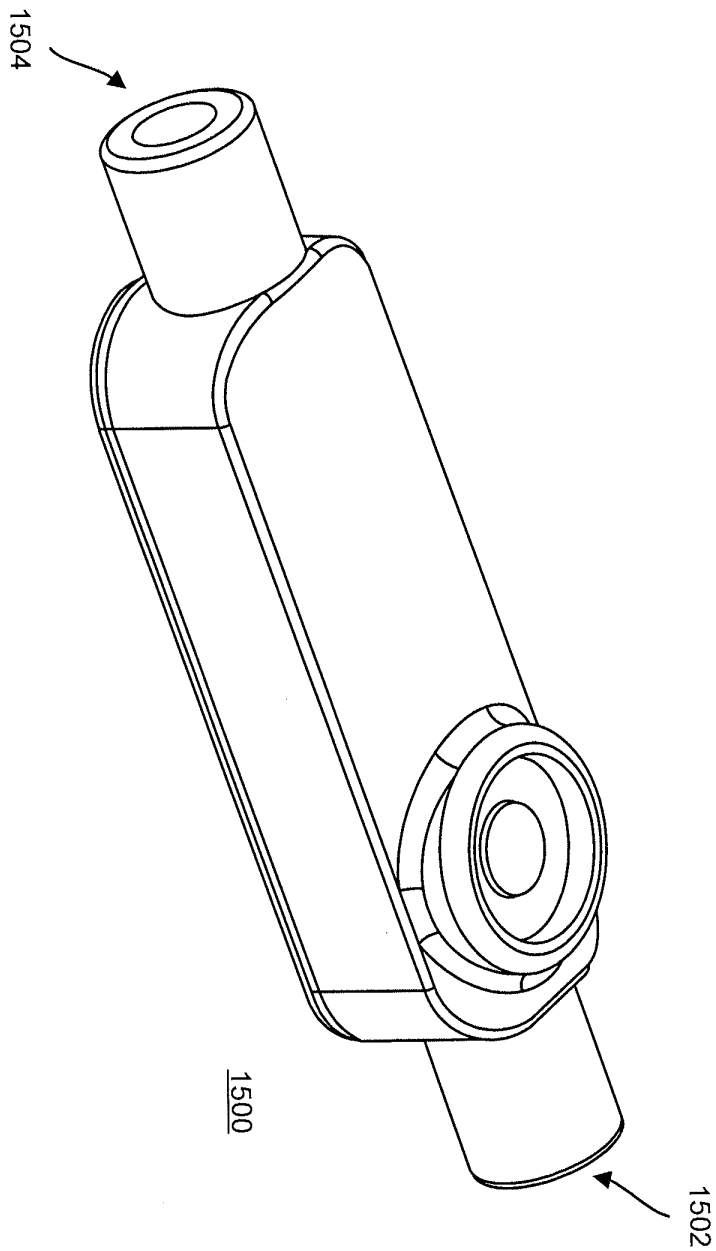


FIG. 15A

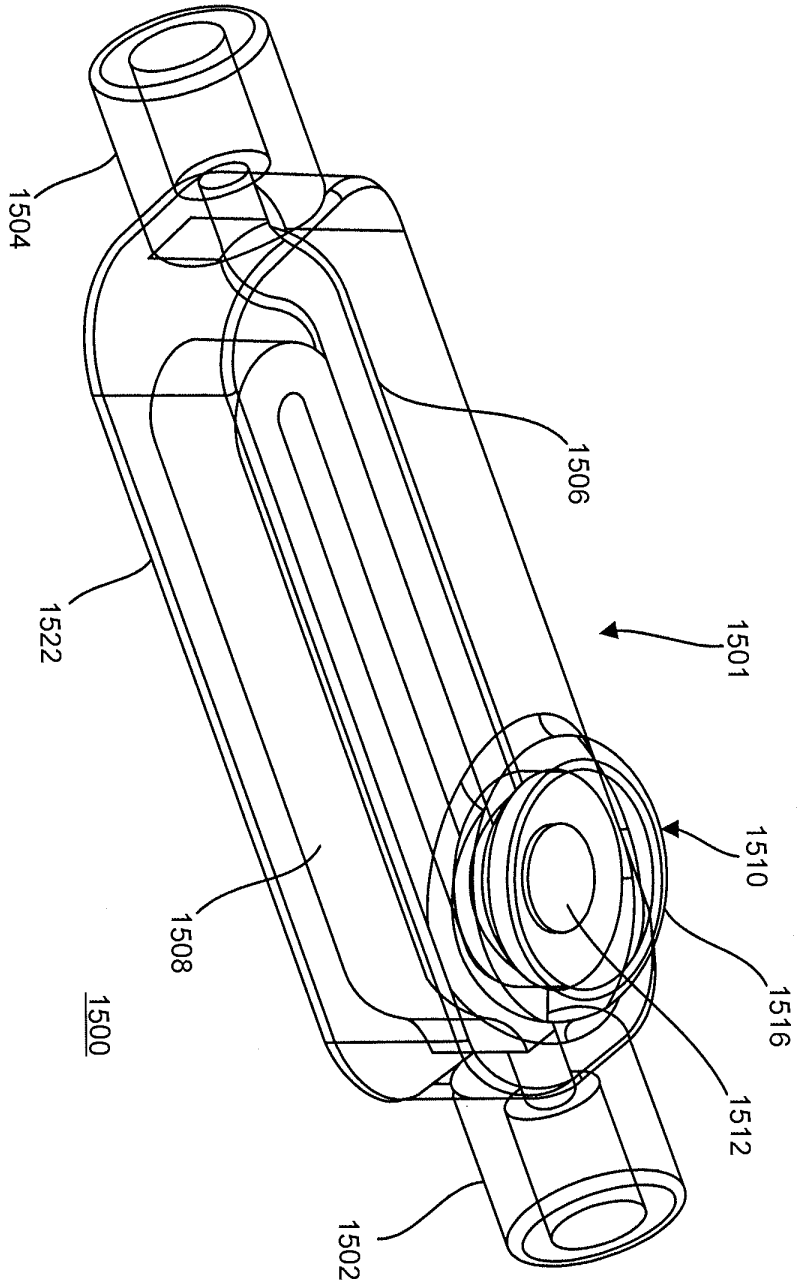


FIG. 15B

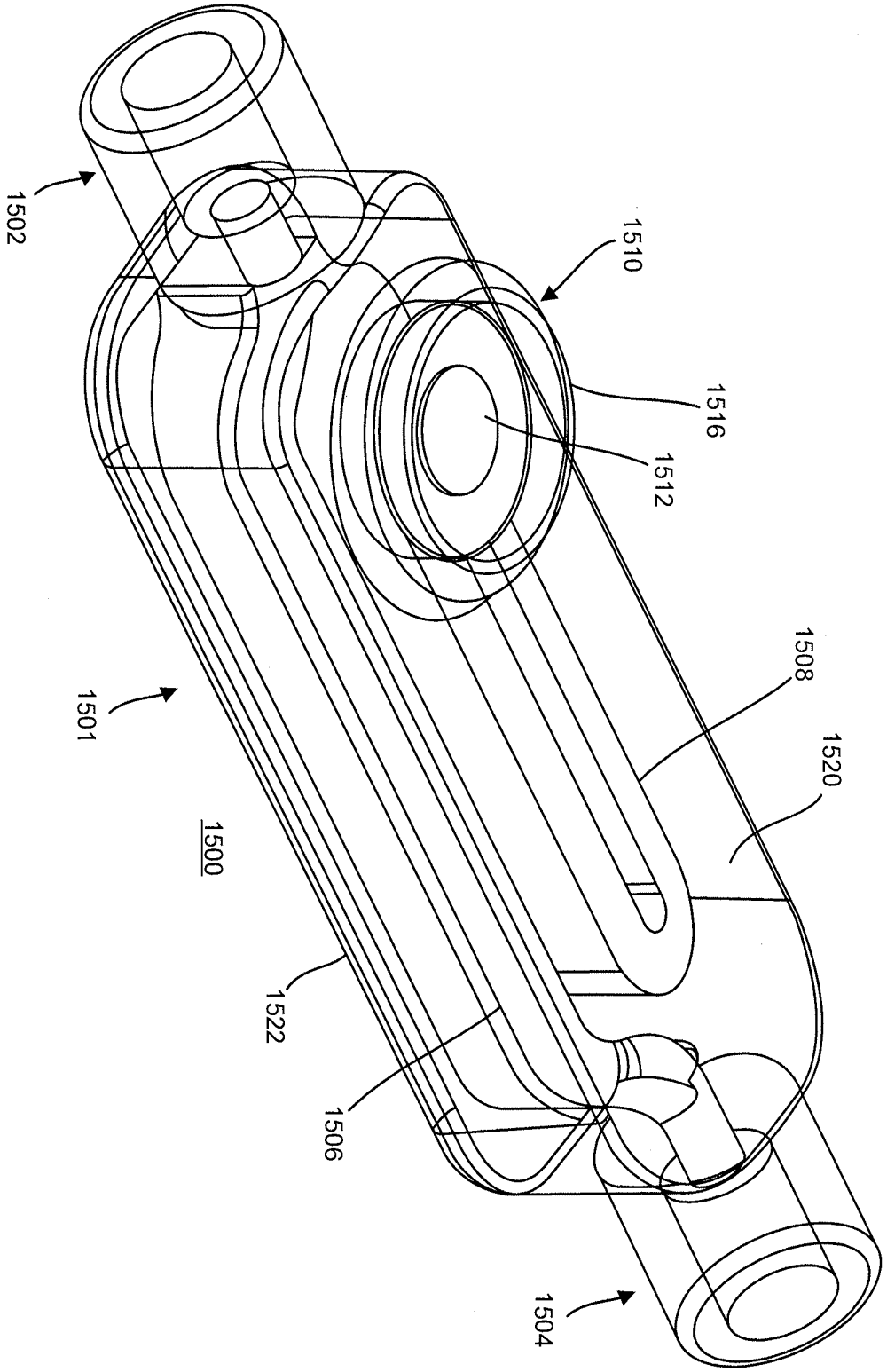


FIG. 15C

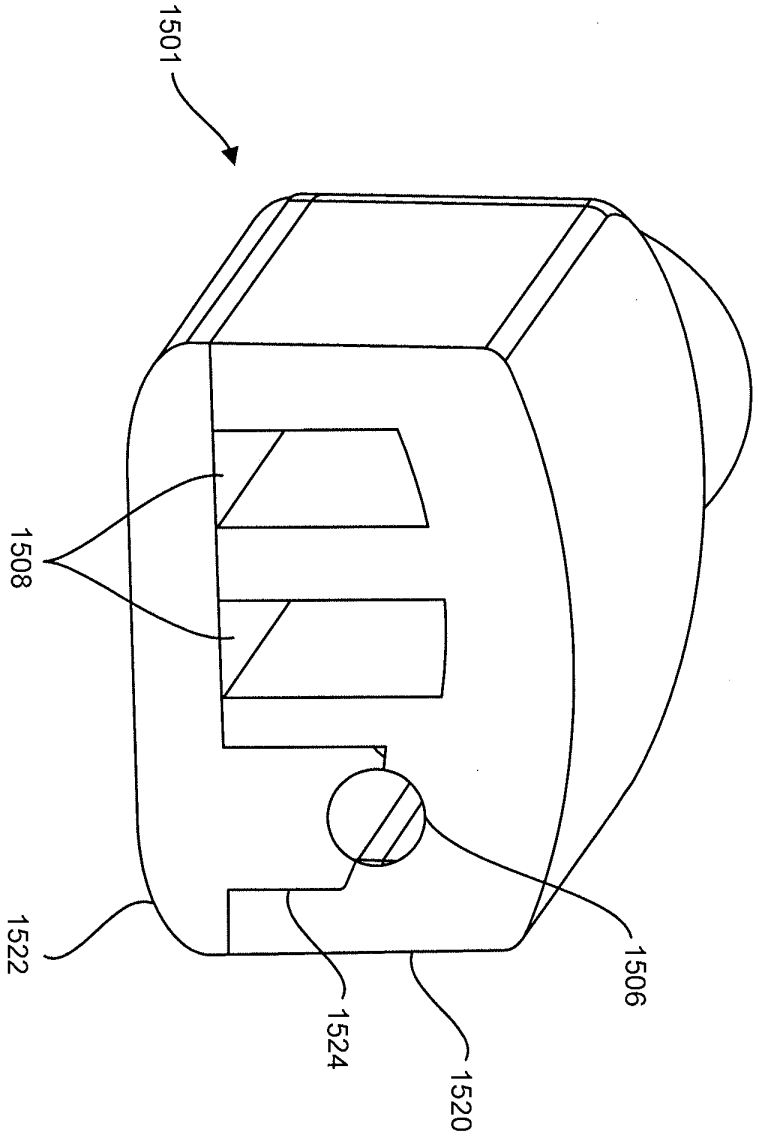


FIG. 15D

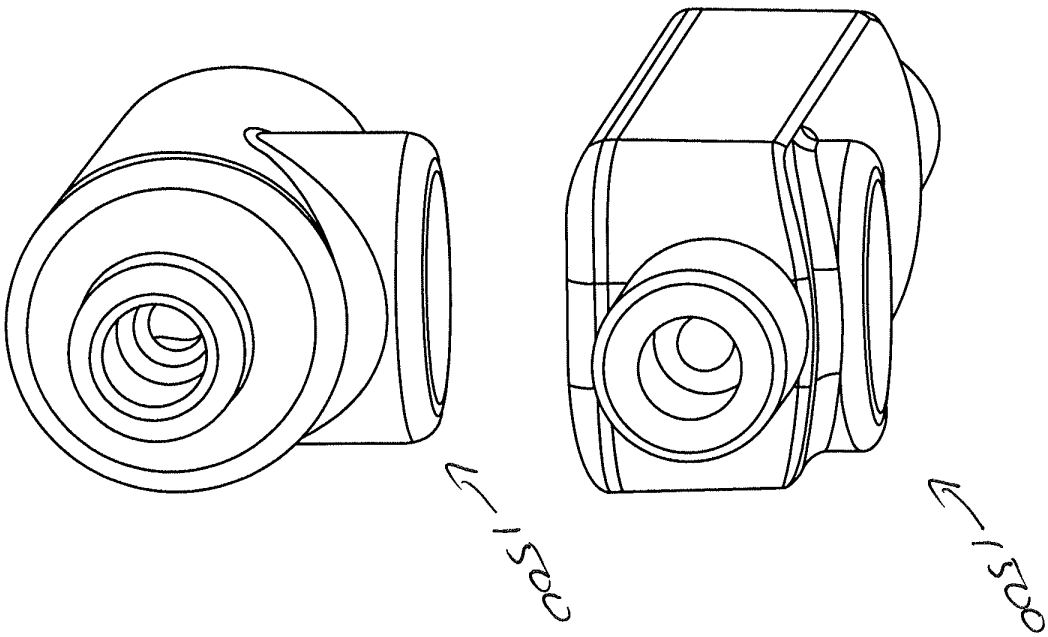


FIG. 15E

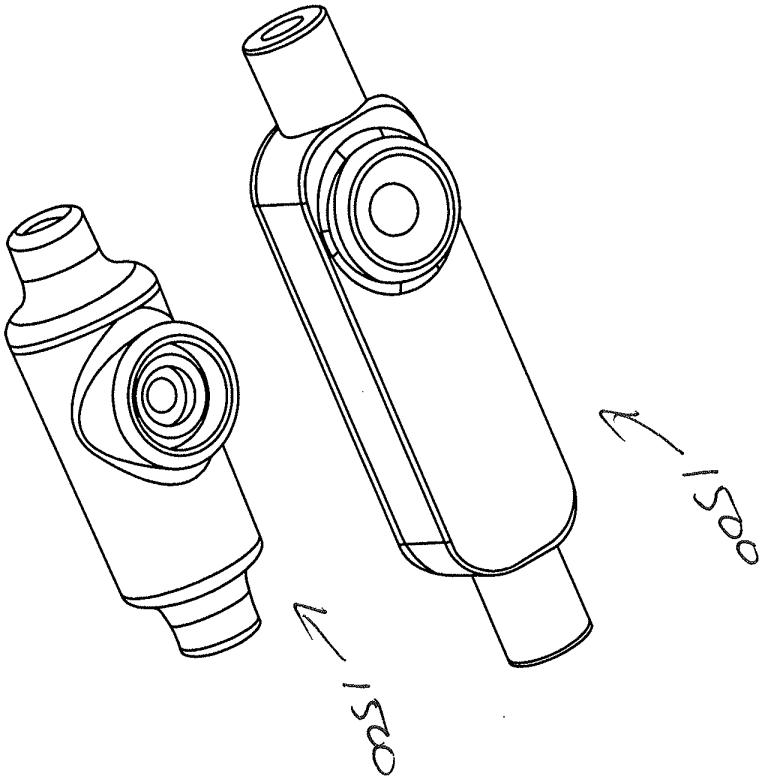


FIG. 15F

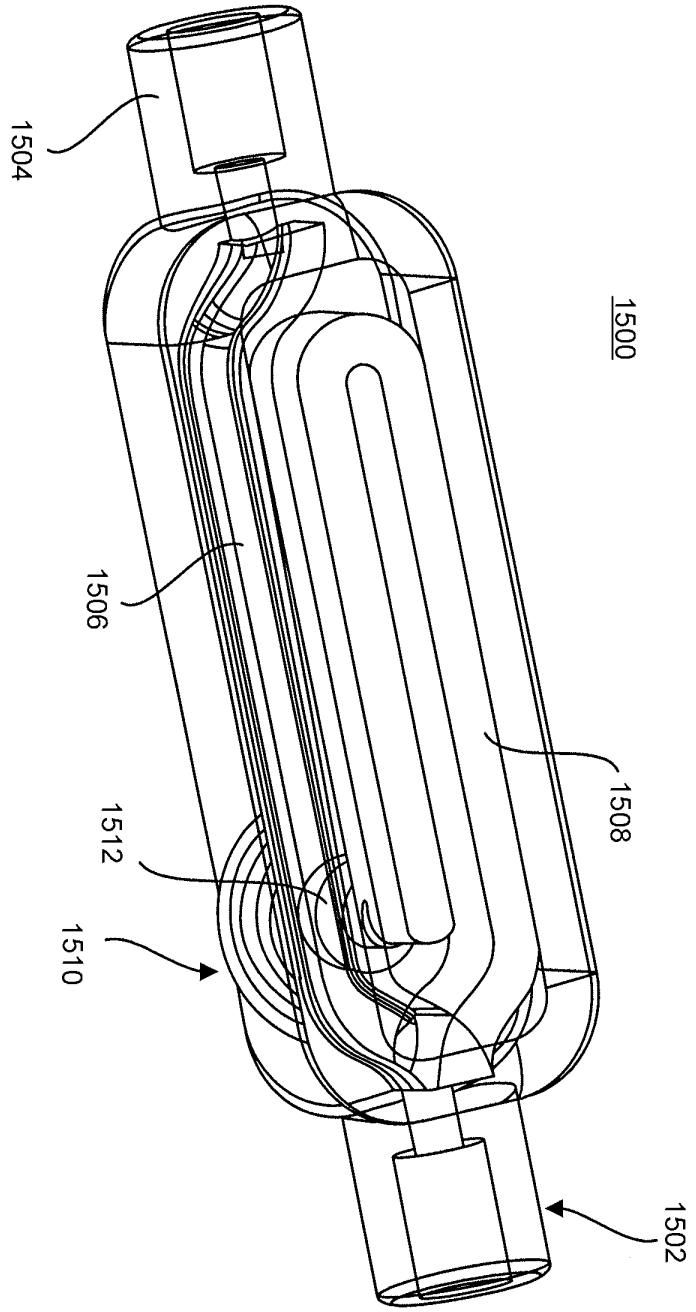


FIG. 15G

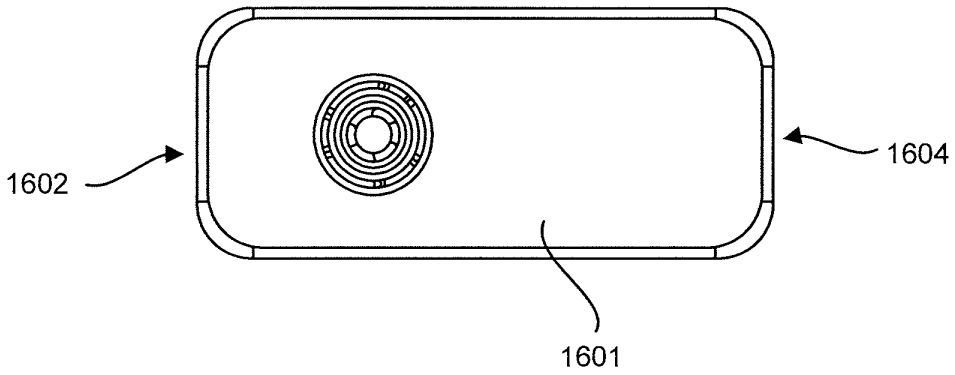


FIG. 16A

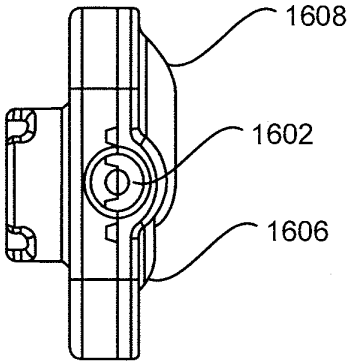


FIG. 16C

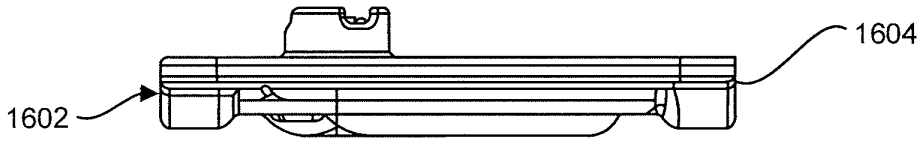


FIG. 16B

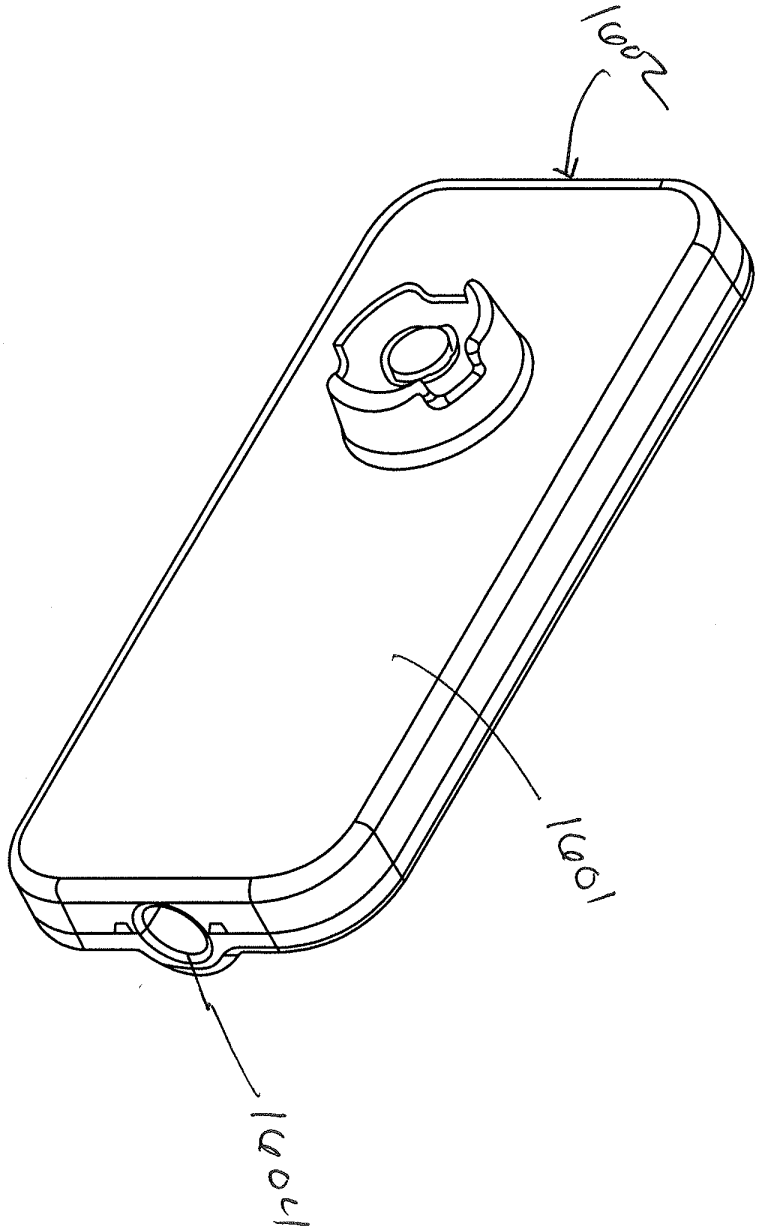


FIG. 16D

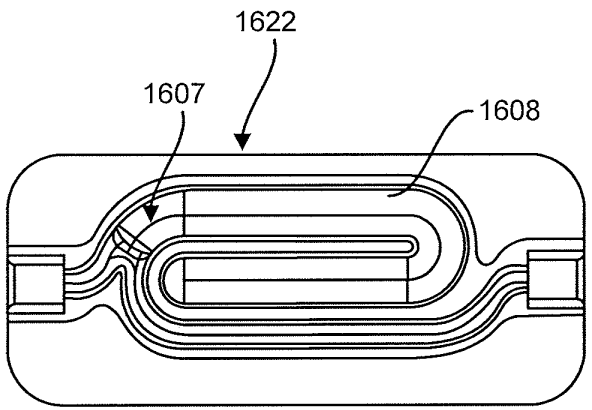


FIG. 17A

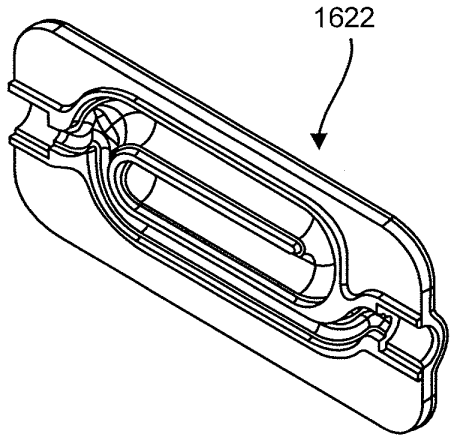


FIG. 17B

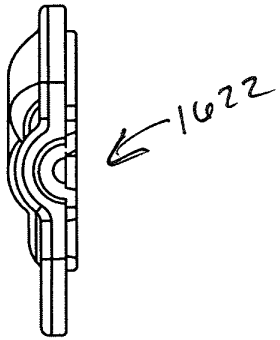


FIG. 17C

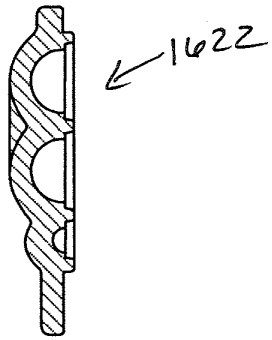


FIG. 17D

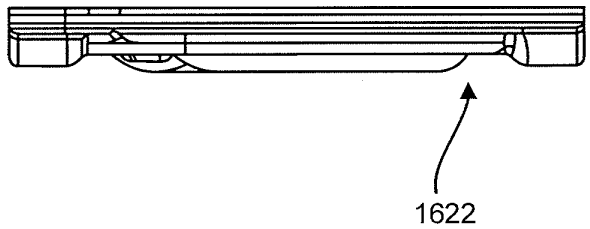


FIG. 17E

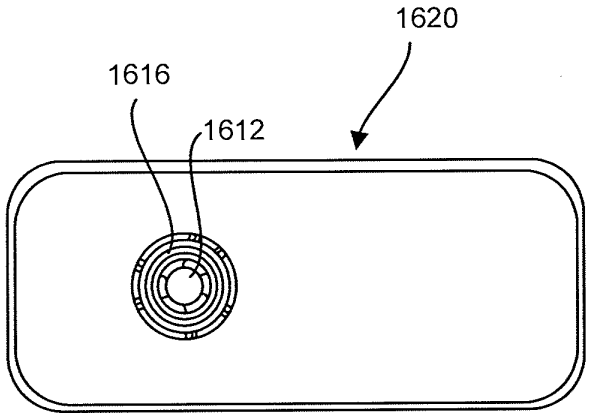


FIG. 18A

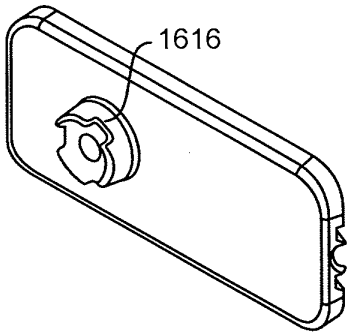


FIG. 18B

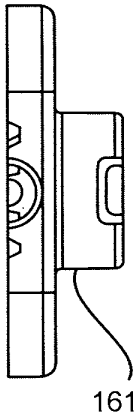


FIG. 18C

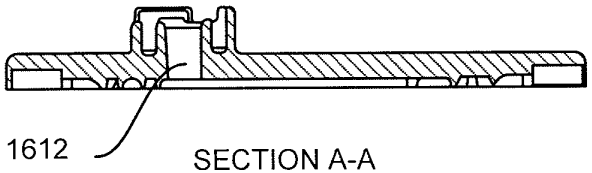


FIG. 18D

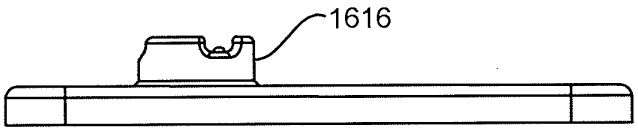


FIG. 18E

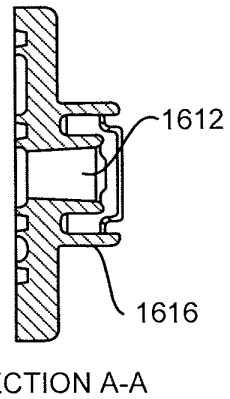


FIG. 18F

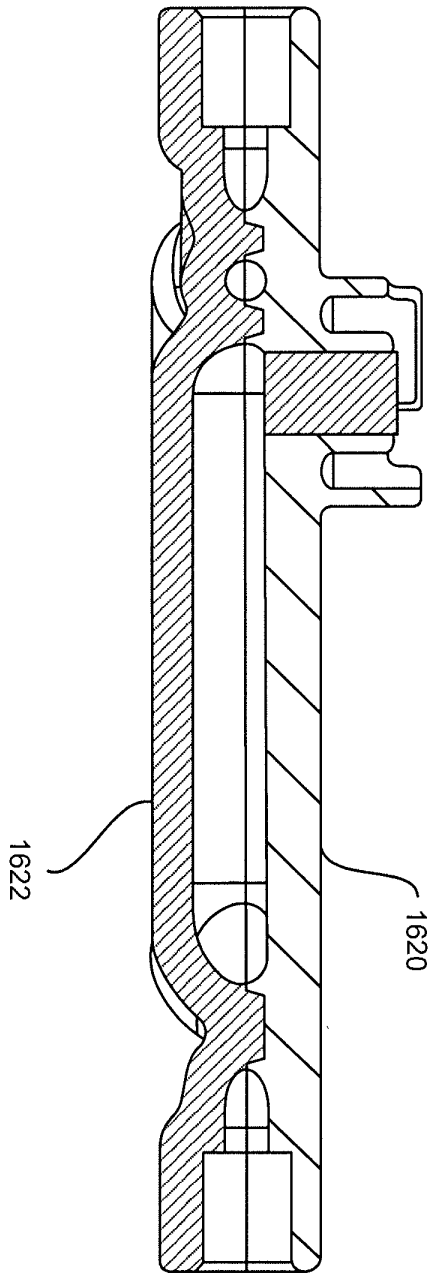


FIG. 19A

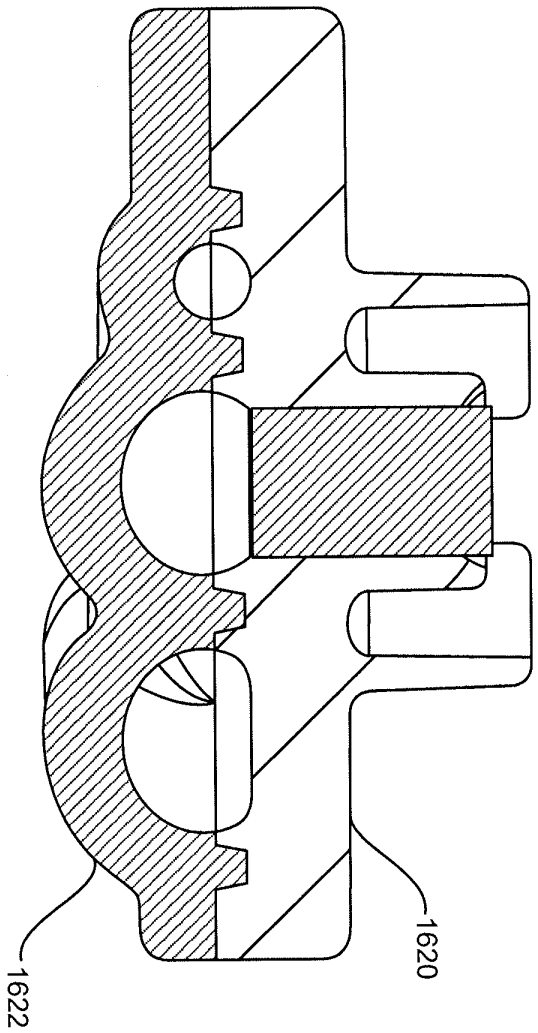


FIG. 19B

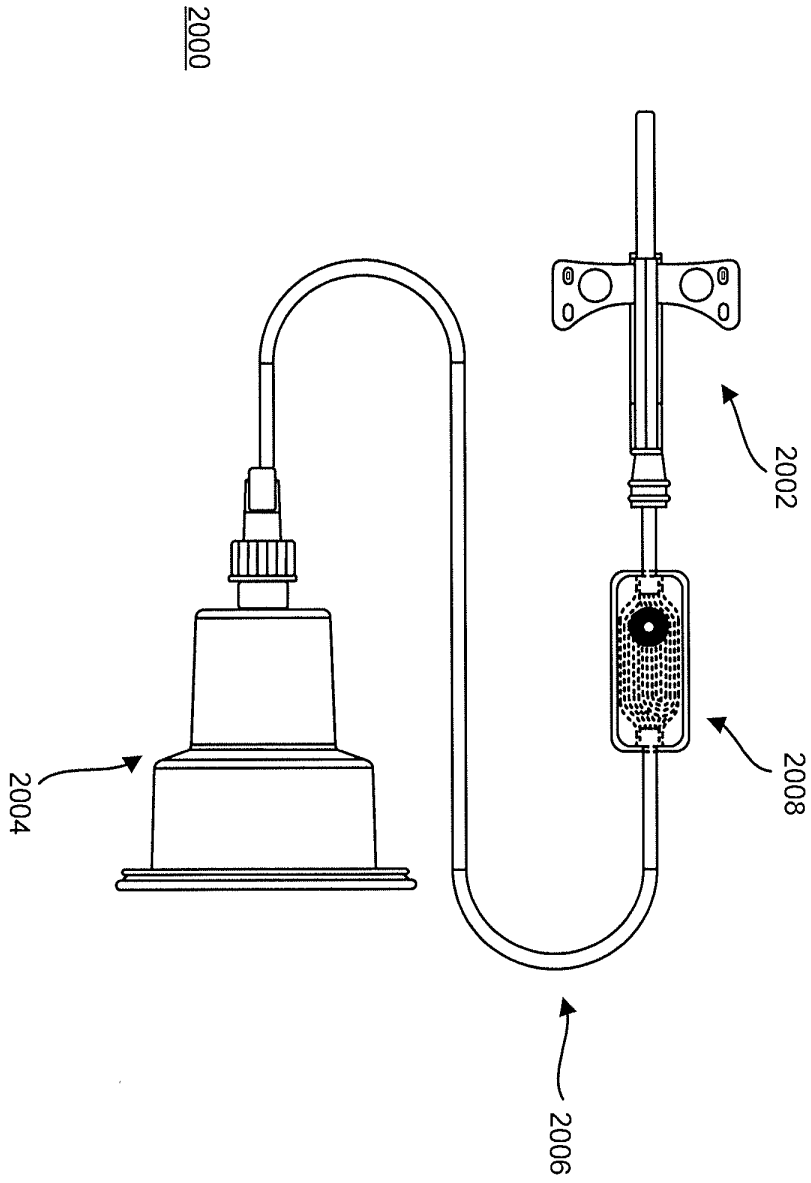


FIG. 20

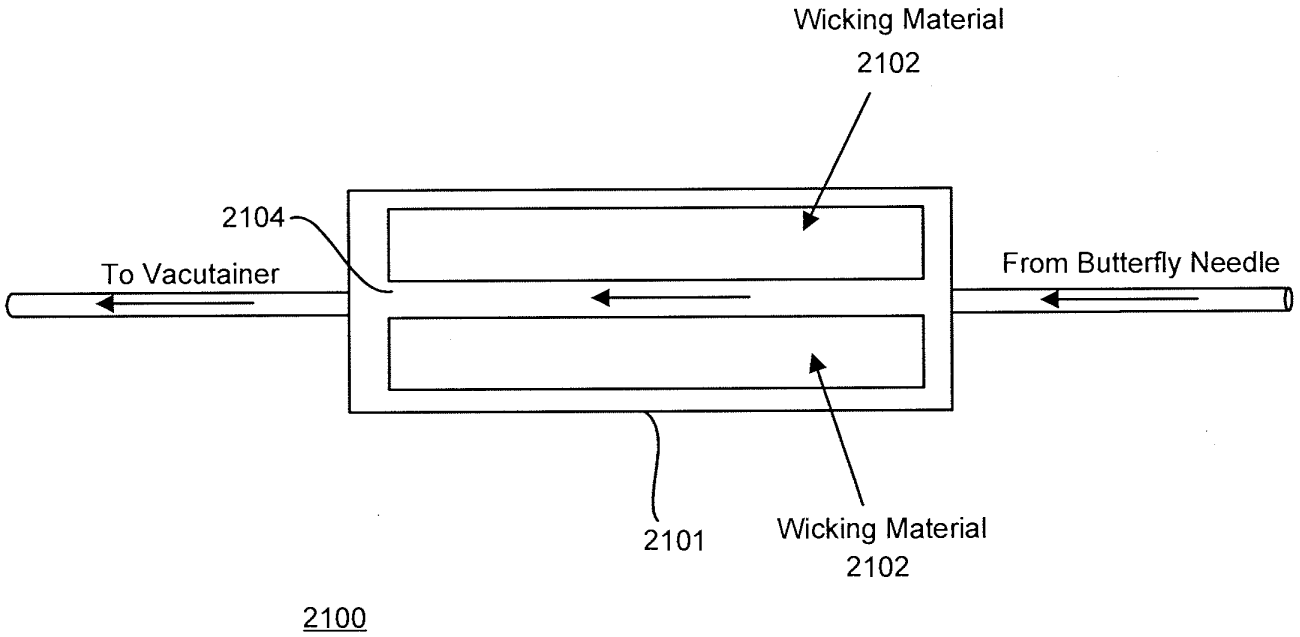

Wicking Material
2102
2104
To Vacutainer
From Butterfly Needle
2101
Wicking Material
2102
2100

FIG. 21

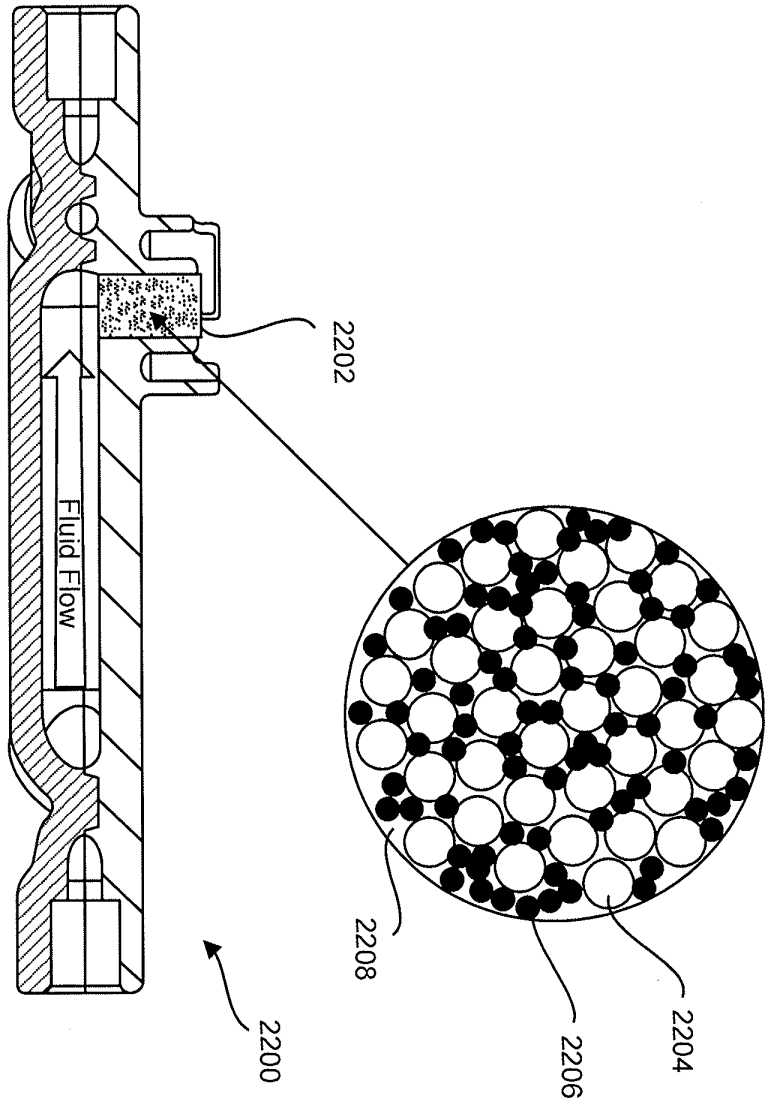


FIG. 22A

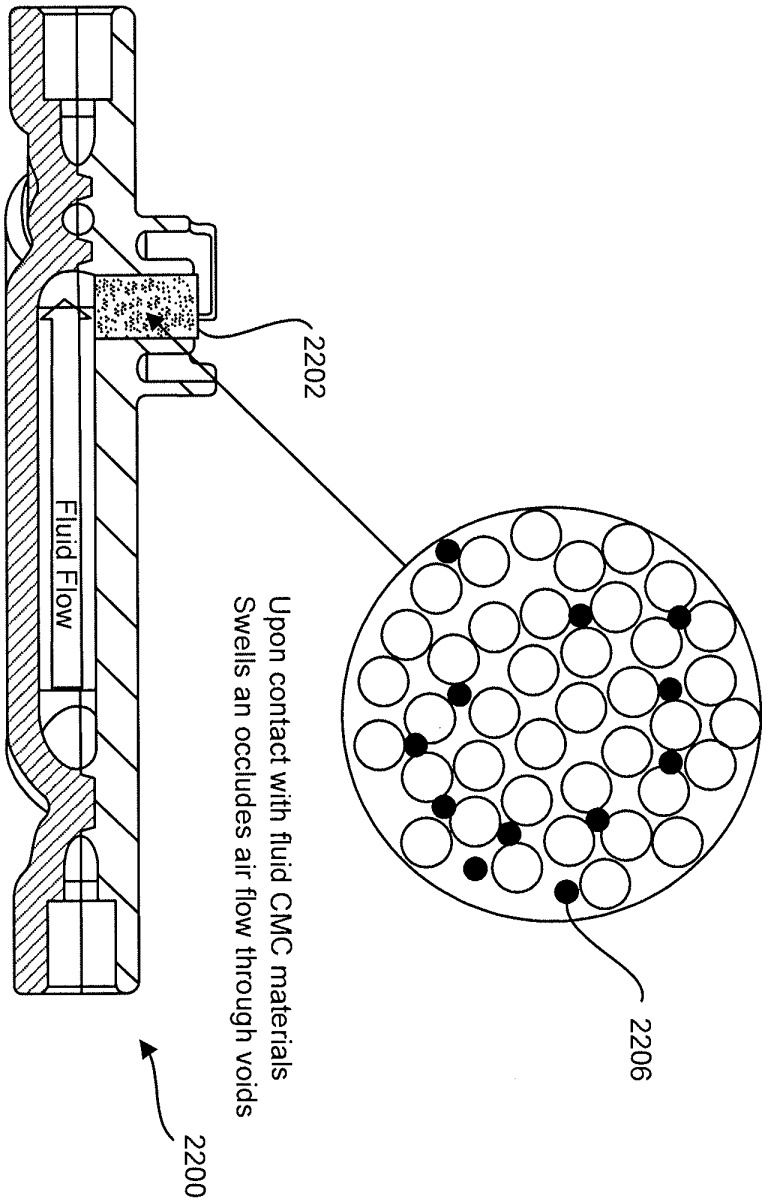

2202
Fluid Flow
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2206
2200

FIG. 22B

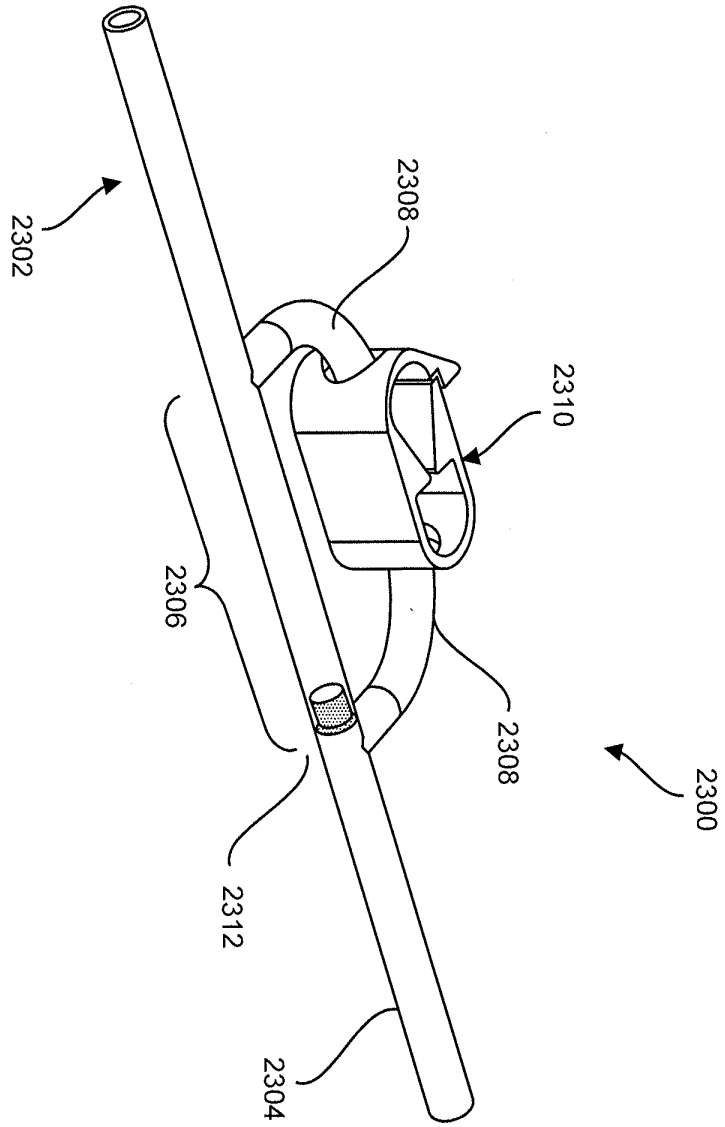


FIG. 23A

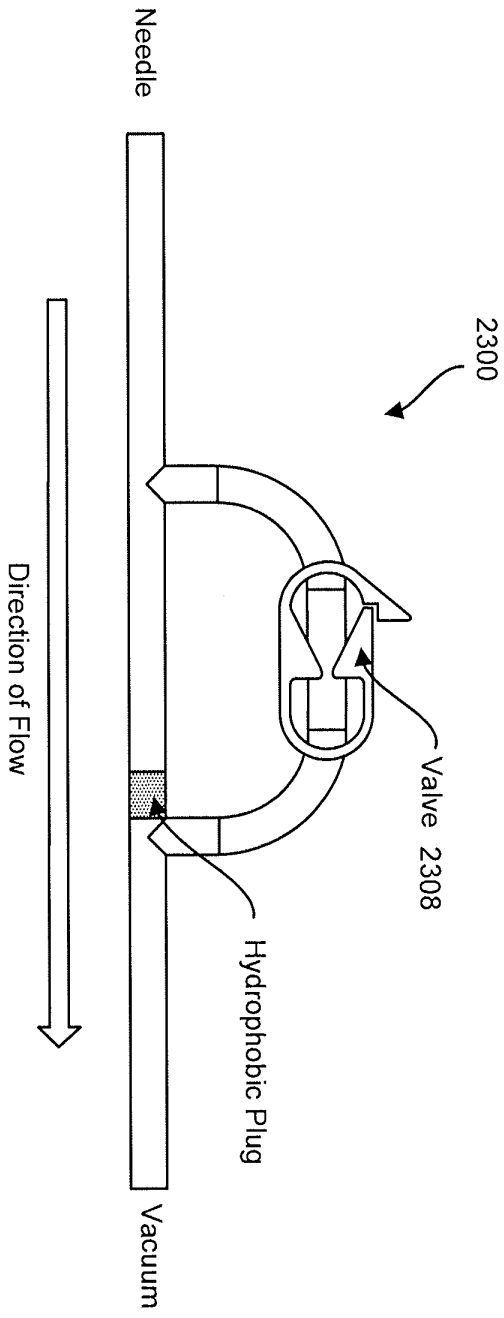

2300
Needle
Valve 2308
Hydrophobic Plug
Vacuum
Direction of Flow

FIG. 23B

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ■ United States application or PCT international application number 15/140,448 filed on April 27, 2016.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Bobby E. Rogers Date (Optional): _____

Signature: Bobby E. Rogers

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.**

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LEGAL NAME OF INVENTOR

Inventor: Gino Kang Date (Optional): 1/22/2018

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.**

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LEGAL NAME OF INVENTOR

Inventor: John Detloff Date (Optional): 1-23-18

Signature: John C. Detloff

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. 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 1.11 and 1.14. This collection is estimated to take 1 minute 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

BLOOD SAMPLE OPTIMIZATION DEVICE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Application No. 18/783,088 filed July 24, 2024, entitled "BLOOD SAMPLE OPTIMIZATION DEVICE," which is a continuation of U.S. Application No. 18/494,622 filed October 25, 2023, entitled "BLOOD SAMPLE OPTIMIZATION DEVICE," which is a continuation of U.S. Application No. 18/113,710 filed February 24, 2023, entitled "BLOOD SAMPLE OPTIMIZATION DEVICE," now U.S. Patent 11,832,994, which is a continuation of U.S. Application No. 17/538,990 filed November 11, 2021, entitled "BLOOD SAMPLE OPTIMIZATION DEVICE," now U.S. Patent 11,963,769, which is a continuation of U.S. Application No. 16/208,559 filed December 4, 2018, entitled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," now U.S. Patent 11,185,266, issued November 30, 2021, which is a Continuation of U.S. Application No. 15/994,559, filed on May 31, 2018 and titled "BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD," now U.S. Patent 10,143,412, issued December 4, 2018; which is a Continuation of U.S. Application No. 15/140,448, filed on April 27, 2016, now U.S. Patent 10,010,282 issued July 3, 2018, which claims the benefit of 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 – 17E 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 – 17E 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 device comprising:

an inlet port for receiving a blood sample;

an outlet port;

a chamber connected with the inlet port and configured to collect a first portion of the blood sample when under a drawing force applied from the outlet port from a blood sample collection device; and

a sampling channel connected with the inlet port and configured to convey a subsequent portion of the blood sample to the outlet port.

2. The device in accordance with claim 1, wherein a blood impermeable membrane is configured to facilitate the chamber collecting the first portion of the blood sample.

3. The device in accordance with claim 1, wherein a blood impermeable membrane causes the first portion of the blood sample to back up into the chamber following application of the drawing force applied from the outlet port.

4. The device in accordance with claim 2, further comprising a housing, separate from the blood impermeable membrane.

5. The device in accordance with claim 1, wherein the device is configured such that, when the drawing force is applied at the outlet port, the first portion of the blood sample is drawn into the chamber to contact a material that is blood impermeable.

6. The device in accordance with claim 1, further comprising a valve configured to initially close off the sampling channel.

7. The device in accordance with claim 1, further comprising a valve configured to initially close off the sampling channel until the first portion of the blood sample is in the chamber.

8. The device in accordance with claim 1, further comprising a valve that is configured to initially close off the sampling channel until the first portion of the blood sample is in the chamber and is further configured such that, upon release, follow-on amounts of the blood sample will bypass the chamber and flow through the sampling channel toward the outlet port.

9. The device in accordance with claim 6, wherein the valve is configured to pinch, shunt, bend or otherwise close off the sampling channel before the first portion of the blood sample is collected in the chamber.

10. The device in accordance with claim 1, further comprising a housing that defines the inlet port, the sampling channel, and the outlet port.

11. The device in accordance with claim 1, further comprising a patient needle and a sample collection device.

12. The device in accordance with claim 1, the chamber having a volume sufficient to collect the first portion of the blood sample that is more prone to contamination and also to minimize an amount of blood to be sequestered.

13. The device in accordance with claim 1, wherein the chamber has a volume of less than 1.5 cubic centimeters.

14. A device comprising:

an inlet port for receiving blood;

an outlet port;

a chamber comprising a flexible material, the chamber connected with the inlet port and configured to collect a first portion of the blood when under a drawing force applied from the outlet port; and

a sampling channel connected with the inlet port and configured to convey a subsequent portion of the blood to the outlet port.

15. The device in accordance with claim 14, wherein the flexible material is a blood impermeable membrane configured to facilitate the chamber collecting the first portion of the blood.

16. The device in accordance with claim 14, wherein the flexible material is a blood impermeable membrane causes the first portion of the blood to back up into the chamber following application of the drawing force applied from the outlet port.

17. The device in accordance with claim 15, further comprising a housing, separate from the blood impermeable membrane.

18. The device in accordance with claim 14, wherein the device is configured such that, when the drawing force is applied at the outlet port, the first portion of the blood is drawn into the chamber to contact a material that is blood impermeable.

19. The device in accordance with claim 14, further comprising a valve configured to initially close off the sampling channel.

20. The device in accordance with claim 14, further comprising a valve configured to initially close off the sampling channel until the first portion of the blood is in the chamber.

21. The device in accordance with claim 14, further comprising a valve that is configured to initially close off the sampling channel until the first portion of the blood is in the chamber and is further configured such that, upon release, follow-on amounts of the blood will bypass the chamber and flow through the sampling channel toward the outlet port.

22. The device in accordance with claim 19, wherein the valve is configured to pinch, shunt, bend or otherwise close off the sampling channel before the first portion of the blood is collected in the chamber.

23. The device in accordance with claim 14, further comprising a housing that defines the inlet port, the sampling channel, and the outlet port.

24. The device in accordance with claim 14, further comprising a patient needle and a sample collection device.

25. The device in accordance with claim 14, the chamber having a volume sufficient to collect the first portion of the blood that is more prone to contamination and also to minimize an amount of blood to be sequestered.

26. The device in accordance with claim 14, wherein the chamber has a volume of less than 1.5 cubic centimeters.

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 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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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bobby	E.	Rogers	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Park City	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	10755 Scripps Poway, Parkway No. 257		
Address 2	c/o Kurin, Inc.		
City	San Diego	State/Province	CA
Postal Code	92131	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Gino		Kang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Irvine	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	10755 Scripps Poway, Parkway No. 257		
Address 2	c/o Kurin, Inc.		
City	San Diego	State/Province	CA
Postal Code	92131	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	John		Detloff	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

City	San Diego	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	10755 Scripps Poway, Parkway No. 257		
Address 2	c/o Kurin, Inc.		
City	San Diego	**State/Province**	CA
Postal Code	92131	**Country**	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	27500		
Email Address	docket_ip@pillsburylaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	BLOOD SAMPLE OPTIMIZATION DEVICE		
Attorney Docket Number	069366-0581370_KUR2C07US	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	50	**Suggested Figure for Publication (if any)**	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	27500		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18783088	2024-07-24
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
18783088	Continuation of	18494622	2023-10-25
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18494622	Continuation of	18113710	2023-02-24	11862944	2023-12-05
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18113710	Continuation of	17538990	2021-11-30	11963769	2024-04-23
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17538990	Continuation of	16208559	2018-12-04	11185266	2021-11-30

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16208559	Continuation of	15994559	2018-05-31	10143412	2018-12-04
Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15994559	Continuation of	15140448	2016-04-27	10010282	2018-07-03
Prior Application Status	Expired				Remove
Application Number	Continuity Type	Prior Application Number			Filing or 371(c) Date (YYYY-MM-DD)
15140448	Claims benefit of provisional	62318194			2016-04-04
Prior Application Status	Expired				Remove
Application Number	Continuity Type	Prior Application Number			Filing or 371(c) Date (YYYY-MM-DD)
15140448	Claims benefit of provisional	62238636			2015-10-07
Prior Application Status	Expired				Remove
Application Number	Continuity Type	Prior Application Number			Filing or 371(c) Date (YYYY-MM-DD)
15140448	Claims benefit of provisional	62196797			2015-07-24
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.					Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Kurin, Inc.

Mailing Address Information For Applicant:

Address 1	10755 Scripps Poway Parkway, No. 257		
Address 2			
City	San Diego	**State/Province**	CA
Country	US	Postal Code	92131
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Kurin, Inc.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	10755 Scripps Poway Parkway, No. 257		
Address 2			
City	San Diego	**State/Province**	CA
Country [i]	US	Postal Code	92131
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Ben Hudson/			Date (YYYY-MM-DD)	2024-09-26
First Name	Benjamin	Last Name	Hudson	Registration Number	71,474

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	069366-0581370_KUR2C07US
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION DEVICE	

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

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. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to 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)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/898,239	**09/26/2024 05:52:39 PM Z ET**	**069366-0581370_KUR2C07US**

Title of Invention

BLOOD SAMPLE OPTIMIZATION DEVICE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7801	FILED BY	Trent Tercenio
PATENT CENTER #	67342093	AUTHORIZED BY	Benjamin Hudson
CUSTOMER #	27500	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Bobby E. Rogers

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 033975	**E20249PH53059335**	**Trent Tercenio**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
033975	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	56.00	1	56.00
2817	REQUEST FOR PRIORITIZED EXAMINATION	1680.00	1	1680.00
2111	UTILITY PATENT APPL. SEARCH FEE	280.00	1	280.00
4011	BASIC FILING FEE- UTILITY	64.00	1	64.00
2311	EXAMINATION OF ORIGINAL PATENT APPLICATION	320.00	1	320.00

2202	EACH CLAIM IN EXCESS OF 20	40.00	6	240.00
			TOTAL AMOUNT:	**$2,640.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

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Application Number: 18898239 Document Date: 09/26/2024

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Form Revision Date: March 1, 2024

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bobby E. Rogers, et al.

Confirmation No: 7801

Application No.: 18/898,239

Art Unit: Not yet assigned

Filed: September 26, 2024

Examiner: Not yet assigned

For: BLOOD SAMPLE OPTIMIZATION DEVICE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to initial examination on the merits, please amend the above-identified application as follows:

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

Please replace all prior listings of claims with the following listing of claims:

1. (Original) A device comprising:

an inlet port for receiving a blood sample;

an outlet port;

a chamber connected with the inlet port and configured to collect a first portion of the blood sample when under a drawing force applied from the outlet port from a blood sample collection device; and

a sampling channel connected with the inlet port and configured to convey a subsequent portion of the blood sample to the outlet port.

2. (Original) The device in accordance with claim 1, wherein a blood impermeable membrane is configured to facilitate the chamber collecting the first portion of the blood sample.

3. (Original) The device in accordance with claim 1, wherein a blood impermeable membrane causes the first portion of the blood sample to back up into the chamber following application of the drawing force applied from the outlet port.

4. (Original) The device in accordance with claim 2, further comprising a housing, separate from the blood impermeable membrane.

5. (Original) The device in accordance with claim 1, wherein the device is configured such that, when the drawing force is applied at the outlet port, the first portion of the blood sample is drawn into the chamber to contact a material that is blood impermeable.

6. (Original) The device in accordance with claim 1, further comprising a valve configured to initially close off the sampling channel.

7. (Original) The device in accordance with claim 1, further comprising a valve configured to initially close off the sampling channel until the first portion of the blood sample is in the chamber.

8. (Original) The device in accordance with claim 1, further comprising a valve that is configured to initially close off the sampling channel until the first portion of the blood sample is in the chamber and is further configured such that, upon release, follow-on amounts of the blood sample will bypass the chamber and flow through the sampling channel toward the outlet port.

9. (Original) The device in accordance with claim 6, wherein the valve is configured to pinch, shunt, bend or otherwise close off the sampling channel before the first portion of the blood sample is collected in the chamber.

10. (Cancelled)

11. (Currently Amended) The device in accordance with claim 1, further comprising a patient needle and [[a]] the blood sample collection device.

12. (Original) The device in accordance with claim 1, the chamber having a volume sufficient to collect the first portion of the blood sample that is more prone to contamination and also to minimize an amount of blood to be sequestered.

13. (Original) The device in accordance with claim 1, wherein the chamber has a volume of less than 1.5 cubic centimeters.

14. (Original) A device comprising:

an inlet port for receiving blood;

an outlet port;

a chamber comprising a flexible material, the chamber connected with the inlet port and configured to collect a first portion of the blood when under a drawing force applied from the outlet port; and

a sampling channel connected with the inlet port and configured to convey a subsequent portion of the blood to the outlet port.

15. (Original) The device in accordance with claim 14, wherein the flexible material is a blood impermeable membrane configured to facilitate the chamber collecting the first portion of the blood.

16. (Original) The device in accordance with claim 14, wherein the flexible material is a blood impermeable membrane causes the first portion of the blood to back up into the chamber following application of the drawing force applied from the outlet port.

17. (Original) The device in accordance with claim 15, further comprising a housing, separate from the blood impermeable membrane.

18. (Original) The device in accordance with claim 14, wherein the device is configured such that, when the drawing force is applied at the outlet port, the first portion of the blood is drawn into the chamber to contact a material that is blood impermeable.

19. (Original) The device in accordance with claim 14, further comprising a valve configured to initially close off the sampling channel.

20. (Original) The device in accordance with claim 14, further comprising a valve configured to initially close off the sampling channel until the first portion of the blood is in the chamber.

21. (Original) The device in accordance with claim 14, further comprising a valve that is configured to initially close off the sampling channel until the first portion of the blood is in the chamber and is further configured such that, upon release, follow-on amounts of the blood will bypass the chamber and flow through the sampling channel toward the outlet port.

22. (Original) The device in accordance with claim 19, wherein the valve is configured to pinch, shunt, bend or otherwise close off the sampling channel before the first portion of the blood is collected in the chamber.

23. (Cancelled)

24. (Original) The device in accordance with claim 14, further comprising a patient needle and a sample collection device.

25. (Original) The device in accordance with claim 14, the chamber having a volume sufficient to collect the first portion of the blood that is more prone to contamination and also to minimize an amount of blood to be sequestered.

26. (Original) The device in accordance with claim 14, wherein the chamber has a volume of less than 1.5 cubic centimeters.

REMARKS

By this amendment, Claims 10 and 23 have been cancelled without prejudice or disclaimer and Claim 11 has been amended. The claims find support throughout the specification. No new matter has been added. Upon entry of this amendment, Claims 1-9, 11-22, and 24-26 are pending.

Allowability over the prior art

Independent Claims 1 and 14 are identical to the original Claims 1 and 14 of parent application U.S. 18/783,088, which were rejected in the non-final office action mailed September 17, 2024 (hereinafter the "Office Action"). While Applicant amended the claims of the parent application to obtain a prompt allowance (without traversing the rejection of independent Claims 1 and 14), Applicant believes the instant claims are allowable over the cited art for at least the reasons discussed below.

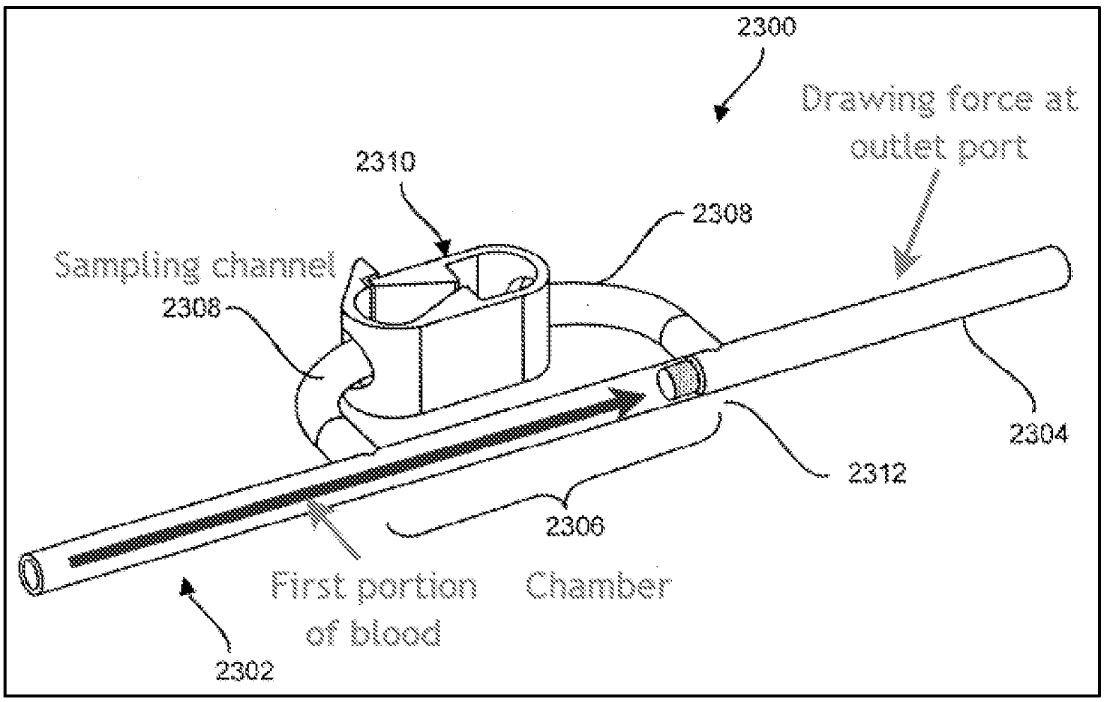
Claim 1

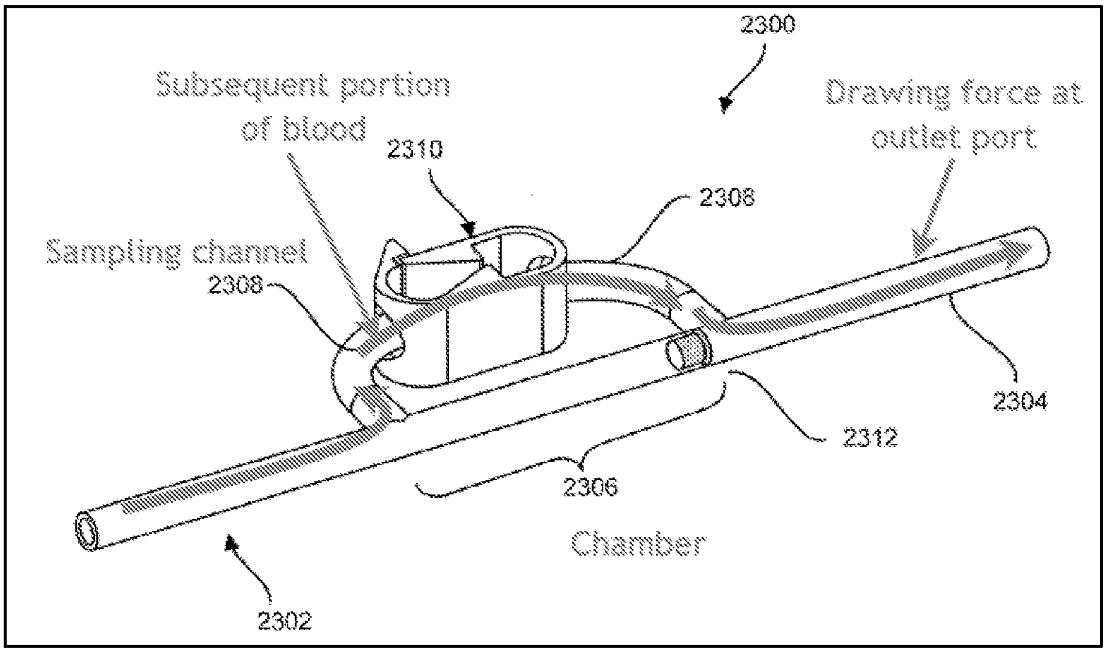
The (parent) Office Action rejected Claim 1 as allegedly anticipated under 35 U.S.C. § 102 in view of Patton (U.S. Publication 2008/0145933). However, Patton fails to disclose or suggest at least the following elements of Claim 1:

> "a chamber connected with the inlet port and configured **to collect a first portion of the blood sample when under a drawing force applied from the outlet port** from a blood sample collection device; and
>
> a sampling channel connected with the inlet port and configured to convey a **subsequent** portion of the blood sample to **the outlet port**."

As an illustrative example of the features of Claim 1, below are annotated versions of the instant application's Figure 23A. The first figure shows an example of the **first** portion of blood going into chamber 2306 due to **a drawing force applied from outlet port 2304**. The next

diagram shows the same drawing force bringing a **subsequent** portion of blood through sample channel 2308 to **the same outlet port 2304**.





In contrast, the first portion of blood in the cited Patton reference, which fills a "pre-sample reservoir 504," is not drawn in by a force applied from outlet port 510, as claimed, but rather by a vacuum in the pre-sample reservoir (e.g., from a vacutainer). See, e.g., Paragraph [0024] and Figure 5:

> "For example, in at least some embodiments, **the pre-sample reservoirs 104 are BD Vacutainers™** with buffered citrate, manufactured by Becton Dickenson."

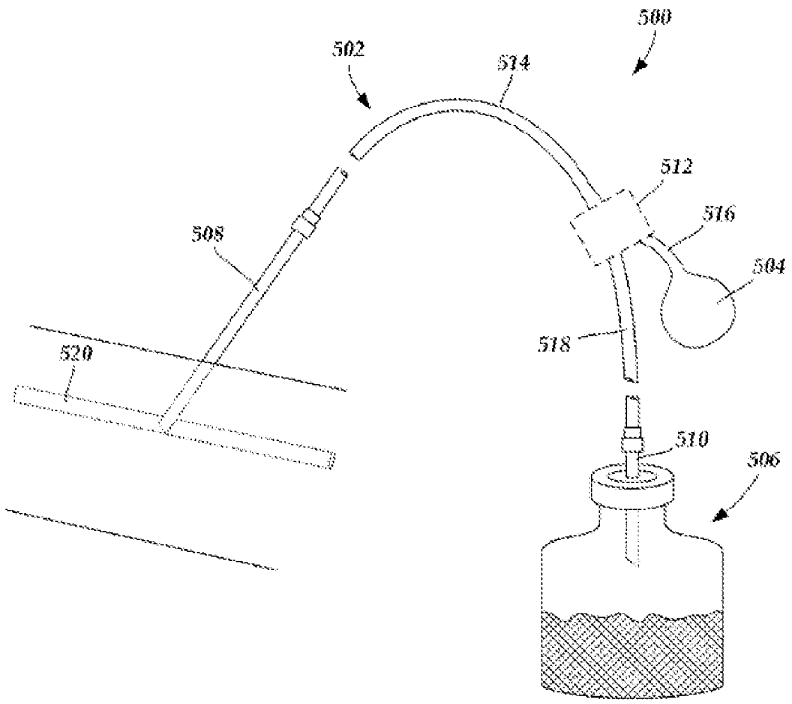


Fig. 5

It is clear from the configuration of Patton that a drawing force at its **outlet** 510 cannot "collect a **first** portion of the blood sample" in its alleged **chamber 504**. As such, Claim 1 is not anticipated by Patton.

Claim 14

The same arguments apply to the similar limitation in independent Claim 14, which was

also rejected in the parent application as allegedly anticipated by Patton.

For at least the reasons given above, the art of record fails to disclose or suggest each of the elements of Claim 1 and Claim 14 and thus should not be rejected under §102 or §103.

Each of the remaining pending claims depends from one of independent Claims 1 or 14 and thus each is likewise patentable for at least the reasons discussed above.

Prompt and favorable consideration of this amendment is respectfully requested as it is believed that the instant claims are in condition for allowance over the prior art.

Please charge any needed fees associated with the submission of this paper to Deposit Account Number 033975 (Ref. No. 069366-0581370_KUR2C07US). The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,
PILLSBURY WINTHROP SHAW PITTMAN LLP

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APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/898,239	**09/26/2024 06:05:50 PM Z ET**	**069366-0581370_KUR2C07US**

Title of Invention

BLOOD SAMPLE OPTIMIZATION DEVICE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7801	FILED BY	Trent Tercenio
PATENT CENTER #	67342621	FILING DATE	-
CUSTOMER #	27500	FIRST NAMED INVENTOR	Bobby E. Rogers
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Benjamin Hudson

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
069366-0581370_KUR2C07US-Preliminary-Amendment.pdf		9	-	215 KB
069366-0581370_KUR2C07US-Preliminary-Amendment-A.PE.pdf	(1-1)	1	Preliminary Amendment	95 KB
069366-0581370_KUR2C07US-Preliminary-Amendment-CLM.pdf	(2-5)	4	Claims	124 KB
069366-0581370_KUR2C07US-Preliminary-Amendment-	(6-9)	4	Applicant Arguments/Remarks Made in an Amendment	177 KB

REM.pdf

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
069366-0581370_KUR2C07US-Preliminary-Amendment.pdf	B778977B11321C55C30225A7AA59B6F380669B0B629FAF26E3E03BF1CFE0E8549447E3FD99F3BC11EF7CC6449C795895D6CF2E7CB09F4E2021205521121B35BE
069366-0581370_KUR2C07US-Preliminary-Amendment-A.PE.pdf	DC48B200D869A622922AD3C143A4F94D3CFFFBD39C89FE76612C650A8B011A5DC7CC496A30223F55955033B193DDFD5DE18713E900F525D79A096A2E239197A0
069366-0581370_KUR2C07US-Preliminary-Amendment-CLM.pdf	94789A431ECA10D8FABC9092EB068176932E58DEA0B0ADB7DFA87408AF794D74DB415BE98944956BDB087557075EC348E0C69241F01E3F7F0BA72869C4EFECC3
069366-0581370_KUR2C07US-Preliminary-Amendment-REM.pdf	777CAFFEF95C423CACF00C5A7EFBC78F1E869DEEDEA3A32E8CFD75592FF3936026A915D4F5907C836D160459F2C24D3593C1862467F41FCFDB4345D2206CE971

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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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Literature display help

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(51) [International Patent Classification]
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B01F 5/06 (2006.01)
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[Number of claims] 35

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Judge: Toyohide Watanabe
Judge: Tsuyoshi Kumakura
(56) References: References
: Japanese Unexamined Patent Publication No. 2003-210957 (JP, A)
[Document] Japanese Unexamined Patent Publication No. 2003-1076 (JP, A) [Document] National Publication of International Patent Application No. 2000-509330 (JP, A) [Document] Japanese Unexamined Patent Publication No. 10-146523 (JP, A) (58) [Investigated field] (Int.Cl., DB name)B01F3/04

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 parti cles dispersed in the first and/or second fluid streams and is in the form of the fluidized bed; i ncludes surface features formed in and/or on one or more of the inner walls thereof to alter fl ow within said process microchannel; or said surface features are stacked on top of each othe r; and or comprising two or more layers intertwined in a three-dimensional pattern, or wherei n said surface features are circular, elliptical, square, rectangular, checkerboard, V-shaped, co rrugated or combinations thereof; Alternatively, the surface features include sub-elements, an d the main wall of the surface features is notched, corrugated, jagged, perforated, burr-shape d, checkered, fan-shaped, or a combination thereof. 35. The process of Claim 34, further com prising 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 mi crochannel process technology. BACKGROUND OF THE INVENTION The dispersion of air bub bles in liquids, with or without chemical reaction, is useful for gas-liquid contact to promote ab sorption or stripping or for foam product production . can be Examples of these are air injectio n to meet the BOD (Biological Oxygen Demand) requirements of waste streams, air injection t o mix liquids in baths, stimulation of bacterial growth for hazardous waste treatment. Nitroge n 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, blowin g 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 reac tions, air or natural gas blowing for oil removal from well spring water, for bleaching pulp in th e 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 st erilize ultrapure water systems in pharmaceutical plants, waste or process streams CO2 or NH 3 to adjust the pH in

Blowing, efficient heating, and direct steam injection to quell steam hammering, air blowing f or 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

.

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

.

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

.

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

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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

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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)

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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

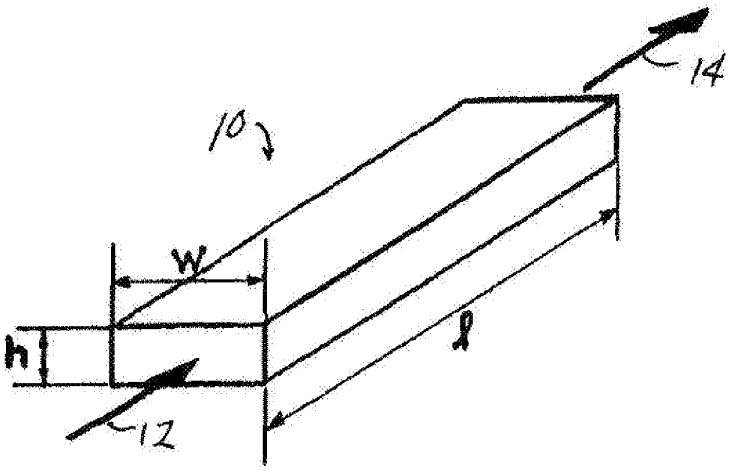
FIG. 29 shows examples of flow pathlines in microchannels initiated along the horizontal centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

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.

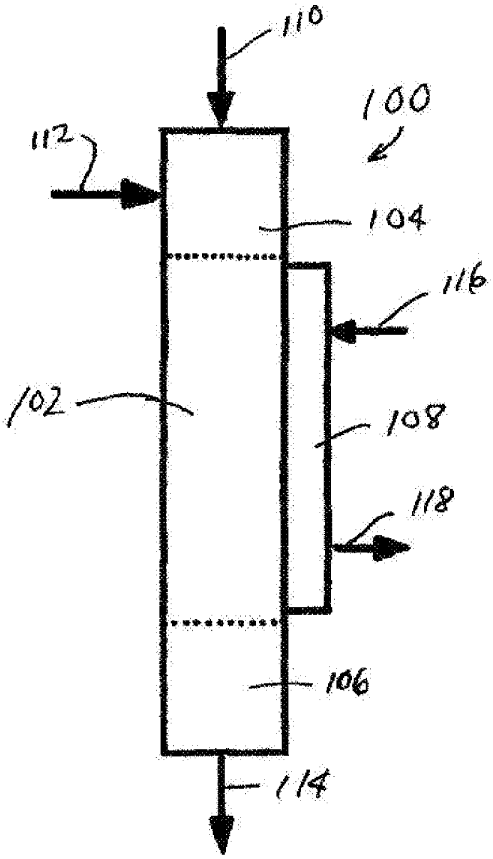
Figure 31 shows flow pathlines in the microchannel initiated along the vertical centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

drawing open —

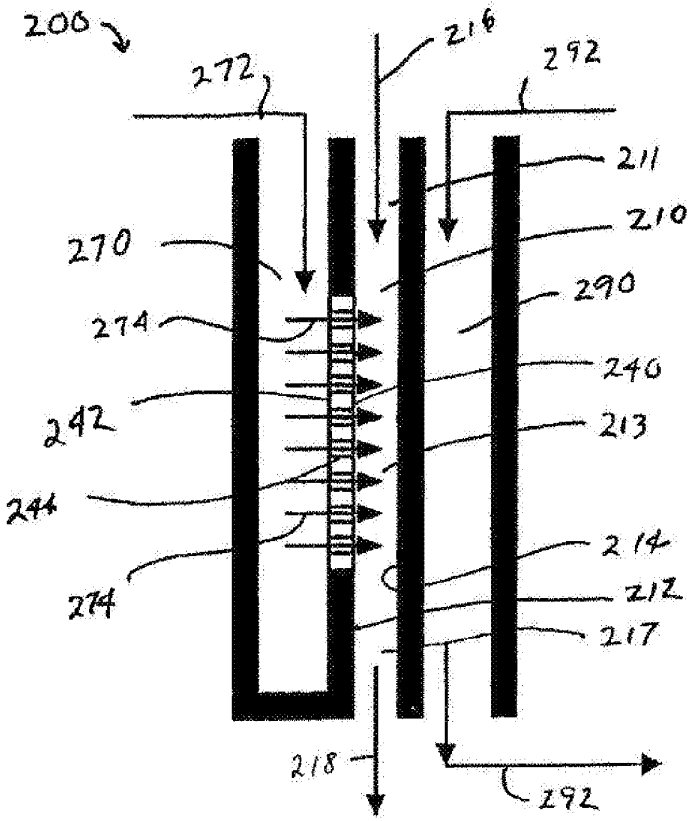
[Fig. 1]



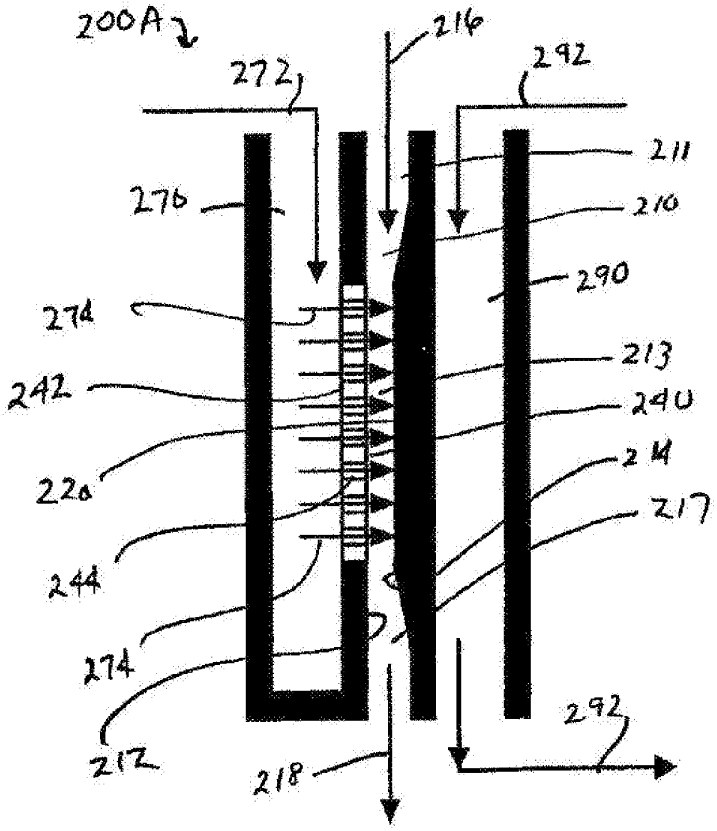
[Figure 2]



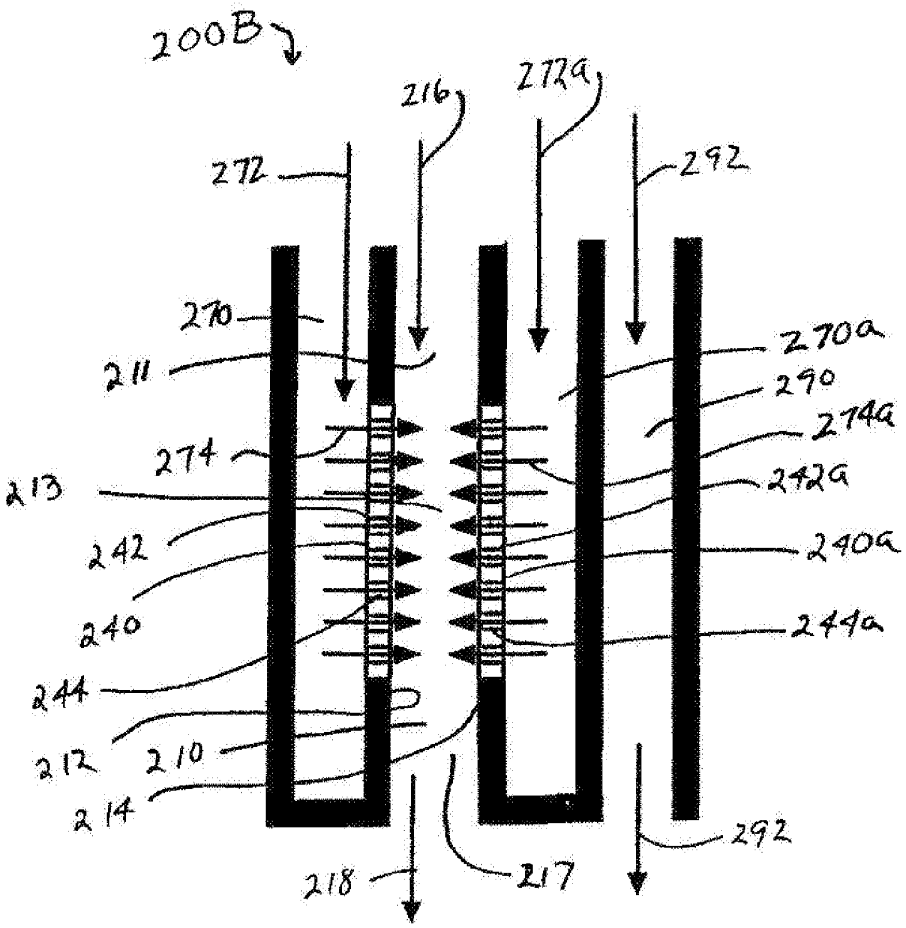
[Figure 3]


200
272
216
292
211
210
270
290
274
240
242
213
244
214
274
212
217
218
292

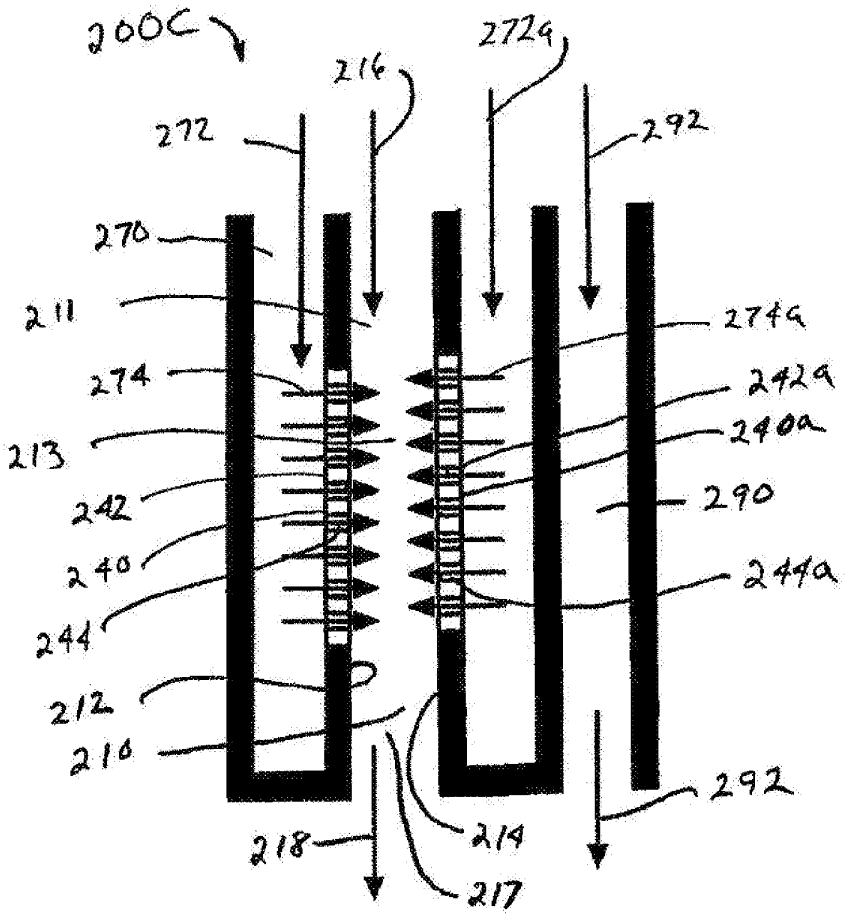
[Figure 4]


200A
216
272
292
211
276
210
290
274
213
242
240
220
214
244
217
274
212
218
292

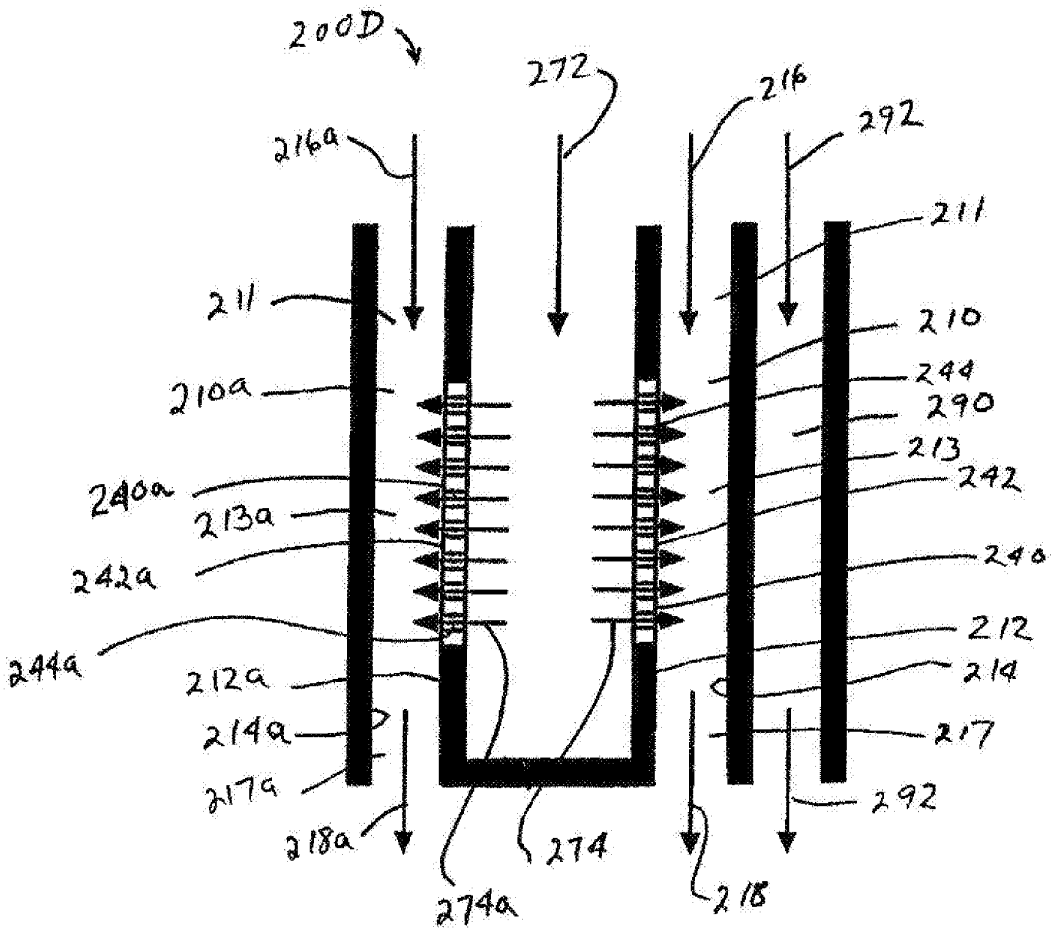
[Figure 5]


200B
216
272a
272
292
270
211
270a
290
274a
274
213
242a
242
240a
240
244a
244
212
210
214
292
218
217

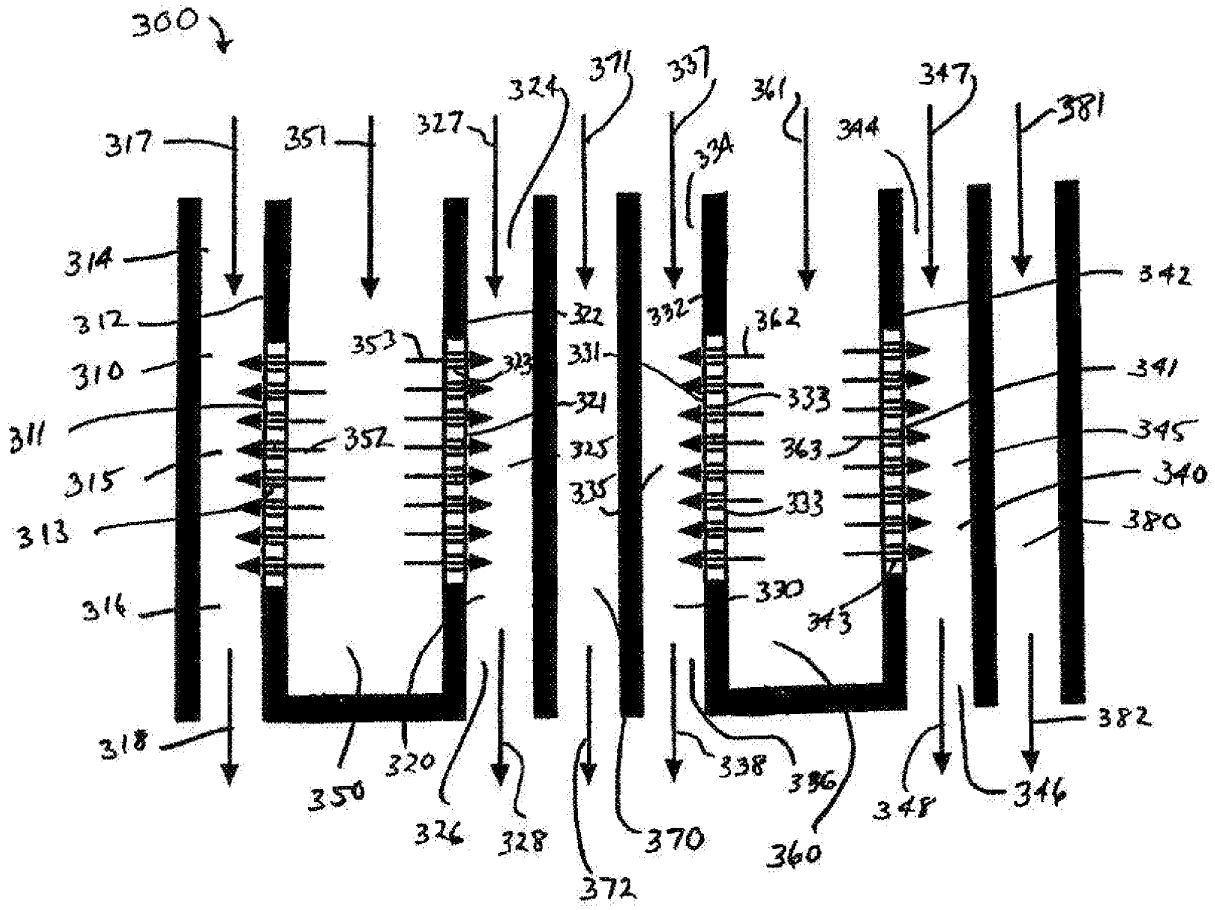
[Fig. 6]


200C
216
272a
292
272
270
211
274a
274
242a
213
240a
242
290
240
244a
244
212
210
292
218
214
217

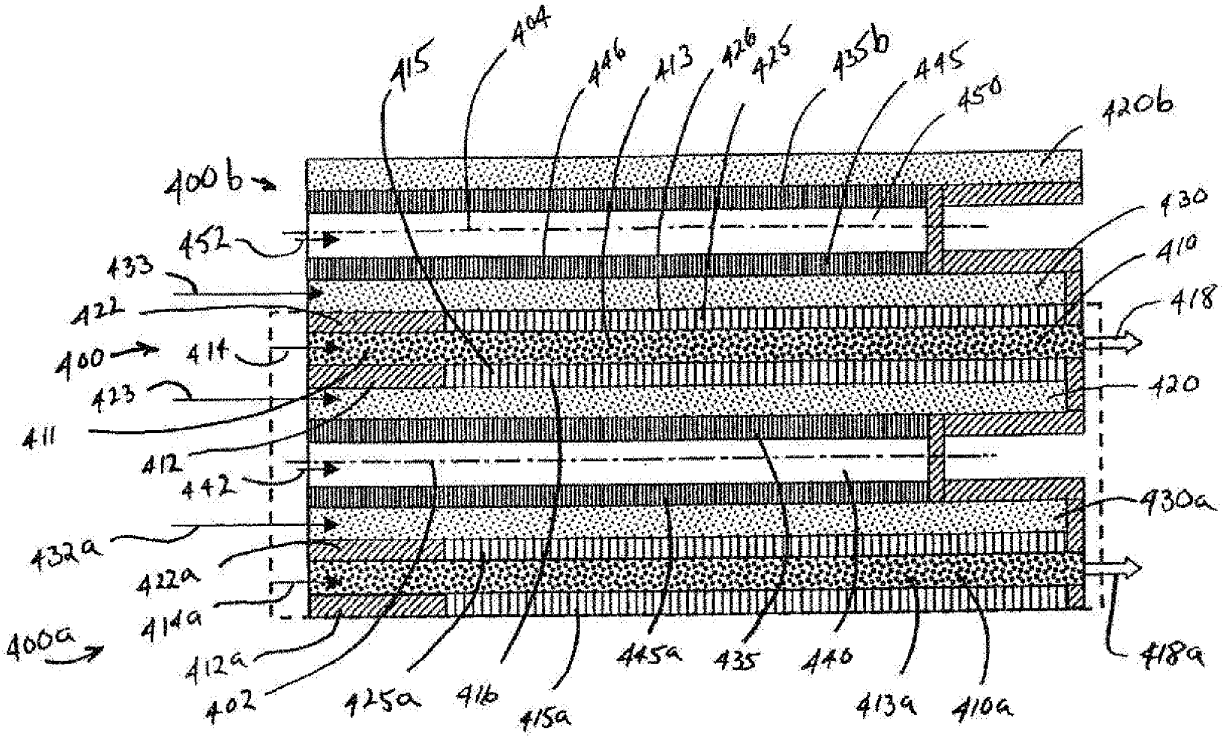
[Fig. 7]


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

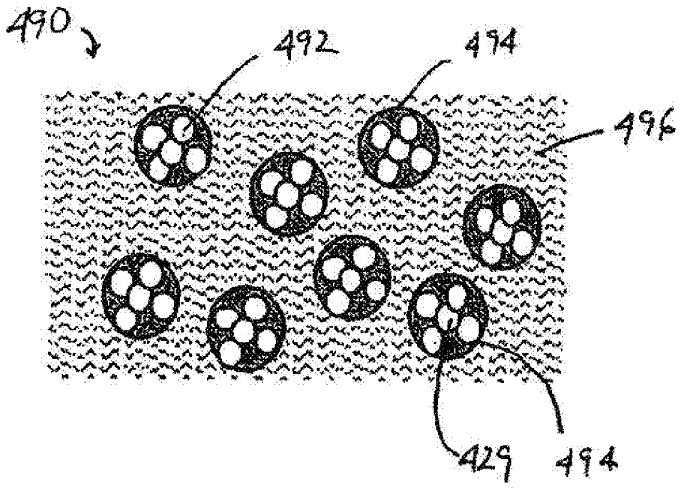
[Fig. 8]


300
317
351
327
324
371
337
361
347
381
344
334
314
312
310
311
315
313
316
318
353
352
322
331
321
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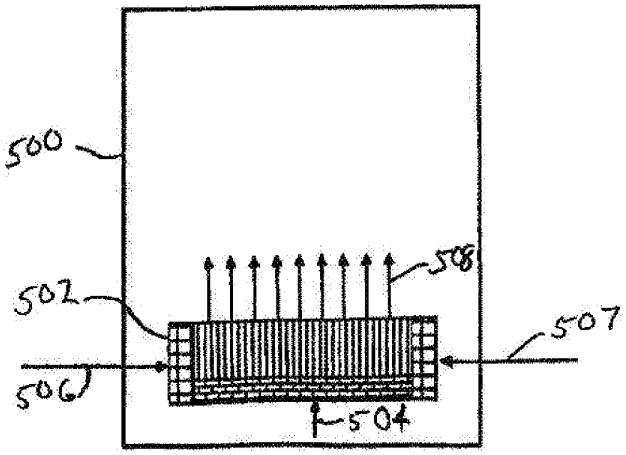
[Fig. 9]


415
404
446
413
426
425
435b
445
450
420b
400b
452
430
433
410
422
418
400
414
420
423
411
412
442
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435
440
413a
410a
418a

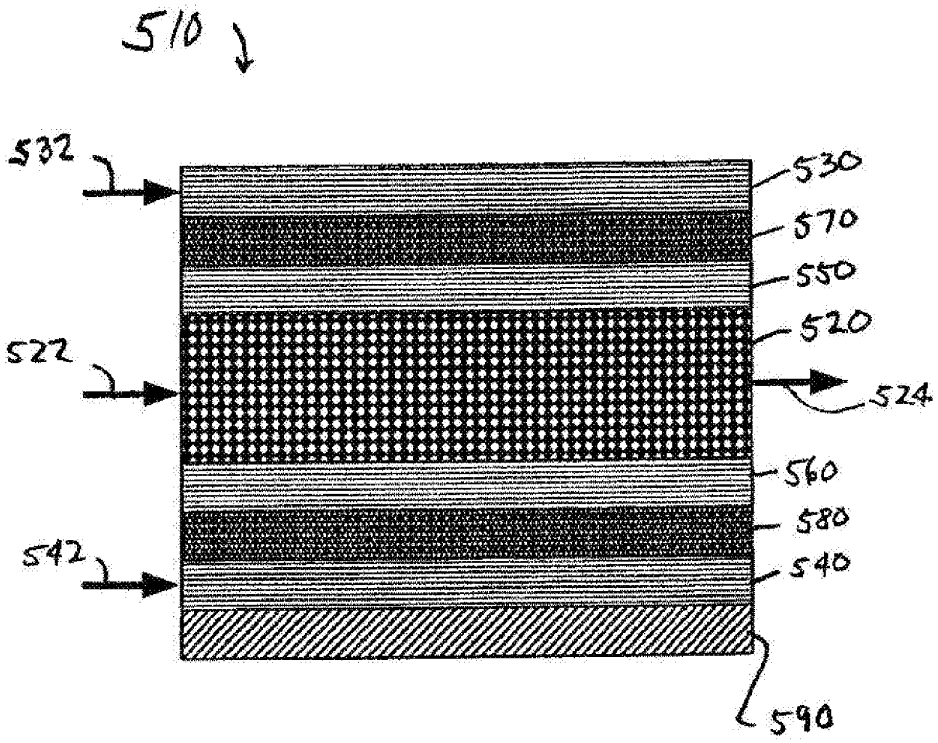
[Fig. 10]



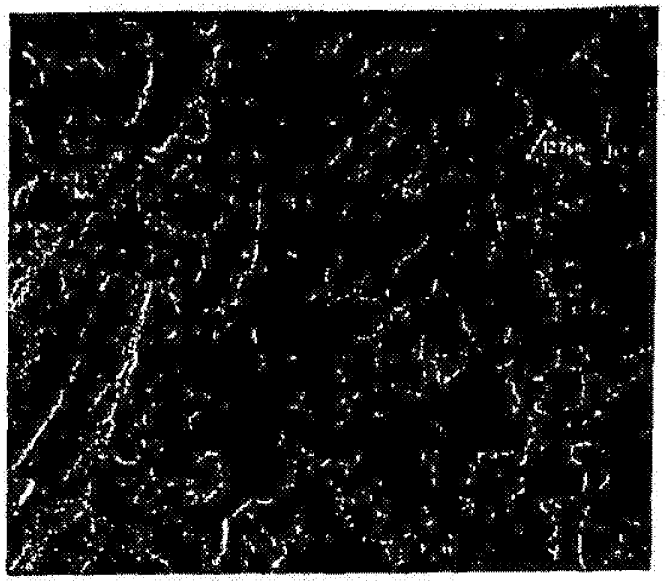
[Fig. 11]



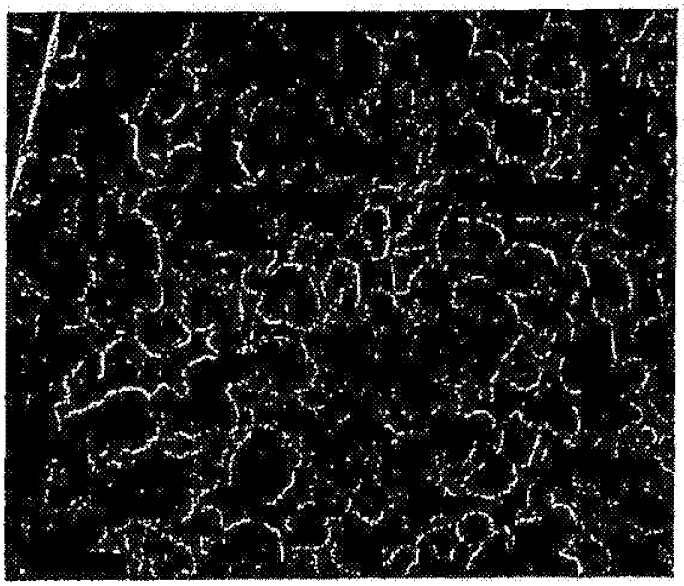
[Fig. 12]



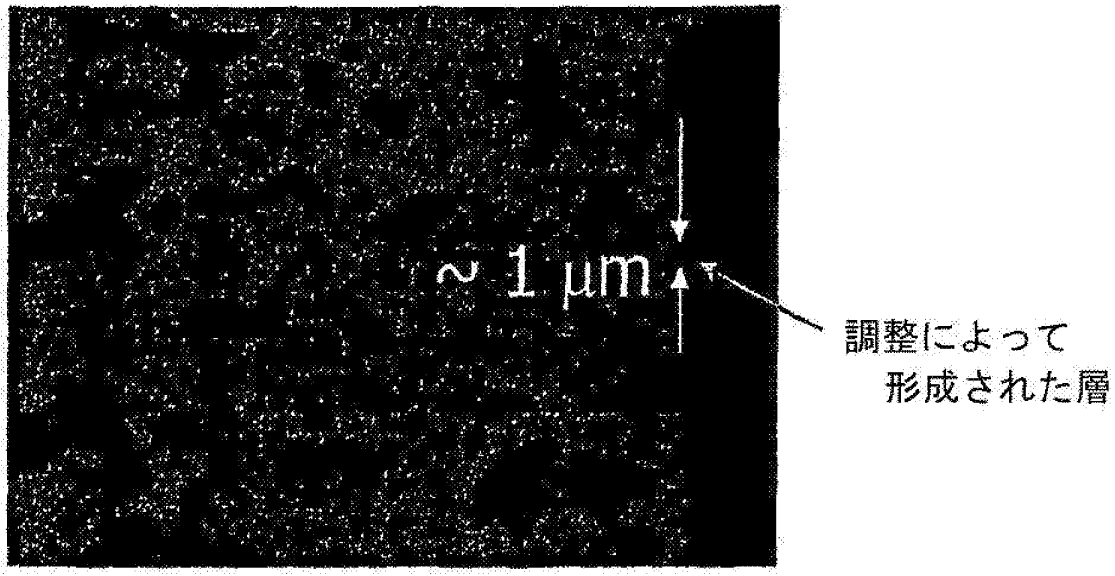
[Fig. 13]



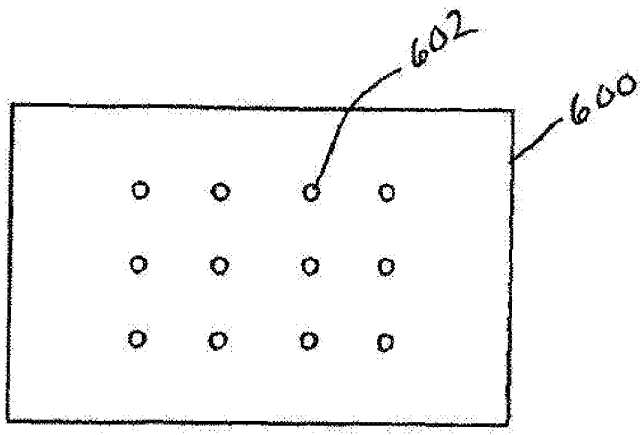
[Fig. 14]



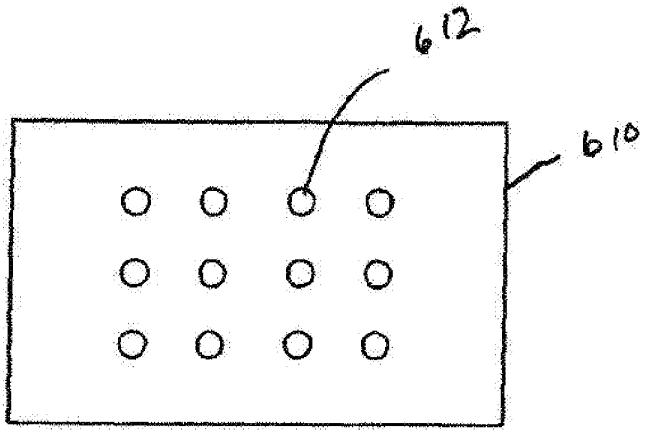
[Fig. 15]



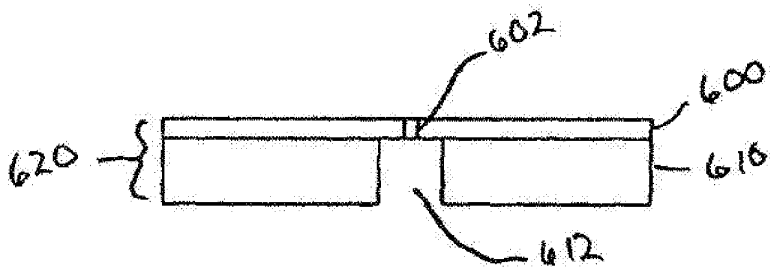
[Fig. 16]



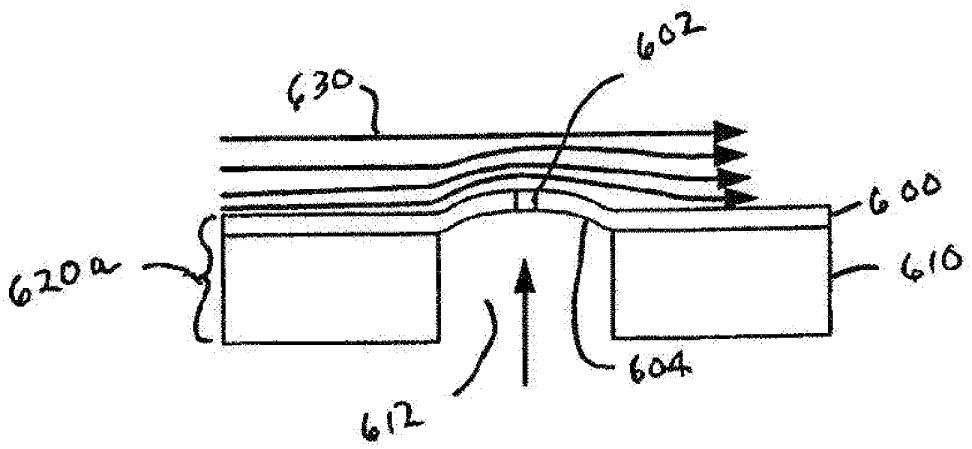
[Fig. 17]



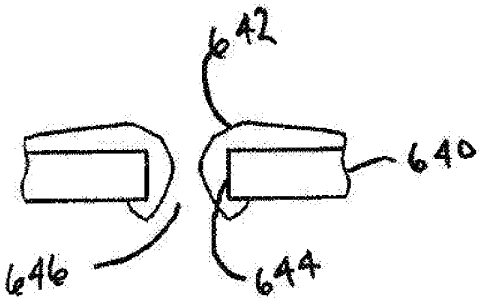
[Fig. 18]



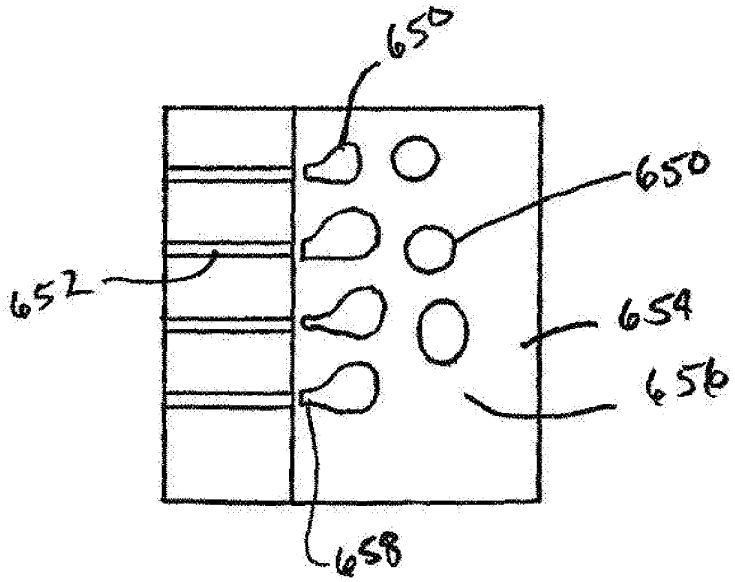
[Fig. 19]



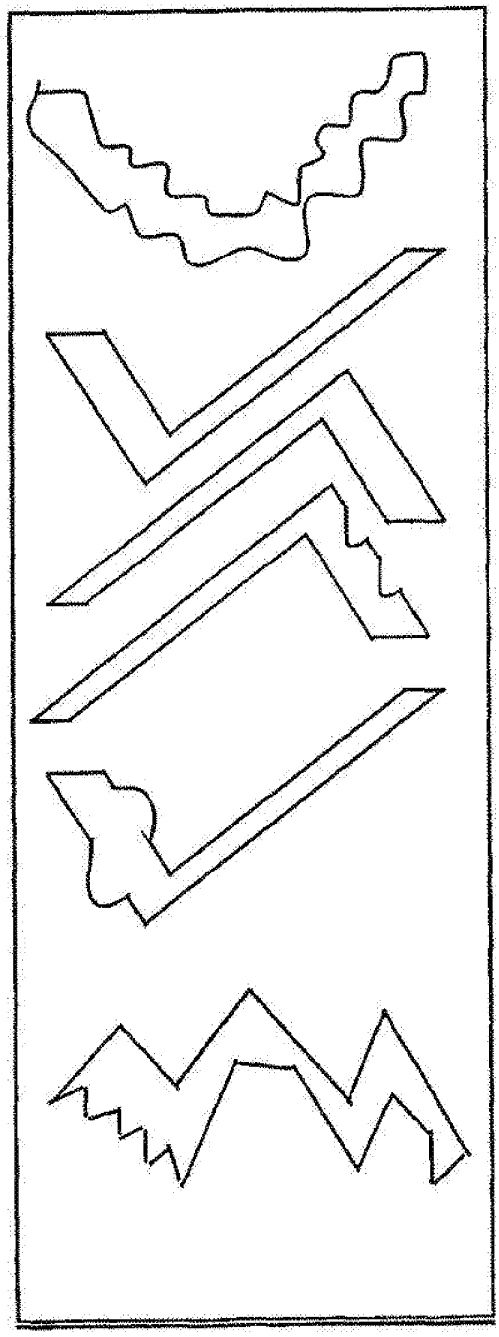
[Fig. 20]



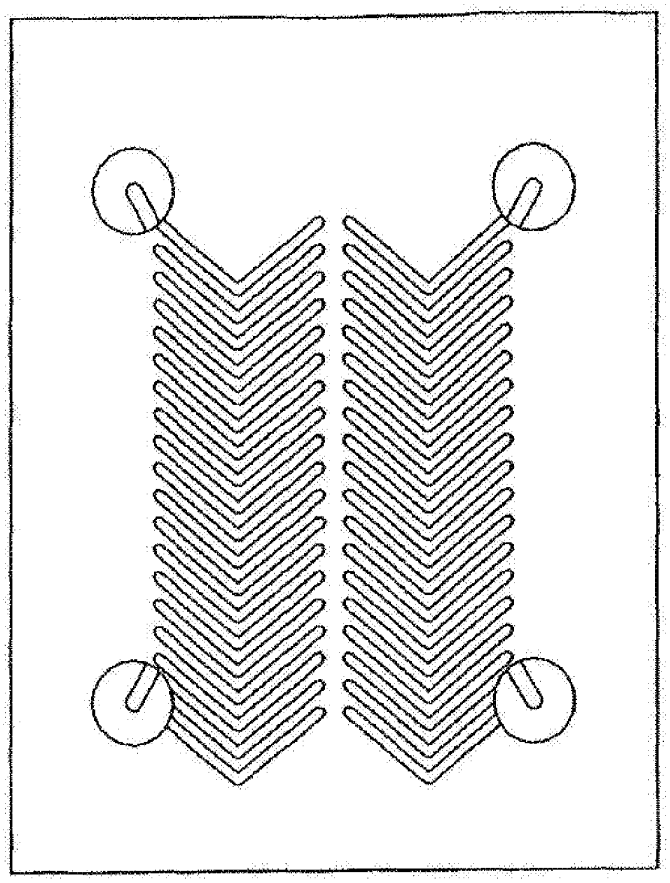
[Fig. 21]



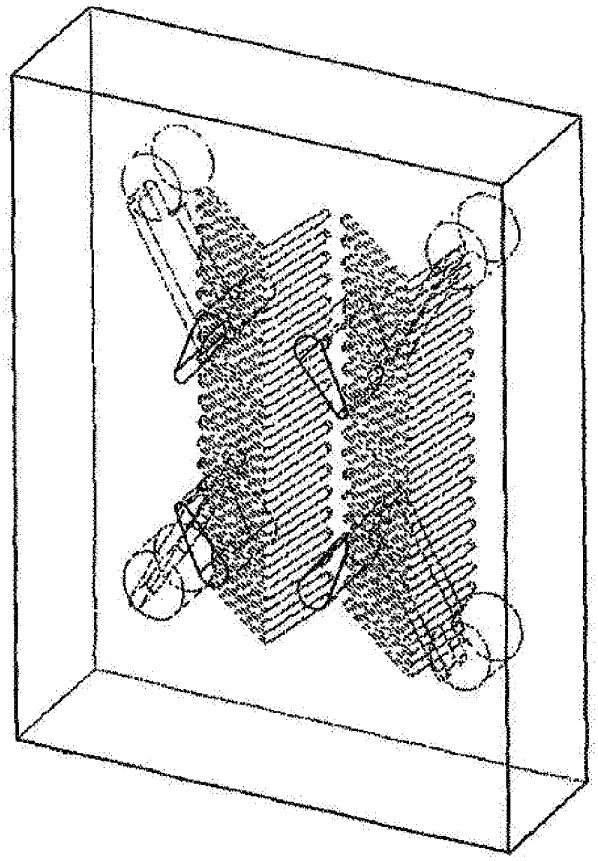
[Fig. 22]



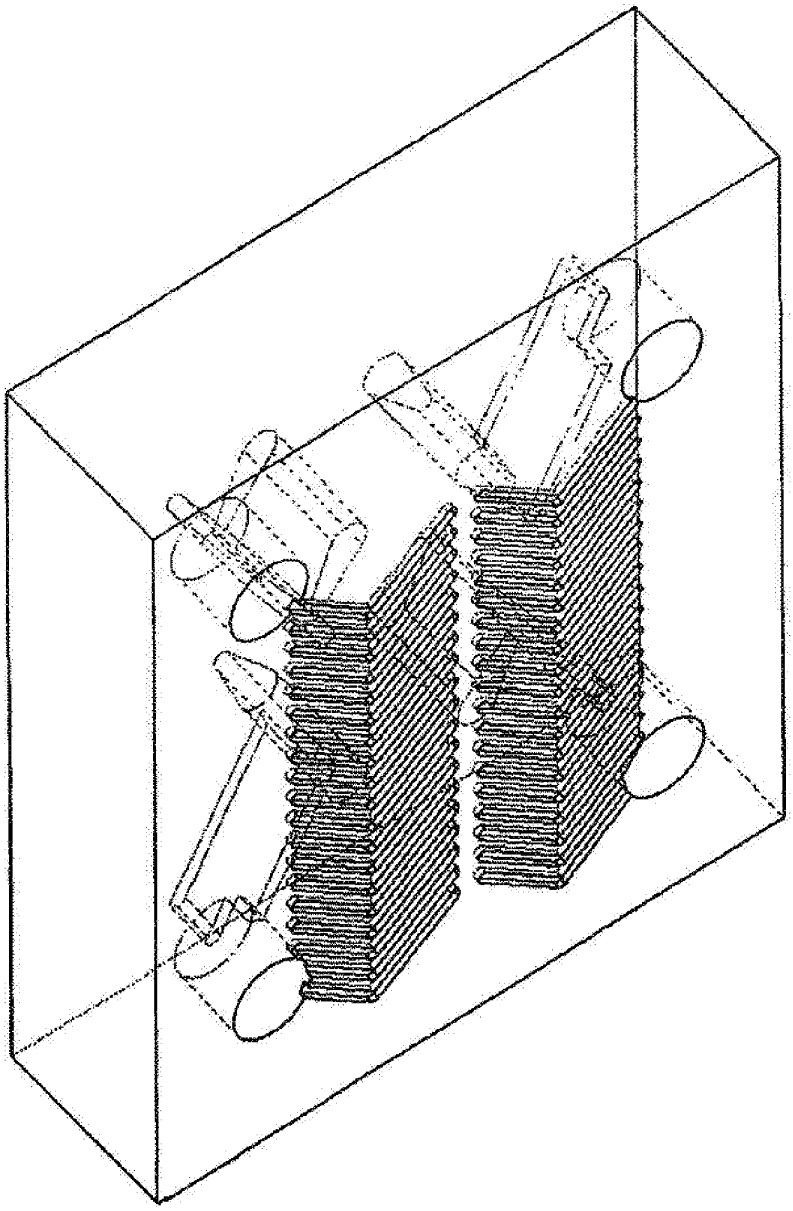
[Fig.23]



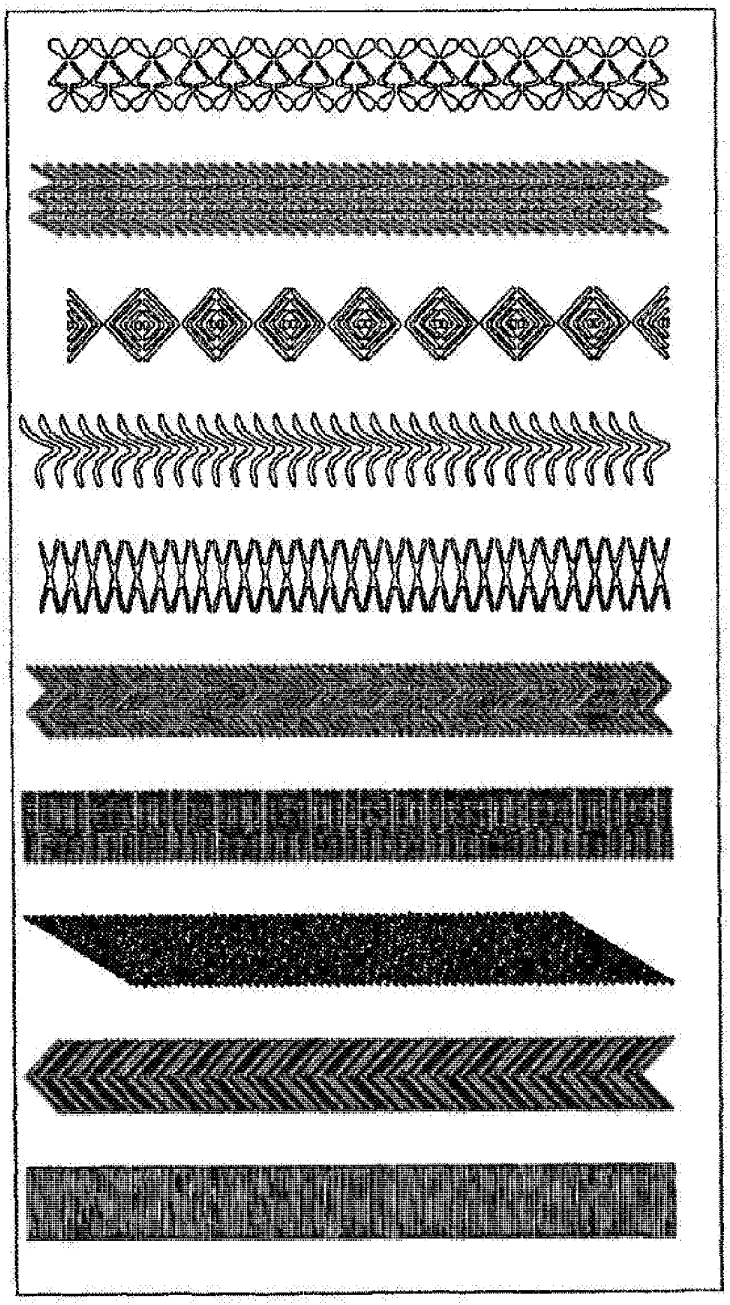
[Fig.24]



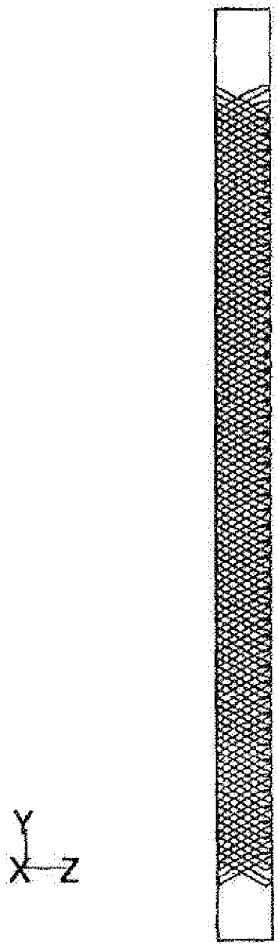
[Fig.25]



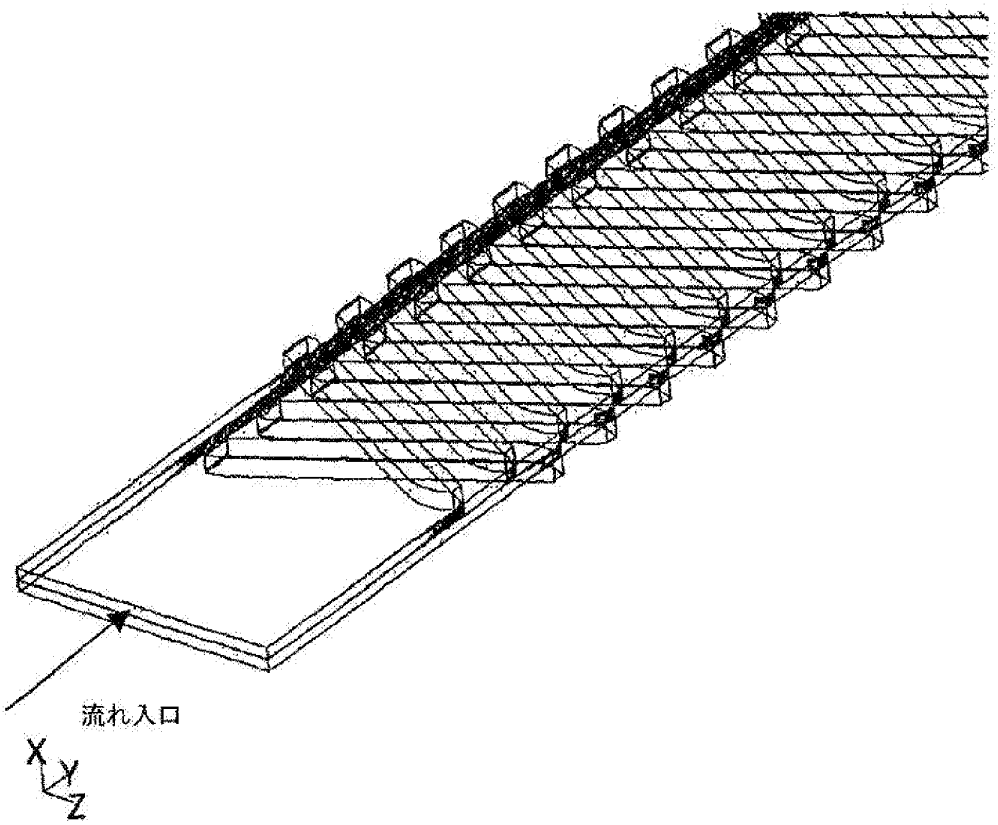
[Fig.26]



[Fig.27]



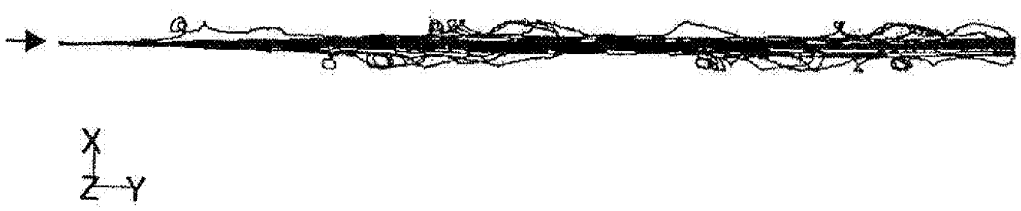
[Fig.28]



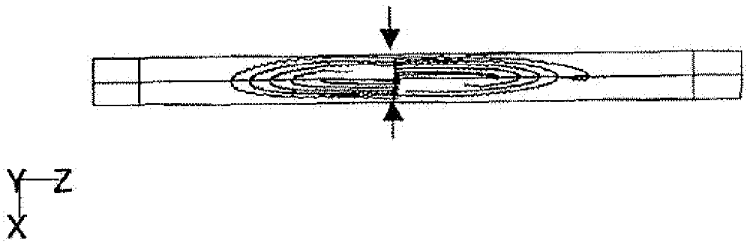
[Fig.29]



[Fig. 30]



[Fig. 31]



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1 2 3 Four Five 6 7 8 9 Ten ...

Magnify and Rotate

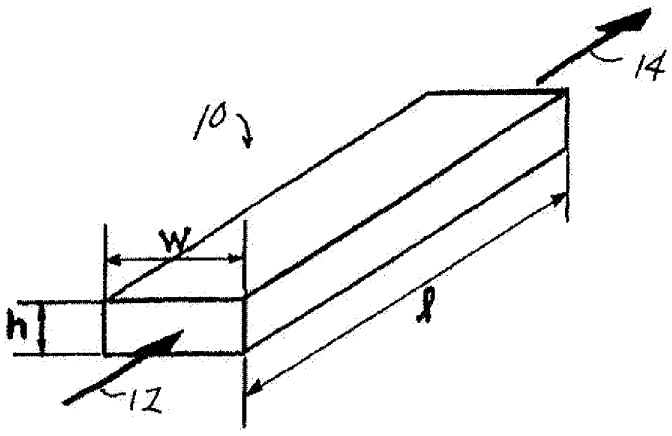


Figure 1

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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 ．

Classification: - international: ***A23L27/18; A23L27/60; A23L29/00; B01F23/30; C09K23/00***

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Application number: JP20070534825 20050930 Global Dossier

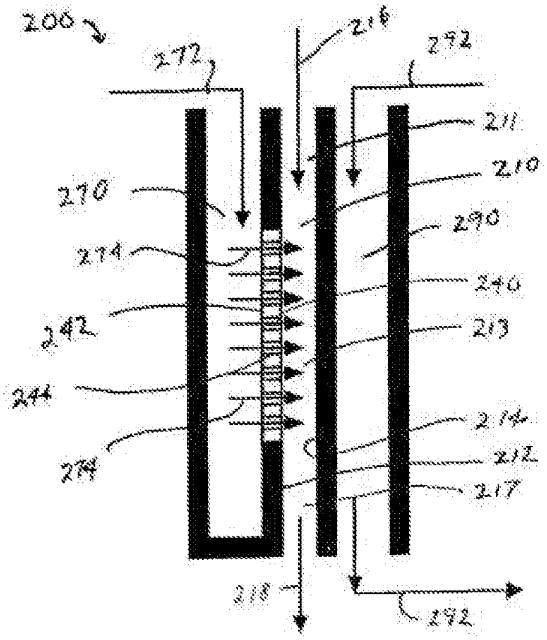
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Abstract not available for JP5643474 (B2)
Abstract of corresponding document: WO2006039568 (A1)

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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B01F	15/06	(2006.01)	B01F	1/00	G
			B01F	5/06	

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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。

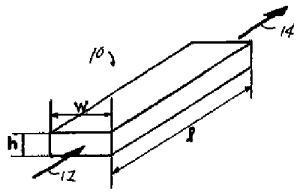
【図２】多相混合物を形成させるためにマイクロチャネルミキサが用いられる、特定の形の本発明のプロセスの例が示されるフローシートである。

【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

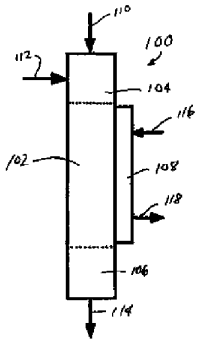
ャネルの中に流入する第二の流体流と混合される。
【図４】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図５】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図６】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図７】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図８】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図９】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【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。

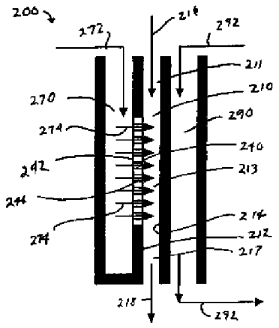
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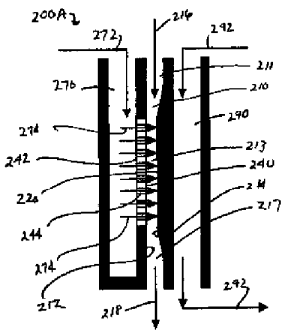
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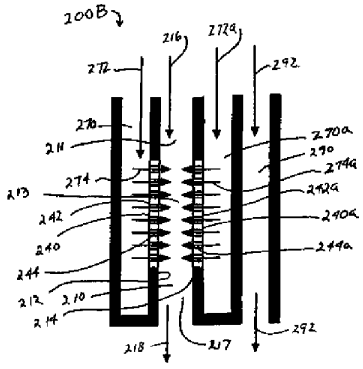
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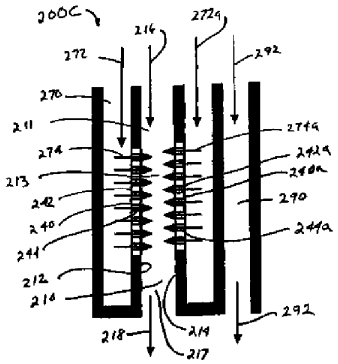
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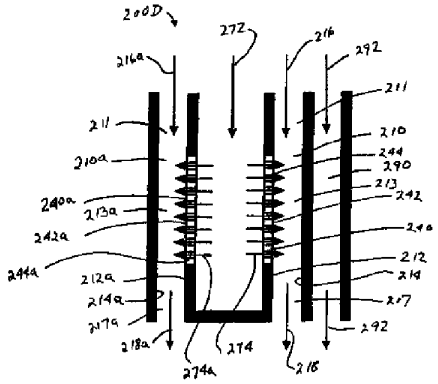
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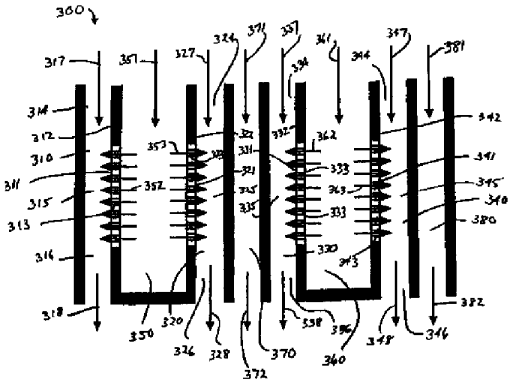
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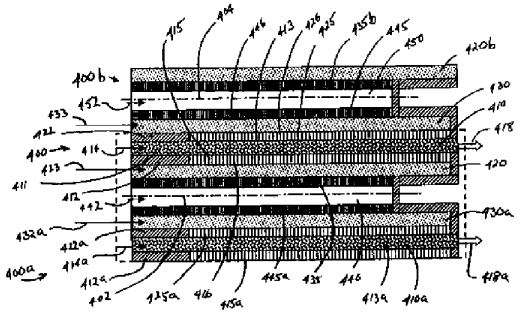
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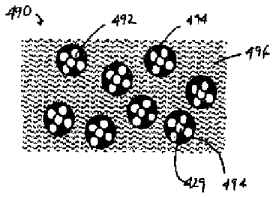
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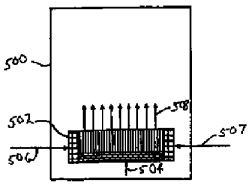
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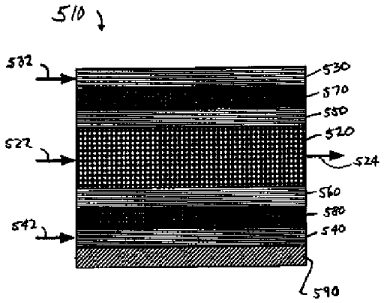
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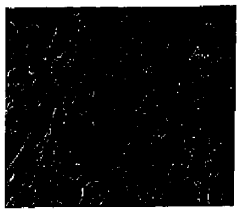
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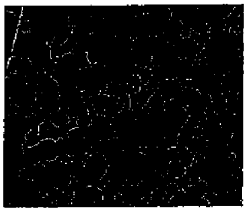
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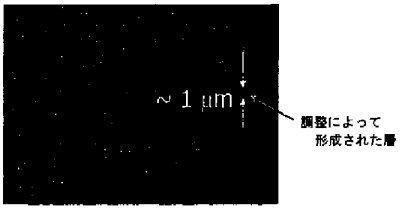
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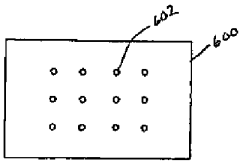
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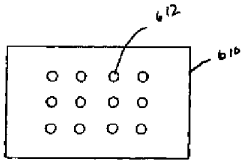
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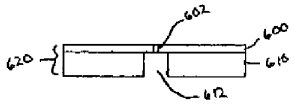
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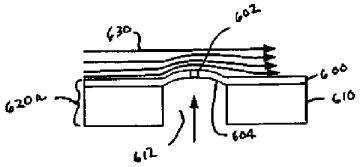
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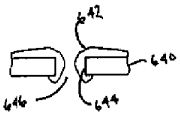
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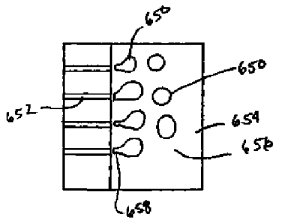
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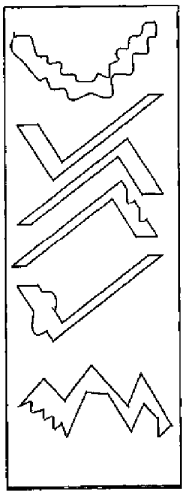
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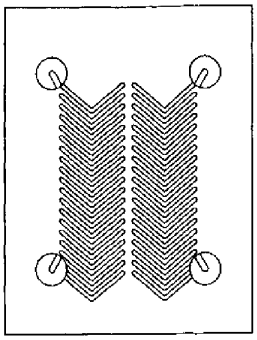
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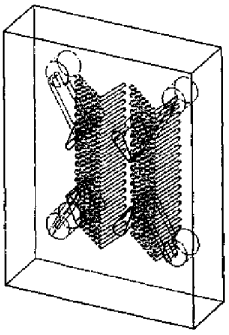
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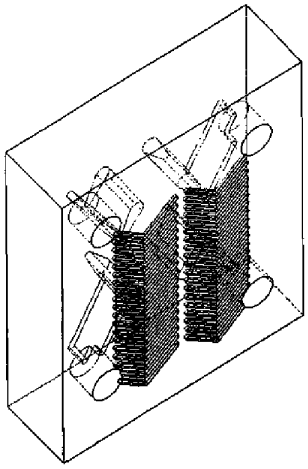
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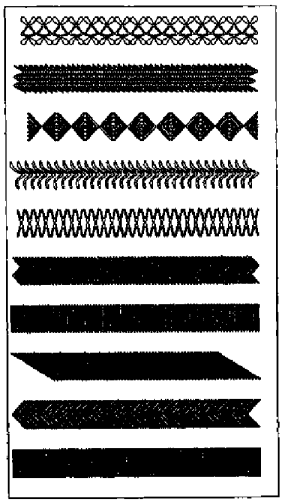
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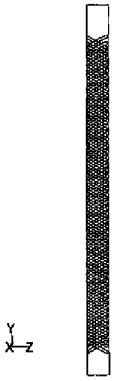
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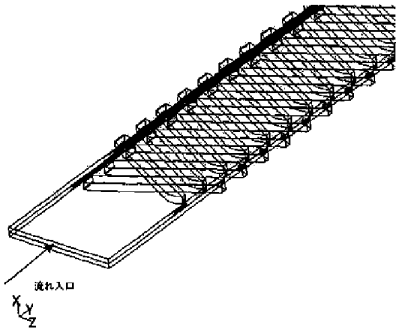
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【図２７】



【図２８】



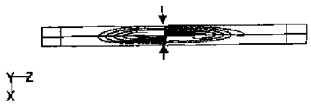
【図２９】



【図３０】



【図３１】



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Blood conservation devices in critical care: a narrative review

Catherine Page*, Andrew Retter and Duncan Wyncoll

Abstract

Anaemia is associated with inferior outcomes in critically ill patients. It is difficult to prevent and is treated commonly with the transfusion of packed red cells. However, transfusion to augment oxygen delivery has not been shown to consistently offer a survival advantage when the haemoglobin concentration exceeds 7 g/dL. Several studies point to inferior outcomes when patients are transfused. Observational studies have confirmed that critically ill patients have frequent blood draws as part of their routine daily care. Cumulatively large volumes of blood are frequently taken, which contribute significantly towards the development of anaemia. Reducing iatrogenic blood loss may reduce the risk of developing anaemia and possibly the need for transfusion. Blood conservation devices may help to achieve this goal. The integration of blood conservation devices into routine care has been relatively slow in critical care. This review summarises the current evidence base and confirms that blood conservation devices do reduce the volume of iatrogenic blood loss. In the most recent studies, these devices have been shown to reduce transfusion requirements even in those intensive care units that follow a restrictive transfusion strategy.

Keywords: Critical care, Blood conservation devices, Anaemia, Transfusion

Review

Introduction

Anaemia and the transfusion of allogenic red blood cells (RBC) are common in the critically ill [1,2]. Observational studies indicate that almost 90% of patients become anaemic by the third day of intensive care unit (ICU) admission [3]. Anaemia is associated with poor patient outcomes, especially amongst those patients with cardiovascular disease [4-7]. Current guidelines strongly support policies of restrictive transfusion, but despite this 40% of ICU patients still receive transfused blood, accounting for approximately 8% of the national blood supply in the UK [8].

Multiple pathogenic mechanisms contribute towards the development of anaemia in critically ill patients. RBC life span is reduced, and there is decreased production of erythropoietin and a blunted marrow response to its action [9]. Hepcidin synthesis is greatly increased in inflammation, trapping iron in macrophages, decreasing plasma iron concentrations, and causing iron-restricted erythropoiesis [10]. In addition to this cytokine milieu, repeated phlebotomy makes a very significant contribution. In one study, weekly blood loss due to phlebotomy was reported to be between 340 to 660 ml [11]. The SOAP study reported a positive correlation between organ dysfunction and the number of blood draws ($r = 0.34$; $P < 0.001$) and the total volume drawn ($r = 0.28$; $P < 0.001$) [1].

Given the high prevalence of anaemia and its detrimental consequences, it appears intuitive to transfuse patients with RBCs in an attempt to restore oxygen delivery and mitigate tissue dysoxia. However, the administration of blood is subject to increased scrutiny. Although the risks related to transfusion, such as infection, febrile, allergic and haemolytic transfusion reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload are very low, concern remains about adverse outcomes associated with blood transfusion [12]. There also is now greater appreciation of the less recognized risks of transfusion relating to RBC storage effects and to the immunomodulatory effects of RBC transfusion [13]. Critically ill patients are likely to be more at risk of the immunosuppressive and microcirculatory complications of blood cell transfusions than the general population. It is due to these risks that minimising the use of blood

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transfusions in the critically ill has become such an important topic. One of the most significant findings during the past decade has been that using transfusions to augment oxygen delivery within the critically ill has not been shown to offer a survival advantage when the haemoglobin (Hb) concentration exceeds 7 g/dL [14]. The strongest evidence guiding transfusion policy in adult critically ill patients comes from the Transfusion Requirements In Critical Care (TRICC) study (Hebert et al., 1999) [15]. Patients with Hb ≥90 g/l were randomized to either the "liberal" group (transfusion trigger of <100 g/l) or the "restrictive" group (transfusion trigger of <70 g/l). The restrictive group received 54% fewer units of blood and 33% received no blood transfusions in the ICU, whereas all of the liberal group received transfusions. Overall, there was a nonsignificant reduction in 30-day mortality for the restrictive group. Significantly, those critically ill patients <55 years and patients with an APACHE score <20, the risk of death at 30 days was significantly lower with the restrictive strategy. For patients aged <55 years, those in the restrictive group had a 5.7% mortality vs. 13% for those in the liberal group (95% confidence interval (CI) for the absolute difference 1.1–13.5%; $P = 0.028$) [14].

The results of the TRICC study have now been corroborated by three recent studies. The Transfusion Requirements After Cardiac Surgery (TRACS) study found no difference in a composite end-point of 30-day mortality and severe comorbidity in cardiac patients prospectively randomized to a liberal or restrictive transfusion strategy [16]. The "FOCUS" study of restrictive transfusion in high-risk patients after hip surgery also showed no difference in mortality or morbidity in the group assigned to the restrictive transfusion strategy [17]. Most recently Villaneuva published the first study examining restrictive transfusion in acute upper gastrointestinal bleeding. There was improved survival in patients with variceal and peptic ulcer bleeding and decreased rates of rebleeding in patients randomized to a lower transfusion threshold [18]. In summary, the most recent literature consistently shows no advantage in transfusing against a liberal transfusion strategy. A restrictive approach to transfusion now is supported by national guidelines [15].

Therefore, the key to conserving RBC transfusions within critical care is by modifying transfusion practice, but this seems difficult to implement. In-line blood conservation devices, which eliminate the need for "discarded" blood when taking blood draws from central and arterial lines, offer a simple solution to try and reduce the need for RBC transfusion. In a survey of members of the Society of Critical Care Medicine in the United States, most agreed that blood conservation devices are useful in preventing anaemia [19]. There is evidence that phlebotomy volumes can be reduced by the use of in-line blood conservation devices. Despite their potential benefits, a survey in 2001 found that only 18% of adult ICUs in England and Wales use blood conservation devices [20]. The reasons for this are not clear but may relate to the cost or a lack of evidence that such devices reduce transfusion requirements.

In recent years, evidence has been published that supports the use of blood conservation devices. This review explores the contribution of phlebotomy to the development of anaemia in the critically ill and examines the role that blood conservation devices may have in its prevention. We searched PubMed looking for articles published on blood conservation devices. The studies identified are summarized in Table 1. The authors reviewed the literature with a particular emphasis on four questions.

1. Is there evidence that blood conservation devices reduce the volume of blood taken from critically ill patients?
2. Does the use of a blood conservation device have an impact on patients' transfusion requirements?
3. Do blood conservation devices have an effect in reducing the number of catheter-related blood stream infections?
4. Are blood conservation devices cost-effective?

Is there evidence that blood conservation devices reduce the volume of blood taken from critically ill patients?

The SOAP study examined phlebotomy practice in 1,136 patients, suggesting a mean blood loss due to phlebotomy of about 41 ml/day/patient [1]. This equates to approximately 280 ml per week; the volume of a unit of packed red cells ranges from 280 to 340 ml. Routine blood tests and arterial blood gas sampling are the commonest interventions in critically ill patients with arterial blood gases accounting for almost 40% of blood drawn from ventilated patients [19]. Patients with arterial catheters are phlebotomized twice as often, and have a threefold increase in blood loss compared with patients who do not have intra-arterial access [29]. The mean frequency of blood draws varies from 5 to more than 24 samples per day [30], with a correlation between the severity of illness and the number of blood draws [1,25,31]. The total volume of diagnostic blood taken is a significant independent predictor of subsequent transfusion [32]. Thus, the sickest patients are at the greatest risk of iatrogenic anaemia and allogenic transfusion.

Conventional arterial line systems require that an initial blood sample be removed to "clear the line". This initial volume is discarded, so that a second sample of undiluted blood can then be obtained. The fraction of "discarded" blood is a major contributory factor in the anaemia of critical illness. The volume of discarded blood typically varies from 2-10 ml. Only the dead space volume of the arterial line is required to be cleared,

Table 1 Current studies relating to the use of blood conservation devices in critical care

Study and year of publication	Design	Outcome
Silver - 1993 [11]	Prospective, randomized crossover comparing the Safedraw device and conventional arterial line.	31 patients enrolled, study period 7 days. Over 7-day period, the control group had a larger blood discard volume by an average of 156.8 ml ($p < 0.001$).
Peruzzi - 1993 [21]	Prospective, randomized, controlled trial comparing the VAMP system to control.	100 patients enrolled, mean study period 4 days. Total volume of blood discarded significantly lower in the VAMP group (19.4 ml vs. 103.5 ml, $p < 0.001$). Hb decreased by 1.4 g/dL in the control vs. 1 g/dL in the VAMP group (p = nonsignificant). Transfusion requirements similar in both groups –no transfusion protocol.
Peruzzi - 1996 [22]	Prospective, randomized trial comparing microbial contamination between the VAMP and Safedraw device.	40 patients studied for an average of 3 days. No difference in contamination rates between the two devices. No catheter-related infections
Thorpe - 2000 [23]	Prospective, randomized trial comparing VAMP device to conventional arterial line.	100 patients followed for 15 days. No significant difference in Hb concentration or transfusion requirements between the two groups. Mean Hb remained >10 throughout study - no transfusion protocol.
MacIsaac - 2003 [24]	Randomized, unblinded, control trial comparing VAMP to control.	160 patients, mean study period 3 days. Total volume of blood discarded significantly lower in the VAMP group (1 ml vs. 62 ml, $p < 0.001$). No significant change in Hb concentration between groups but unadjusted for transfusion. Fewer patients transfused within VAMP group (17 vs. 30 $p = 0.04$)- no transfusion protocol
Mahdy - 2009 [25]	Prospective, randomized, unblinded controlled clinical study. Comparing VAMP plus paediatric vials to control plus adult vials.	39 patients, study period 3 days Total volume of blood discarded significantly less in the VAMP group (0 ml vs. 25 ml, $p < 0.001$) No statistical difference in fall of Hb concentration (0.79 vs. 1.3 g/dL, $p = 0.09$) - no patient required transfusion.
Rezende - 2010 [26]	Prospective, randomized, controlled trial comparing transfusion rates and Hb loss between VAMP system and control.	127 patients followed for 14 days. Smaller decline in Hb within the VAMP group ($p = 0.03$) - no difference in transfusion rate; transfusion threshold 7 g/dL.
Mukhopadhyay - 2010 [27]	Before and after intervention study assessing the impact of a restrictive transfusion strategy when comparing VAMP to control.	250 patients followed for 28 days or until discharge from ICU. Smaller decline in Hb within the VAMP group (1.44 vs. 2.13 g/dL, $p = 0.02$) VAMP group required less transfusions (0.068 vs. 0.131 units/patient/day, $p = 0.02$); transfusion threshold of 7.5 g/dL.
Oto - 2011 [28]	Prospective, randomized study comparing bacterial contamination between VAMP and control.	216 patients followed for a median of 4 days. No statistically significant change in tip colonization between the two groups. No catheter-related infections.

which is actually closer to 2 ml. Closed blood sampling devices (blood conservation devices), where return of the initial discarded sample occurs, can help to reduce the volume of blood "lost". The most common closed arterial system used within the UK is the VAMP (venous-arterial management protection) device produced by Baxter Healthcare, although there are other manufacturers with similar devices. These devices allow blood and flush solution to be drawn into a reservoir distal to the sampling port. Blood is then collected at the sampling port without being diluted with the flush solution. The blood held in the reservoir is reinfused into the patient. It can be used on both arterial and central venous lines and can be accessed with a blunt needle [23]. An image of the system is shown in Figure 1.

During the past 20 years, a number of trials have shown that the use of a blood conservation device can reduce the volume of blood taken from critically ill patients. Silver and colleagues demonstrated that an average of 49 ml less blood was lost per patient per day, and

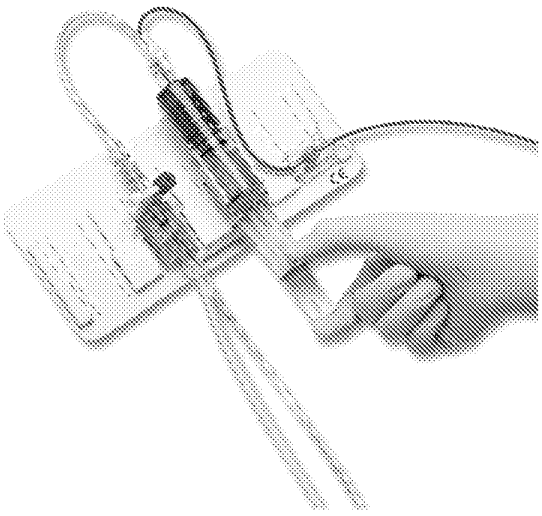


Figure 1 Edwards VAMP system. The port to the right of the image is the sampling port, which is accessed by a needless device. The middle syringe is the reservoir where the previous "discarded" blood is held before being reinfused back into the patient. Picture submitted with permission from Edwards Lifesciences Ltd.

that during a 7-day period an average of 340 ml of blood were saved per patient by using a blood conservation device [11]. A prospective, randomized, controlled trial by Peruzzi showed a marked reduction in the volume of blood discarded daily: 96 ml in the conventional arm compared with 5 ml in patients with the conservation device during the mean study period of 4 days. Although the mean Hb concentration remained consistently higher in the conservation device group, statistical significance was not reached until 9.5 days of ICU care [21].

Thorpe et al. reported the fall in Hb levels during 7 days between the VAMP device and a control group in 102 patients. No significant difference was seen in Hb levels during the 7-day stay; however, their study was small and no data were provided regarding the amount of blood draws taken or volume of phlebotomy between the two groups [23]. MacIsaac published a larger randomized, controlled trial involving 160 patients. The blood conservation device group lost significantly less blood for diagnostic testing (63 ml vs. 133 ml for controls), but the study failed to demonstrate a significant fall in Hb levels between admission and discharge when comparing the two groups [24]. Mahdy reported a small unblinded, randomized, controlled trial comparing the use of a VAMP system plus paediatric bottles against a standard arterial line system plus adult phlebotomy bottles in 39 patients. As expected, there was a statistically significant difference in terms of the volume of blood taken for analysis over the first 72 hours: 15 ml compared with 45 ml [25].

In summary, in all trials the volume of blood taken for diagnostic testing between the blood conservation devices and control groups was significantly less; however, only in the larger trials did this result in a reduced rate of fall in Hb. This could be explained by the small numbers and short study periods, the frequent exclusion of patients receiving renal replacement therapy, and those admitted with a primary bleeding issue. Ironically, it would seem likely that these "excluded patients" may actually be the most at risk of anaemia and might benefit most from a blood conservation device.

Does the use of a blood conservation device have an impact on patient transfusion requirements?

Before 2010, no study provided unequivocal evidence that a blood conservation system reduced transfusion requirements in critically ill patients [21,23,25]. In 2003, MacIsaac et al. published a prospective randomized, unblinded, controlled trial (n = 80) that examined the influence of the VAMP system on anaemia in ICU patients. They demonstrated a statistically significant reduction in transfusion requirements within the VAMP group. Because this was not their primary end point and because no transfusion triggers were set, the results need to be interpreted with caution.

Chant published a retrospective chart review of 155 patients in a medical-surgical ICU that had a greater than 30-day ICU stay [33]. This study found that of patients transfused, daily phlebotomy volume was significantly higher. The unit had a relatively low Hb transfusion trigger of 7.7 g/dL after day 21. They concluded even that small increases in daily phlebotomy volumes were associated with a doubling of the chances of being transfused after day 21.

Mukhopadhyay et al. in 2010 undertook the largest study to date of the VAMP system [27]. They performed a before and after study to investigate whether the use of a blood conservation device in the presence of a standardized, restrictive, transfusion practice could reduce the number of units transfused per patient per day. They showed both a smaller drop in Hb levels between admission and discharge in the intervention group, and most importantly that the use of a blood conservation device was independently associated with lower RBC transfusions (control group 0.13 units vs. active group 0.068 units RBC/patient/day, $p = 0.02$). In most patients, a transfusion threshold of 7.5 g/dL was used, but in 23.8% of the control and 29% of the active group patients were transfused above the threshold. This is very much in keeping with routine clinical practice where clinicians, especially treating patients with significant coronary disease, find it difficult to comply with restrictive transfusion thresholds.

The authors suggested that a blood conservation system is of maximal benefit in patients with higher APACHE II scores, those receiving renal replacement therapy, initial low admission Hb, and longer ICU stays [27]. Interestingly both the ICU (38% vs. 21%) and hospital (53% vs. 30%) mortality in the control group was significantly higher ($P = 0.001$). These findings must be interpreted with care, because the study was not a randomized, controlled trial and mortality was not the primary or secondary endpoint. Nevertheless, even after adjusting for all other variables, mortality in the intervention group remained significantly less.

In summary, of the six studies looking at the impact of blood conservation devices on the rates of transfusion, only one study has shown a positive impact leading to reduced blood product support. However, the majority of studies to date have not incorporated a standardised transfusion threshold, and some studies report patients being transfused at levels as high as 10 g/dL. Therefore, no definitive conclusions can be drawn, but the most recent results are interesting and encouraging.

Do blood conservation devices have an effect in reducing the number of catheter-related blood stream infections?

Although infection is most frequently associated with venous lines, arterial catheterisation also leads to catheter-related bloodstream infection secondary to fluid stagnation and manipulation of the device. When the system is opened for blood sampling, there is a small risk of microbial contamination. In theory, closed blood conservation device systems reduce this risk by minimising access through open sampling ports [28].

Oto et al. reported a prospective randomized study comparing contamination resulting from the use of the VAMP system or a 3-way stopcock that had been in use for >24 hours within the radial artery. Of 216 patients, there was a statistically significant difference in the colonisation of intraluminal fluid (test device 2/109 vs. 9/107 in the control group). There was no difference in colonisation of the tip between the two groups and no arterial catheter-related blood stream infections seen in either group. In both groups the incidence of tip contamination was related to time in situ and frequency of accesses [28]. Similar trends have been observed in other studies during a 7-day period where more lines were colonised in the control group (37/99) compared with the VAMP system (29/96) [23]. These studies confirm earlier findings that suggest blood conservation devices can be used without concern of exacerbating infectious processes [22].

Are blood conservation devices cost effective?

As yet, there is no published data on the cost-effectiveness of these in-line blood conservation devices. However, given that the typical acquisition costs are only marginally above standard transducer systems (approximately 15 Euros for a 72-hour system) and given that blood in Europe is typically approximately 150 Euros per unit, at worst their introduction is likely to be cost neutral. It is difficult to quantify financial savings from the potential patient benefits of reducing transfusion requirements related to subsequent improvements in outcome (reduced mortality/length of stay, etc.) from limiting the effects of "harmful blood". The systems are simple to use and limited training is required.

Conclusions

Only a small number of studies have examined the utility of blood conservation devices. Their advantages are appealing with a reduced risk of needle stick injuries and splashes to staff, along with reduced blood wastage through routine phlebotomy. The literature consistently reports that patients lose less blood when blood conservation devices are used. This combined with a trend towards a reduction in transfusion requirements when blood conservation devices are used alongside restrictive transfusion triggers is encouraging. However, they are only one part of good blood practice. The most effective blood conservation strategies remain the simplest and likely least costly, most importantly complying with restrictive RBC transfusion guidelines and avoidance of excessive testing. In reality, these remain the hardest to implement. Practice is starting to change with increased awareness of the most recent literature and new national guidelines to help support physicians in their decisions surrounding transfusions. We feel that increasing compliance to restrictive transfusion practice by actively auditing against the national guidelines should be encouraged within critical care units. Additionally reducing the number of blood draws is a continuing issue within the critical care community. It is difficult to form guidelines as the requirements for each individual patient will vary on a day-to-day basis. Improved education on the impact phlebotomy has on iatrogenic anaemia, limiting the use of order sets, and improved guidance from senior members of the critical care team towards the junior doctors and nursing staff who frequently are the team members who order the bloods can help to try and change practice. However, from our experience critical care units continue to take high number of blood draws and it would seem sensible to use a blood conservation device that limits discarded blood whilst units continue to try and change their own transfusion practice. If these interventions are combined, there is the potential to reduce significantly iatrogenic anaemia and any adverse consequences of transfusion.

Abbreviations

VAMP: Venous arterial blood management protection; ICU: Intensive care unit; RBC: Red blood cell; Hb: Haemoglobin.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
Dr. DW developed the initial idea and plan for the review, and edited the document. Dr. CP and Dr. AR were primarily responsible for the literature search and writing the initial draft of the article. All authors read and approved the final manuscript.

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Combined blood withdrawal and transfusion appts - for obtaining blood plasma by plasmaphaeresis

Inventor(s):

Applicant(s): IMMUNO AG FUER CHEM-MED PROD

Classification: **- international:** ***A61B5/15; A61M1/02; A61M5/14;*** (IPC1-7): A61M1/00
- cooperative: **A61M1/0236 (EP, US); A61M5/14 (EP, US)**

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Abstract not available for DE7203008 (U)
Abstract of corresponding document: DE2203858 (B2)

Combined blood withdrawal and re-transfusion appts. is intended for obtaining large quantites of plasma by means of plasmaphaeresis; the blood is removed through is needle implanted in a vein and collected in the recipient which is partly filled with an anticoagulation agent. The recipient is taken out of the system and is centrifuged to separate the plasma from the erythrocytes, w which are retained in the recipient. After washing the latter free from plasma, they are made into a suspension in physiological sodium chloride soln. and transfused back to the patient. While this treatment is in progress, a slow current of sodium chloride soln. is infused into the patient from recipient, through the tube and the drop-counting chamber. The recipient, after the process mentioned above, is attached to the connector of the tube. Sodium chloride is transferred to the recipient to form the suspension of the erythrocytes. The suspension is then infused into the patient. The appts., is simple to handle and has the great advantage that the donor is protected because a blood sample can be taken at any moment through the connector to avoid any confusion of blood groups during the plasmaphaeresis.

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DESCRIPTION DE7203008U

[0001]

13 IMMUNO

[0002]

17 Public limited company for chemiscli-medizirii sclie

[0003]

21 Products Vienna (Austria.

22)

[0004]

26 Combined blood collection and infusion device

[0005]

30 Plasmapheresis is used to obtain large quantities of plasma. This is a method in which blood is taken from the donor using a suitable blood-sucking device into a container partially filled with an anticoagulant, after which the container is centrifuged.

33 The plasma which is left over after centrifugation is sucked off and the container with the erythrocytes is connected to an infusion device after it has been suspended in physiological saline solution and the erythrocytes are infused into the donor via the venipuncture needle which is still in the donor's vein.

37 This process is repeated once when performing a so-called double plasmapheresis.

[0006]

41 The infusion devices previously used for plasmapheresis contained a drip chamber

[0007]

45 connecting line leading from a storage vessel to the single or double plasmapheresis bag and this has a further connecting line to the venipuncture needle. The devices for double plasmapheresis contained two

[0008]

51 ■■ió. koi.i

[0009]

55 the corresponding connection lines to the venipuncture needle, which are also inextricably connected to the bags. This inextricable connection between the two bags and the venipuncture needle makes it more difficult and expensive to manufacture and use the devices and does not permit any variation in the work program.

59 E.g., it is not possible to collect centrifuged plasma in a reservoir without the bag intermediate stations. Wolters it is not possible with the known double bag devices to repeat the process of collection and reinfusion more than once, because in practice it is impossible in the device to be produced efficiently, which contains more than four bags which are inseparably connected to one another and to the venipuncture needle by means of corresponding connecting lines.

[0010]

67 The invention aims to avoid the disadvantages and difficulties described and consists in a blood collection and infusion device which has a reservoir for an infusion liquid, a connecting line leading via a drip chamber from the reservoir to the venipuncture needle and a further connection from the venipuncture needle to a blood reservoir, that the blood container provided with one or more connection points can be interchangeably connected to a line branching off from the connecting line between the reservoir and the venipuncture needle, which line is preferably provided with a shut-off element.

[0011]

77 The blood container can be designed as a single-chamber bag or as a two-chamber bag and can advantageously consist of flexible, transparent plastic material.

[0012]

82 As a result of the detachable connection of the ulutbehltex-s with the other parts of the device, the manufacture of the container is simpler and cheaper; the work program can be varied and modified in any way.

85 It is thus possible, after the contents of the blood container have been centrifuged, to convey the plasma into a second bag connected to the first bag or into another storage container.

87 It is also possible to repeat the process of removal and infusion not just twice but as often as you like, which z.

89 B. is essential in leukocytopheresis and thrombocytopheresis, in which cases the process is to be repeated up to 10 times.

91 Throughout the manipulation, the venipuncture can be left in the donor's vein

[0013]

95 The subject of the invention is explained in more detail using an exemplary embodiment in the drawing.

97 1 denotes the reservoir for an infusion liquid, with which the line 2 leading to the drip chamber 3 can be connected.

99 h

100 is a shut-off device in this line.

101 A branch piece 5, which is also a shut-off device

102 H

103 y

104 has, carries a coupling piece 6, which is connected to the blood container in the reinfusion phase in a manner to be described later.

106 From the drip chamber 3 leads the line 7, which is also a shut-off device

107 c"

108 has, to the venipuncture needle 8.

109 According to the invention, the line 9 branches off from this connecting line between the reservoir and the venipuncture needle and again has a shut-off element 4

111 nl

112 has and a coupling piece 10 has.

113 The blood container 11 designed as a single-chamber bag can be releasably connected to the line 9 via the attachment piece 12 and the coupling piece 10. The bag is preferably made of flexible and transparent plastic material

116 lk

117 are closable removal openings of the bag

[0014]

121 designated.

122 An embodiment of the invention consists in the fact that the bag 11 is connected to the bag 16, which is otherwise constructed in the same way, by means of a vesicle line; in this case, the blood container is designed as a two-chamber bag

[0015]

128 The function of the device is the following: After connecting the container 1 to the line 2, with the shut-off elements 4 and 4'' open and the shut-off element s 4'' and 4Ml closed, the system is completely filled with physiological before inserting the venipuncture needle into the vein, avoiding air bubbles Saline solution filled. Then the shut-off element 4M in the line 7 is closed and the venipuncture needle inserted into the vein is connected to the B^ätsl 11 by connecting the coupling piece 10 to the attachment 12, the shut-off element 4Mt is opened and blood collection begins.

135 After the desired amount of blood has been removed, the shut-off element 4''' is closed and the container 11 is separated from the system.

137 Now another bag is connected to the coupling piece 10.

138 Then, with the shut-off element 4 still open, the shut-off element 4'' is opened and a slow flow of physiological saline solution is infused into the donor's vein.

140 After removal from the system, the bag 11 is centrifuged and the supernatant plasma is separated from the sediment and collected.

142 The sediment remains in the blood bag 11 .

143 In the next phase, the shut-off device 4n in the line 7 is closed, the blood bag 11 is connected to one of the connectors 13 or 14 with the coupling piece 6 of the line 5, 4'' is closed. 41 is opened and physiological saline solution is transferred into the bag 11 until a infusable suspension of erythrocytes in the physiological saline is formed.

147 Then the obturator 4 is

[0016]

151 closed, kopened and the suspension infused into the vein. The process can be repeated as often as desired, whereby, as mentioned earlier, the blood container can be designed either as a single or as a double bag.

154 As can be seen, the device is easy to use; Compared to the known devices, it also has the further great advantage that, to protect the donor during the plasmapheresis procedure, the blood group of the donor can be checked at any time by taking a blood sample at the coupling piece 10 in order to avoid mixing up the blood group when the erythrocytes are reinfused.

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1.

13 * Uc/n sayings t

2.

17 1. Combined blood collection and infusion device for carrying out single and multiple plasma.phereses or leukocyto- and thrombocytophereses, with a reservoir for an infusion liquid, a connecting line leading via a drip chamber from the storage vessel to the venipuncture needle and a further connection from the Venipuncture needle to a blood reservoir, characterized in that the blood reservoir (II), which is provided with one or more connection points, can be interchangeably connected to a line (9) branching off from the connecting line (7) between the reservoir (1) and the venipuncture needle (8), which is preferably equipped with a shut-off element (kn1) is provided, can be connected.

3.

28 2, Combined blood collection and infusion device according to Claim 1, characterized in that the blood container (II) is designed as a single-chamber bag or as a two-chamber bag and preferably consists of flexible, transparent plastic material.

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Bekanntmachungstag: 10. 5. 1972

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Vtr: Glawe, R., Dr.-Ing.; Delfs, K., Dipl.-Ing.; Moll, W., Dipl.-Phys. Dr. rer.nat; Pat.-Anwälte, 8000 München und 2000 Hamburg;

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Kombiniertes Blutabnahme- und Infusionsgerät

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Kombiniertes Blutabnahme- und Infusionsgerät

Zur Gewinnung großer Plasma-Mengen wird die Plasmapherese angewendet. Dies ist eine Methode, bei der dem Spender mittels eines geeigneten Abnahmegerätes Blut in ein mit einem gerinnungshemmenden Mittel teilweise gefüllten Behälter abgenommen wird, worauf der Behälter zentrifugiert wird. Das nach dem Zentrifugieren überstehende Plasma wird abgesaugt und der Behälter mit den Erythrocyten wird nach Aufschwemmen mit physiologischer Kochsalzlösung an ein Infusionsgerät angeschlossen und die Erythrocyten werden über die noch in der Vene des Spenders befindliche Venenpunktionsnadel dem Spender infundiert. Dieser Vorgang wird bei Durchführung einer sogenannten Doppelplasmapherese einmal wiederholt.

Die für Plasmapheresen bisher verwendeten Infusionsgeräte enthielten eine über eine Tropfkammer führende Verbindungsleitung von einem Vorratsgefäß zum Einfach- oder Doppelplasmapheresebeutel und dieser besitzt eine weitere Verbindungsleitung zur Venenpunktionsnadel. Die Geräte für Doppelplasmapheresen enthielten zwei

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miteinander unlösbar verbundene Blutabnahmebeutel mit den entsprechenden, ebenfalls mit den Beuteln unlösbar verbundenen Verbindungsleitungen zur Venenpunktionsnadel. Diese unlösbare Verbindung der beiden Beutel und der Venenpunktionsnadel untereinander erschwert und verteuert die Herstellung und Handhabung der Geräte und erlaubt keinerlei Variation im Arbeitsprogramm. Z.B. ist es nicht möglich, zentrifugiertes Plasma ohne die Beutelzwischenstationen in einem Vorratsbehälter zu sammeln. Weiters ist es mit den bekannten Doppelbeutelgeräten nicht möglich, den Vorgang der Abnahme und Reinfundierung mehr als einmal zu wiederholen, weil es in der Praxis unmöglich ist, ein Gerät rationell herzustellen, welches mehr als vier, durch entsprechende Verbindungsleitungen unlösbar miteinander und mit der Venenpunktionsnadel verbundene Beutel enthält.

Die Erfindung bezweckt die Vermeidung der geschilderten Nachteile und Schwierigkeiten und besteht bei einem Blutabnahme- und Infusionsgerät, welches einen Vorratsbehälter für eine Infusionsflüssigkeit, eine über eine Tropfkammer führende Verbindungsleitung vom Vorratsgefäß zur Venenpunktionsnadel und eine weitere Verbindung von der Venenpunktionsnadel zu einem Blutbehälter aufweist, darin, daß der mit einer oder mehreren Anschlußstellen versehene Blutbehälter austauschbar an eine von der Verbindungsleitung zwischen Vorratsbehälter und Venenpunktionsnadel abzweigenden Leitung, die vorzugsweise mit einem Absperrorgan versehen ist, anschließbar ist.

Der Blutbehälter kann als Einkammerbeutel, oder als Zweikammerbeutel ausgebildet sein und vorteilhaft aus flexiblem transparentem Kunststoffmaterial, bestehen.

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Infolge der lösbaren Verbindung des Blutbehälters mit den übrigen Teilen des Gerätes ist die Herstellung des Behälters einfacher und billiger; das Arbeitsprogramm kann in beliebiger Weise variiert und modifiziert werden. So ist es möglich, nach Zentrifugieren des Inhaltes des Blutbehälters das Plasma in einen mit dem ersten Beutel verbundenen zweiten Beutel oder in einen sonstigen Vorratsbehälter zu fördern. Es ist ferner möglich, den Vorgang der Abnahme und Infusion nicht nur zweimal sondern beliebig oft zu wiederholen, was z.B. wesentlich ist bei der Leukozyto- und Thrombozytopherese, in welchen Fällen der Vorgang bis zu 10 mal zu wiederholen ist. Während der gesamten Manipulation kann die Venenpunktionsnadel in der Vene des Spenders verbleiben.

Der Erfindungsgegenstand ist an einem Ausführungsbeispiel in der Zeichnung näher erläutert. Mit 1 ist der Vorratsbehälter für eine Infusionsflüssigkeit bezeichnet, mit dem die zur Tropfkammer 3 führende Leitung 2 verbindbar ist. 4 ist ein Absperrorgan in dieser Leitung. Ein Abzweigstück 5, welches ebenfalls ein Absperrorgan 4' aufweist, trägt ein Kupplungsstück 6, welches in später noch zu beschreibender Weise mit dem Blutbehälter in der Reinfusionsphase verbunden wird. Von der Tropfkammer 3 führt die Leitung 7, die ebenfalls ein Absperrorgan 4" aufweist, zur Venenpunktionsnadel 8. Von dieser Verbindungsleitung zwischen Vorratsbehälter und Venenpunktionsnadel zweigt erfindungsgemäß die Leitung 9 ab, die wieder ein Absperrorgan 4"' aufweist und ein Kupplungsstück 10 besitzt. Der als Einkammerbeutel ausgebildete Blutbehälter 11 ist über das Ansatzstück 12 und das Kupplungsstück 10 lösbar mit der Leitung 9 verbindbar. Der Beutel besteht vorzugsweise aus flexiblem und transparentem Kunststoffmaterial. Mit 13 und 14 sind verschließbare Entnahmeöffnungen des Beutels

bezeichnet. Eine Ausführungsform der Erfindung besteht darin, daß der Beutel 11 durch eine Verbindungsleitung 15 mit dem sonst in gleicher Weise ausgebildeten Beutel 16 verbunden ist; in diesem Fall ist der Blutbehälter also als Zweikammerbeutel ausgebildet.

Die Funktion des Gerätes ist die folgende: Nach Verbinden des Behälters 1 mit der Leitung 2 wird bei geöffneten Absperrorganen 4 und 4" und geschlossenen Absperrorganen 4' und 4"' das System vor Einführen der Venenpunktionsnadel in die Vene unter Vermeidung von Luftblasen vollständig mit physiologischer Kochsalzlösung gefüllt. Dann wird das Absperrorgan 4" in der Leitung 7 geschlossen und die Venenpunktionsnadel in die Vene eingeführt. Dann wird durch Verbinden des Kupplungsstückes 10 mit dem Ansatzstück 12 der Beutel 11 angeschlossen, das Absperrorgan 4"' geöffnet und die Blutabnahme beginnt. Nach Entnahme der gewünschten Blutmenge wird das Absperrorgan 4"' geschlossen und der Behälter 11 vom System abgetrennt. Nun wird ein weiterer Beutel an das Kupplungsstück 10 angeschlossen. Sodann wird bei noch offenem Absperrorgan 4 das Absperrorgan 4" geöffnet und ein langsamer Fluß von physiologischer Kochsalzlösung in die Vene des Spenders infundiert. Der Beutel 11 wird nach Abnahme vom System zentrifugiert und das überstehende Plasma von dem Sediment getrennt und gesammelt. Im Blutbeutel 11 bleibt das Sediment übrig. In der nächsten Phase wird das Absperrorgan 4" in der Leitung 7 geschlossen, der Blutbeutel 11 mit einem der Anschlußstücke 13 oder 14 mit dem Kupplungsstück 6 der Leitung 5 verbunden, 4" geschlossen, 4' geöffnet und physiologische Kochsalzlösung in den Beutel 11 übergeführt, bis eine infundierbare Suspension von Erythrocyten in der physiologischen Kochsalzlösung gebildet ist. Dann wird das Absperrorgan 4 ge-

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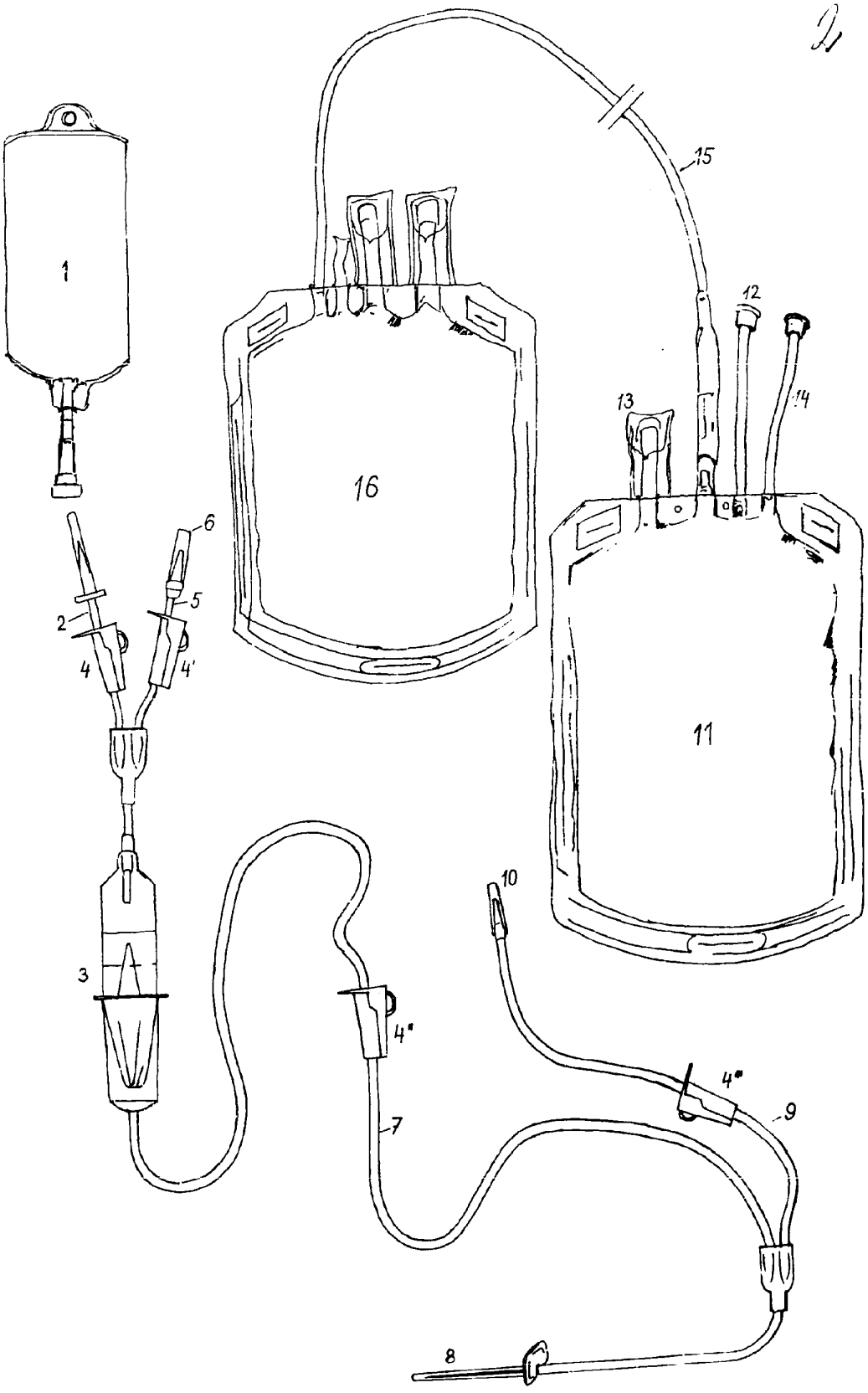
schlossen, 4" geöffnet und die Suspension in die Vene infundiert. Der Vorgang kann beliebig oft wiederholt werden, wobei, wie früher erwähnt, der Blutbehälter entweder als Einfach- oder als Doppelbeutel ausgeführt sein kann. Wie ersichtlich, ist das Gerät einfach zu bedienen; es hat gegenüber den bekannten Geräten auch noch den weiteren großen Vorteil, daß zum Schutz des Spenders während der Plasmapheresеprozedur jederzeit die Blutgruppe des Spenders durch Entnahme einer Blutprobe beim Kupplungsstück 10 kontrolliert werden kann, um eine Verwechslung der Blutgruppe bei der Reinfusion der Erythrocyten zu vermeiden.

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Patentansprüche:

1. Kombiniertes Blutabnahme- und Infusionsgerät zur Durchführung von Einfach- und Mehrfachplasmapheresen bzw. von Leukozyto- und Thrombozytopheresen, mit einem Vorratsbehälter für eine Infusionsflüssigkeit, einer über eine Tropfkammer führenden Verbindungsleitung vom Vorratsgefäß zur Venenpunktionsnadel und einer weiteren Verbindung von der Venenpunktionsnadel zu einem Blutbehälter, dadurch gekennzeichnet, daß der mit einer oder mehreren Anschlußstellen versehene Blutbehälter (11) austauschbar an eine von der Verbindungsleitung (7) zwischen Vorratsbehälter (1) und Venenpunktionsnadel (8) abzweigenden Leitung (9), die vorzugsweise mit einem Absperrorgan (4''') versehen ist, anschließbar ist.

2. Kombiniertes Blutabnahme- und Infusionsgerät nach Anspruch 1, dadurch gekennzeichnet, daß der Blutbehälter (11) als Einkammerbeutel oder als Zweikammerbeutel ausgebildet ist und vorzugsweise aus flexiblem transparentem Kunststoffmaterial besteht.



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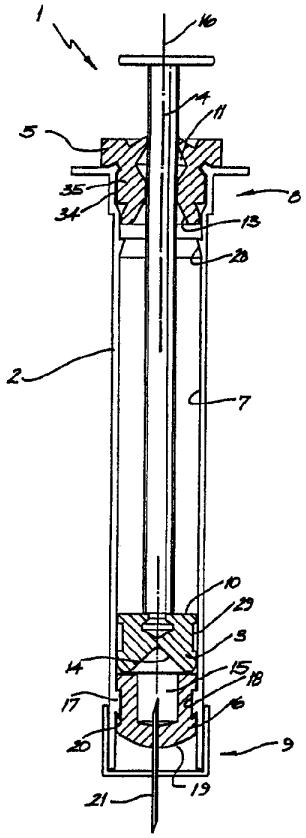
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(54) Title: BODY FLUID EXTRACTION DEVICE

(57) Abstract

A device (1) for extracting body fluid in which depression of a plunger (4) into a tubular body (2) during a preparatory stroke creates a pressure reduction in a first chamber (12). After the preparatory stroke, the pressure reduction in the first chamber (12) exerts a force on a piston (3) to cause it to move and thereby to draw body fluid into a second chamber (15). The rate of extraction of the body fluid is governed by a frictional force on the plunger (4) which can be controlled by a cam arrangement (5).



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BODY FLUID EXTRACTION DEVICE

Field of the Invention

The present invention relates to devices for extracting body fluid, and more particularly to a device for extracting body fluid in which a pressure reduction is created by depression of a piston into a tubular body, and the pressure reduction so created is used to draw fluid into the tubular body.

Background

A conventional apparatus for extracting a body fluid, such as blood from a patient, usually comprises a cannula and an evacuated vial which is sealed with a rubber-like membrane. It is common practice to extract the body fluid by inserting a first end of the cannula into a part of the patient's body which contains the body fluid, followed by piercing the rubber-like membrane with a second end of the cannula. Body fluid is then drawn through the cannula into the evacuated vial.

A first disadvantage of the conventional apparatus for body fluid extraction is that the rate of flow of body fluid into the evacuated vial cannot be accurately and easily controlled, but depends on such parameters as the diameter of the cannula and the pressure inside the evacuated tube. In the case of blood extraction, it is desirable to control the rate of extraction, especially from weak patients, to avoid causing the patient's blood vessels to collapse.

A second disadvantage of the conventional apparatus for body fluid extraction is that it is potentially hazardous. In order that they may have sufficient strength to sustain a required low internal pressure, the evacuated vials are usually constructed from glass. However, this presents a potential hazard because glass vials can be shattered easily to expose sharp edges which can cut workers or technicians. This can be especially

dangerous when the vials contain hazardous substances such as blood infected with viruses.

A third disadvantage of the conventional apparatus for body fluid extraction is that it requires the maintenance of a stock of evacuated vials. Over time, the low pressures in such vials may degrade such that the vials may not be effective in receiving body fluid.

A fourth disadvantage of the conventional apparatus for body fluid extraction is that the evacuated vial cannot be pre-filled easily and accurately to predetermined levels with such fluids as anticoagulants or agents for separating red and white blood cells.

A fifth disadvantage of the conventional apparatus for body fluid extraction is that, once the body fluid is extracted, withdrawal of a sample of the body fluid from the evacuated vial for analysis can be difficult or dangerous. To withdraw a sample from the conventional apparatus, one end of the evacuated vial is usually removed, and the sample is sucked into a pipette. This can lead to spread of disease.

Summary of the Invention

In preferred embodiments the present invention overcomes at least some of the above deficiencies of conventional body fluid extraction devices.

According to one broad form of the invention, there is provided a device for extracting body fluid having a syringe-type construction. The device includes a tubular body having a proximal end, a distal end, and a bore.

A piston is disposed within the bore. The piston has a proximal face, a distal face, and an outer face which is in slidable contact with the bore.

A plunger, which has a shank, is mounted slidably at the proximal end of the tubular body and removably attached to the proximal face of the piston for pushing the piston from the proximal end of the tubular body

towards the distal end of the tubular body during a preparatory stroke in which external pressure is applied to the plunger.

A sealing means is used to seal the shank slidably to the proximal end of the tubular body so as to form a first chamber defined by the bore, the shaft, the proximal face of the piston and the distal face of the sealing means. A pressure reduction is formed in the first chamber during the preparatory stroke of the plunger.

Closure means are provided to close the distal end of the tubular body so as to form a second chamber defined by the bore, the distal face of the piston and the closure means. The closure means is adapted to cooperate with filling means which places the body fluid in communication with the second chamber.

After the preparatory stroke when external pressure is removed from the plunger, the pressure reduction in the first chamber causes the piston to move towards the proximal end of the tubular body and to draw the body fluid into the second chamber.

The rate of extraction of body fluid is preferably made controllable by providing a cam arrangement in which rotation of the sealing means causes a variation of a frictional force on the plunger. Non-circular cross sections are preferably provided on a lip at the proximal end of the tubular body and to a groove around an outer surface of the sealing means which engages with the lip. The sealing means can be rotated within the lip about an axis of rotation. The sealing means is constructed from a compressible elastic material such that, during rotation, its motion relative to the lip, combined with the non-circular cross sections, causes a variation in an internal pressure in the compressible elastic material. The magnitude of the internal pressure is determined by an angle of rotation of the sealing means relative to the

lip. The shaft of the plunger passes through a hole in the sealing means so that the internal pressure is communicated as a controllable pressure of the sealing means on the shaft. This results in a controllable frictional force between the sealing means and the shaft, and this retards the rate of movement of the plunger, the rate of movement of the piston, and the rate of body fluid extraction.

In a preferred embodiment of the invention a bung is situated within the bore between the piston and the distal end of the tubular body and constitutes the closure means. The bung has an outer wall which is in slidable contact with the bore, so as to form the second chamber defined by the bore, the distal face of the piston, and the bung. At the end of the preparatory stroke, an arresting means retains the bung at the distal end of the tubular body.

In the abovementioned preferred embodiment, the arresting means which retains the bung at the distal end of the tubular body preferably comprises a circumferential rib around the bore and a circumferential groove around the outer wall of the bung. The bung is constructed from an elastic material and has a distal surface with a generally convex shape so that, during the preparatory stroke, the distal surface passes the circumferential rib. At the end of the preparatory stroke, the circumferential rib is substantially aligned with the circumferential groove. The circumferential rib has a cross section with an acute edge proximate the distal end of the tubular body. The acute edge engages with the circumferential groove so as to impede the movement of the bung towards the proximal end of the tubular body, and thus acts to retain the bung at the distal end of the tubular body.

In this way, a body fluid extraction device is

provided in which the rate of body fluid extraction can be controlled easily and accurately. In addition, the body fluid extraction device can be constructed from a plastic-like material so that hazards due to shattering of evacuated vials are eliminated. Further, the pressure reduction in the first chamber need only be created immediately before the device is to be used; thus avoiding the problems due to loss of low pressure in the evacuated vial. The device can be pre-filled easily and accurately to predetermined levels with fluids such as anticoagulant agents. Finally, samples containing precise amounts of body fluid can be withdrawn from the body fluid extraction device because a cannula can be fitted to the distal end of the tubular body, and the fluid can be expelled from the device in the same way that fluids can be expelled from a hypodermic syringe.

Brief Description of the Drawings

The invention will now be further described with reference to the accompanying drawings in which:

Fig. 1 is a longitudinal section of a body fluid extraction device in accordance with a preferred embodiment of the invention in which the device is shown before use;

Fig. 2 is a longitudinal section of the body fluid extraction device of Fig. 1 in which the device is shown at the end of a preparatory stroke;

Fig. 3 is a longitudinal section of the body fluid extraction device of Fig. 1 in which the device is shown after body fluid has been extracted;

Fig. 4 is an end view of a sealing means adapted to fit into a proximal end of the body fluid extraction device of Fig. 1, viewed from the proximal end of the device;

Fig. 5 is an end view of the body fluid extraction device of Fig. 1, viewed from the proximal end of the

device;

Fig. 6 is a longitudinal sectional view of a needle like device which can be utilised in the withdrawal of body fluid from the body fluid extraction device; and

Fig. 7 is a longitudinal section of a body fluid extraction device according to a second embodiment of the invention in which the device is shown before use.

Detailed Description of the Preferred Embodiment

Figs. 1 to 3 show an illustrative embodiment of the body fluid extraction device 1 which comprises syringe-like tubular body 2, piston 3, plunger 4, sealing means 5, and bung 6. Bore 7 is situated inside tubular body 2 and extends from proximal end 8 to distal end 9. Bore 7, piston 3, plunger 4, and bung 6 all have longitudinal axes which are substantially coincident.

Piston 3 is disposed within tubular body 2 in slidable contact with bore 7 and is shaped so as to form a substantially air-tight seal against bore 7.

Plunger 4 is removably attached to proximal face 10 of piston 3 and extends out of proximal end 8 of tubular body 2 through hole 11 in sealing means 5.

Sealing means 5 forms substantially air-tight seals against bore 7 and plunger 4. In addition circular lip 23 surrounding the proximal end of body 2 is sealingly engaged by groove 22 in sealing means 5. Plunger 4 can slide through hole 11 while retaining a substantially air-tight seal with sealing means 5.

First chamber 12 is defined by proximal face 10 of piston 3, bore 7, plunger 4, and face 13 of sealing means 5. The position of piston 3 relative to proximal end 8 defines a volume of first chamber 12.

Bung 6 is disposed within tubular body 2 in slidable contact with bore 7 between distal face 14 of piston 3 and distal end 9 of tubular body 2. Bung 6 is shaped so as to form a substantially air-tight seal against bore 7.

Distal face 14 of piston 3, tubular body 2, and bung 6 define second chamber 15 in which body fluid is to be collected and temporarily stored and into which anti-coagulants and other reagents may be pre-filled.

Fig. 1 shows body fluid extraction device 1 in a state before use. In this state, proximal face 10 of piston 3 is close to sealing means 5 so that the volume of first chamber 12 is small.

Body fluid extraction device 1 is prepared for use by a preparatory stroke in which external pressure is applied to plunger 4 along longitudinal axis 16 of tubular body 2 to cause plunger 4, piston 3, and bung 6 to move away from proximal end 8 toward distal end 9.

During the preparatory stroke, the movement of piston 3 causes the volume of first chamber 12 to increase. Because sealing means 5 forms substantially air-tight seals with tubular body 2 and plunger 4, substantially no air enters first chamber 12, and so the increase of the volume of that chamber causes a pressure decrease there.

At, or close to, the end of the preparatory stroke, plunger 4, piston 3, and bung 6 reach the position shown in Fig. 2. At this position, an arresting means impedes the movement of bung 6 so that it cannot move freely back toward proximal end 8.

Preferably, the arresting means comprises circumferential rib 17 around bore 7 and circumferential groove 18 around the outer wall of bung 6. Bung 6 is constructed from an elastic material and has a distal surface 19 with a generally convex shape so that, during the preparatory stroke, distal surface 19 passes circumferential rib 17. At the end of the preparatory stroke, circumferential rib 17 is substantially aligned with circumferential groove 18. Circumferential rib 17 has a cross section with an acute edge 20 proximate distal

end 9 of tubular body 2. Acute edge 20 engages with circumferential groove 18 so as to impede the movement of bung 6 back towards proximal end 8 of tubular body 2, and thus acts to retain bung 6 at distal end 9.

With the device in the state illustrated in Fig. 2, a filling means allows body fluid such as blood to be brought into fluid contact with second chamber 15. Preferably, the filling means comprises cannula 21 as shown in Figs. 2 and 3. When distal end 9 is brought into contact with cannula 21, bung 6 is pierced; thus preparing a path for body fluid to flow into second chamber 15.

After the preparatory stroke, external pressure is removed from plunger 4. The pressure reduction in first chamber 12 exerts an attractive force on proximal face 10 of piston 3 to cause it to move toward proximal end 8 and away from distal end 9. This movement of piston 3, together with the arrested position of bung 6, creates a pressure reduction in second chamber 15 which causes body fluid to be drawn into that chamber.

As second chamber 15 fills with body fluid, piston 3 and plunger 4 move away from distal end 9 toward proximal end 8. When piston 3 reaches a position sufficiently close to proximal end 8, the body fluid extraction ceases. At this point, the cannula 21 may be removed, and plunger 4 may be removed from piston 3. In this way, second chamber 15 forms a substantially sealed container for holding body fluid.

The rate of extraction of body fluid can be controlled, for example, by governing the rate at which plunger 4 (and hence piston 3) are allowed to move back towards proximal end 8. In the preferred embodiment, this rate is governed by a cam arrangement which can be used to adjust a frictional force exerted on plunger 4 by sealing means 5.

As illustrated in Figs. 4 and 5, such a frictional

force can be rendered adjustable by providing on sealing means 5 a body portion 35 having a non-circular outer cross section, and a similar non-circular inner cross section to a portion 34 of the tubular body 2 proximal end 8 of tubular body 2. Body portion 35 has a large dimension 24 and a small dimension 25. Similarly, portion 34 of the tubular body has a large dimension 26 and a small dimension 30.

Sealing means 5 is constructed from a compressible elastic material such that any attempt to deform its outer surface results in a variation of an internal pressure within the compressible elastic material. Plunger 4 passes through hole 11 in sealing means 5 so that the internal pressure is communicated as a pressure of sealing means 5 on plunger 4. This results in a frictional force between sealing means 5 and plunger 4 which retards its rate of movement.

Sealing means 5 can be rotated within portion 34 of the tubular body 2 about longitudinal axis 16. When sealing means 5 is rotated relative to portion 34 of tubular body 2 such that large dimensions 26 and 24 are substantially collinear. The internal pressure in sealing means 5 is a minimum. However, when sealing means 5 is rotated relative to portion 34 of tubular body 2 such that large dimension 26 is substantially collinear with small dimension 30, the internal pressure in sealing means 5 is a maximum.

Thus, by varying an angle of rotation of sealing means 5 relative to tubular body 2, a user of the device can control the amount of pressure exerted by sealing means 5 on plunger 4. This results in a controllable frictional force between sealing means 5 and plunger 4 which controllably retards the rate of movement of plunger 4, the rate of movement of piston 3, and the rate of body fluid extraction.

After body fluid extraction device 1 is filled, as illustrated in Fig. 3, cannula 21 and plunger 4 can be removed to form a substantially sealed container in which body fluid can be stored.

Samples of body fluid can be withdrawn from body fluid collection device 1 using several methods. A first method comprises the steps of inserting a needle, cannula or similar device through bung 6 into second chamber 15 containing the body fluid, attaching a plunger to proximal face 10 of piston 3, and applying external pressure along longitudinal axis 16 so as to move piston 3 towards distal end 9 and to expel body fluid through the cannula. Circumferential rib 17 around bore 7 is provided with acute edge 20 to engage with circumferential groove 18 around the outer surface of bung 6 to ensure that the insertion of a cannula or the like through bung 6 does not cause the bung to move into bore 7 toward proximal end 8, but instead causes acute edge 20 to further engage with circumferential groove 18. Preferably, acute angle 20 is thirty degrees.

Fig 6 shows a preferred form of a needle-like device 27 for insertion through bung 6 to allow withdrawal of body fluid from second chamber 15. Device 27 is circular in cross-section and has a bore 28 extending axially through it. A first end portion 29 of device 27 is of narrow external diameter and is sharpened to point 31. Second end portion 32 is frustoconical in shape. An annular ridge 33 is formed between first and second end portions 29 and 32. In use first end portion is pushed through bung 6. The body fluid in second chamber 15 may be expressed through bore 28 by depressing plunger 4 and thus piston 13. This form of device has the advantage that after communication has been established with the contents of the second chamber 15 there are no sharp edges projecting from device 1 on which a user could be cut.

A second method of withdrawing a sample of body fluid from body fluid extraction device 1, for which method piston 3 is constructed from a penetrable material, comprises the steps of inserting a cannula attached to a suitable sampling device such as a hypodermic syringe through hole 11 in sealing means 5 and through piston 3 into second chamber 15, and to withdraw body fluid into the sampling device. Circumferential ledge 28 around bore 7 engages with circumferential slot 29 around the outer surface of piston 3 to ensure that the insertion of the cannula through piston 3 does not cause that piston to move into bore 7 toward distal end 9.

Before use, body fluid extraction device 1 can be operated as a hypodermic syringe to pre-fill tubular body 2 with fluids such as anticoagulants or agents for separating red and white blood cells.

Fig. 7 shows a fluid or blood extracting device quite similar to that of the device shown in Fig. 1 but includes a plug 114 which is screwed, by screw thread 116, into sealing engagement with end 93 of body 91 at the tapered matching surfaces 115. Plug 114 also provides an air seal about plunger 96 at cylindrical region 114.

Plug 114 frictionally grips plunger 96 at cylindrical portion 117, the frictional grip being adjustable by way of adjusting the screw pressure applied to plug 114. Tight screw pressure applied to plug 114 results in tapered surfaces 115 radially compressing the volume of plug 114 that surrounds portion 117, thus increasing the frictional grip between plug 114 and plunger 96. By reducing the screw force applied to plug 114, but not so much as to violate the seal at surfaces 115, the radial pressure applied to surface portion 117 is reduced and the frictional grip reduced.

In the arrangement of Fig. 7 engagement portion 98 of plunger 96 comprises a cylindrical boss separated from the

remainder of plunger 96 by a groove. Engagement portion 98 is resiliently gripped by piston head 95 which is made of rubber or some similar elastomeric material.

Immediately before use the device is in the configuration as illustrated in Fig. 7. Cap 112 is removed and a suitable cannular inserted into sleeve 111. Piston head 95 is then pressed fully down to end 94, by applying pressure to handle 97. By virtue of the seal applied by plug 114 at surface area 118 with plunger 96 and at surfaces 115 with body 91, a substantially evacuated volume is formed between piston head 95 and plug 114.

With piston head 95 fully depressed to end 94, the cannular is inserted into the appropriate vessel and by releasing the pressure applied to handle 97, the evacuated volume behind piston head 95 will retract piston head 5 back toward end 93 and thus allow the collection of the blood sample within the device. The speed of retraction of piston head 95 can be adjusted by adjusting the screw tensioning of plug 114. Thus the device will provide a smooth rate of retraction of piston head 95 at an adjustable speed.

Plug 114 will serve to prevent the complete removal of piston head 95, after removal of the cannular the cap 112 is replaced over sleeve 111, and the sample of blood or other fluid, is now ready for safe and convenient transportation or storage.

CLAIMS:-

1. A device for extracting body fluid comprising:
a tubular body having a proximal end, a distal end, and a bore;

a piston disposed within the bore, the piston having a proximal face, a distal face, and an outer face, the outer face being in slidable contact with the bore;

a plunger mounted slidably at the proximal end of the tubular body and removably attached to the proximal face of the piston for pushing the piston from the proximal end of the tubular body towards the distal end of the tubular body during a preparatory stroke in which an external pressure is applied to the plunger, the plunger having a shank;

sealing means for slidably sealing the proximal end of the tubular body to the shank of the plunger so as to form a first chamber defined by the bore, the shaft, the sealing means, and the proximal face of the piston, so that a pressure reduction is formed in the first chamber during the preparatory stroke of the plunger;

closure means to close the distal end of the tubular body so as to form a second chamber defined by the bore, the distal face of the piston and the closure means;

the closure means is adapted to cooperate with filling means for placing the body fluid in fluid communication with the second chamber so that, after the external pressure is removed from the plunger, the pressure reduction in the first chamber causes the piston to move towards the proximal end of the tubular body and to draw body fluid into the second chamber.

2. A device for extracting body fluid as claimed in claim 1 in which the closure means comprises

a bung situated within the bore between the piston and the distal end of the tubular body, the bung having an outer wall in slidable contact with the bore, so as to

form the second chamber defined by the bore, the distal face of the piston, and the bung and in which arresting means are provided for retaining the bung at the distal end of the tubular body after the preparatory stroke;

3. A device for extracting body fluid as claimed in claim 1 or claim 2 wherein the sealing means is constructed from a compressible elastic material, the shaft of the plunger passes through a hole in the sealing means, and the device for extracting body fluid includes a cam arrangement which comprises:

a first cam means for creating a controllable deformation of the sealing means; and

a second cam means for cooperating with the first cam means to create the controllable deformation of the sealing means, the second cam means being rotatably engaged with the first cam means such that relative rotation of the second cam means with respect to the first cam means causes the controllable deformation of the sealing means and a corresponding controllable internal pressure in the compressible elastic material, thereby creating a controllable frictional force to be applied to the shaft of the plunger to enable the body fluid to be extracted at a controllable rate.

4. A device for extracting body fluid as claimed in claim 3 in which the first cam means has a non-circular inner cross section and the second cam means has a non-circular outer cross section.

5. A device for extracting body fluid as claimed in claim 4 wherein the first cam means comprises a lip at the proximal end of the tubular body.

6. A device for extracting body fluid as recited in claim 4 wherein the second cam means comprises a groove around an outer surface of the sealing means.

7. A device for extracting body fluid as recited in claim 2 wherein the bung is constructed from an elastic

material and has a distal surface with a generally convex shape and the arresting means comprises:

a circumferential rib around the bore proximate the distal end of the tubular body; and

a circumferential groove around the outer wall of bung so that, at the end of the preparatory stroke, the circumferential rib is substantially aligned with the circumferential groove so as to impede a movement of the bung towards the proximal end of the tubular body.

8. A device for extracting body fluid as claimed in claim 5 wherein the circumferential rib has an acute edge proximate the distal end of the tubular body.

9. A device for extracting body fluid as claimed in claim 1 wherein the device includes filling means comprising a needle, cannula or similar device which is removably attached to the distal end of the tubular body.

10. A device for extracting body fluid as claimed in claim 1 wherein the piston is constructed from a penetrable material and samples of body fluid may be withdrawn by inserting a cannula through the piston.

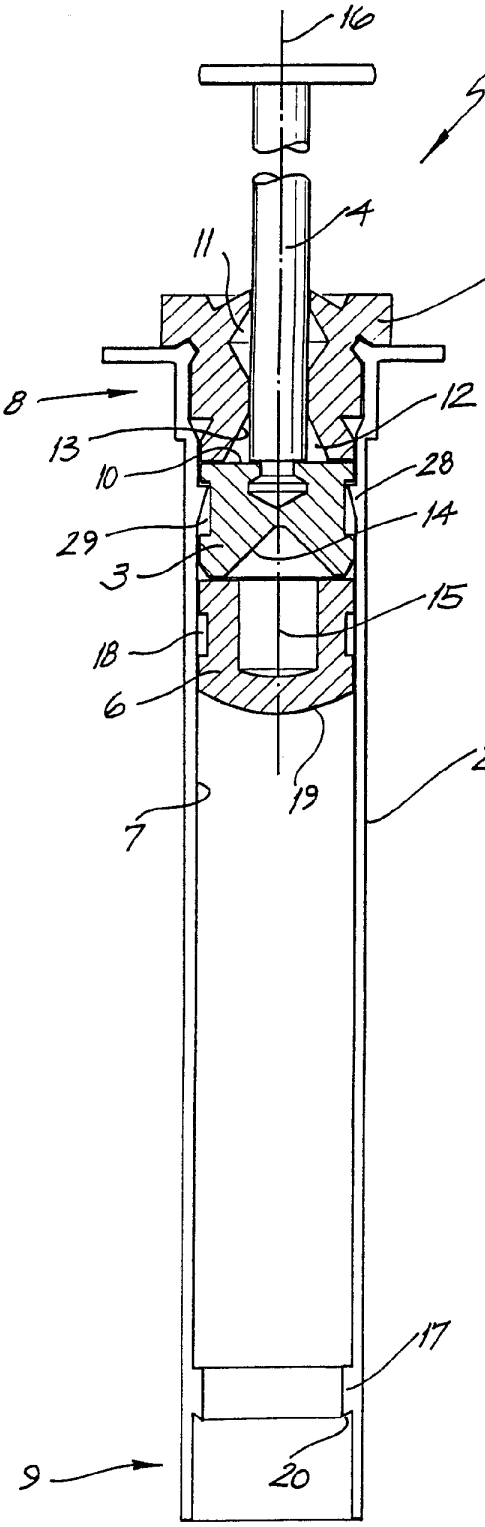

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FIG. 1

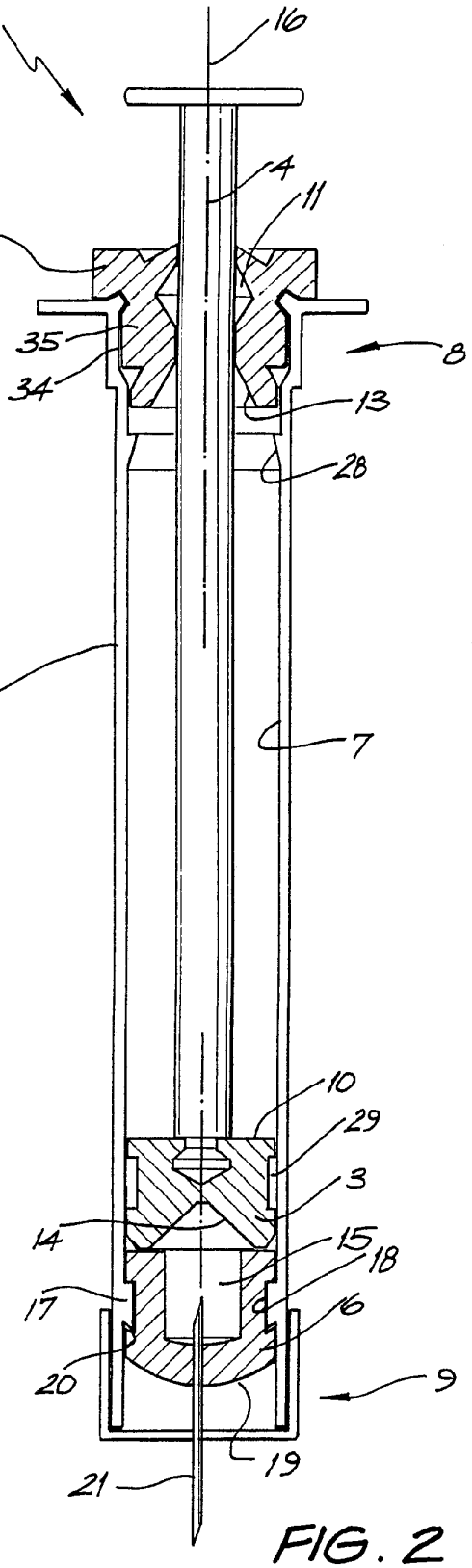

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FIG. 2

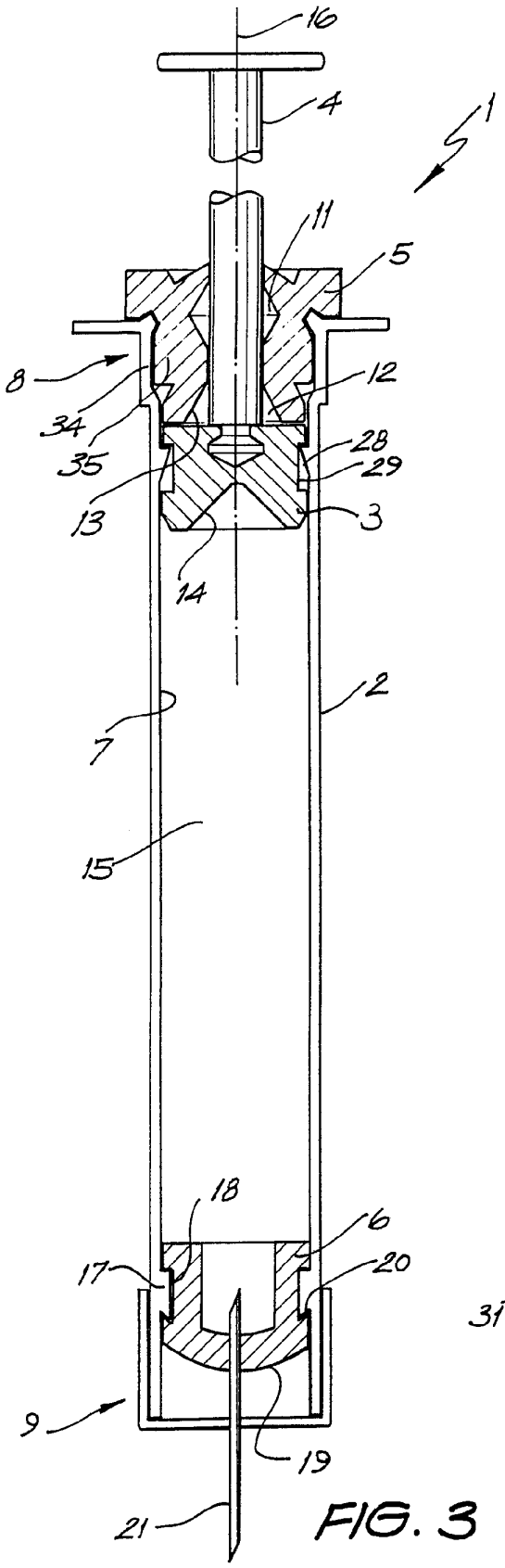


FIG. 3

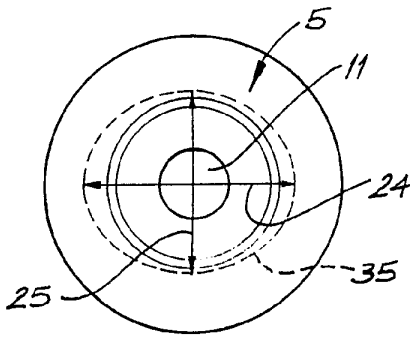


FIG. 4

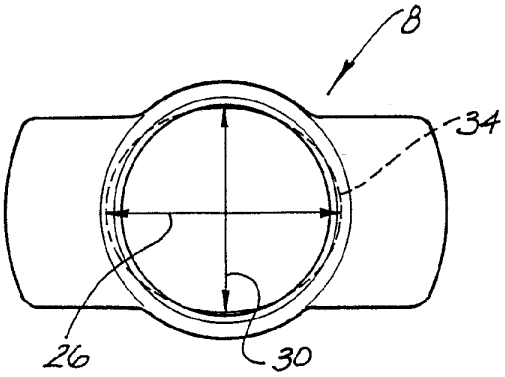


FIG. 5

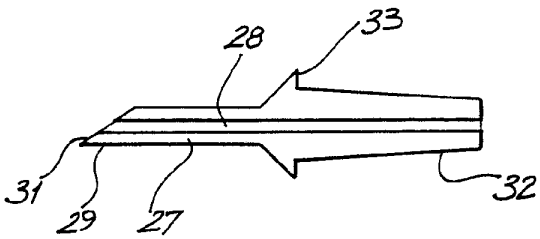


FIG. 6

3/3

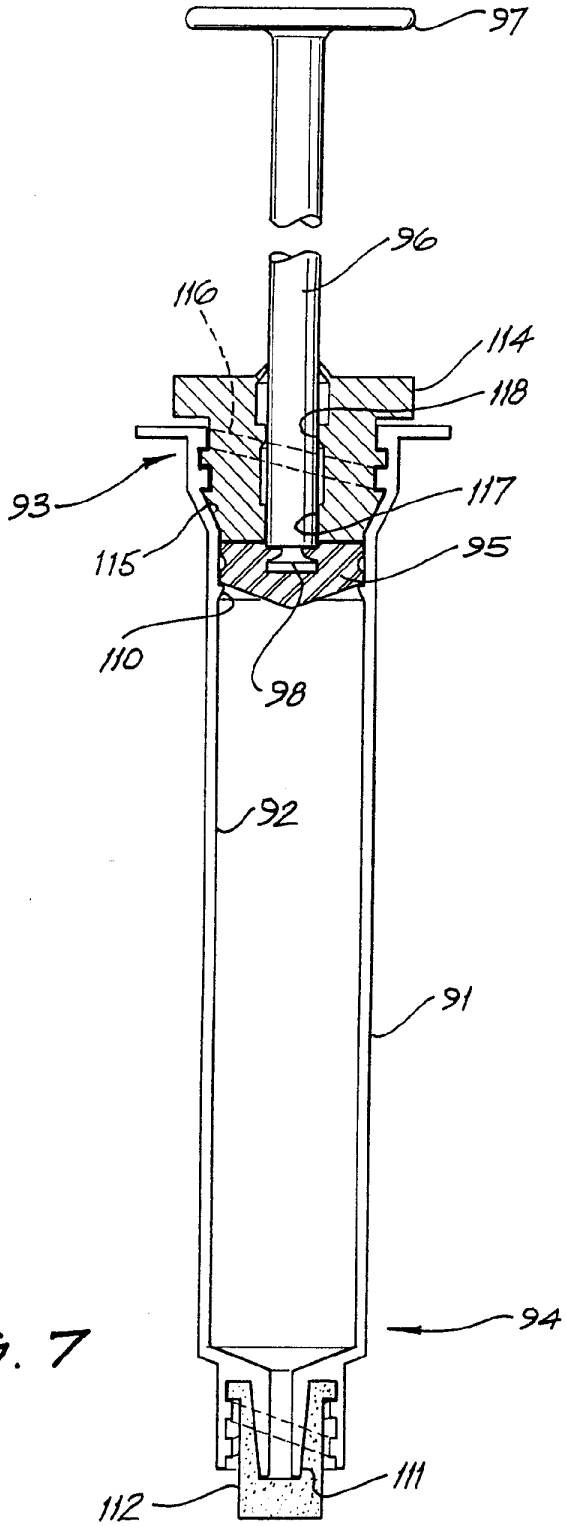


FIG. 7

INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

Int. Cl.[5] A61B 5/14

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61B 5/14

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AU:IPC as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category*	Citation of Document, [11] with indication, where appropriate of the relevant passages [12]	Relevant to Claim No [13]
X,Y	EP,A,0279956 (VAN-TEC INCORPORATED) 31 August 1988 (31.08.88) See whole document, particularly claim 1.	(1,9-10)
Y	US,A,4361155 (ANASTASIO) 30 November 1982 (30.11.82) See column 3, lines 40-45.	(9)
Y	US,A,3930492 (HATSUNO et al) 6 January 1976 (06.01.76) See column 2.	(9-10)
A	US,A,4041934 (GENESE) 16 August 1977 (16.08.77)	

(continued)

* Special categories of cited documents : [10]

"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" dooument whioh 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 t 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 oonflict 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

"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

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 May 1992 (22.05.92)	2 June 1992 (02.06.92)
International Searching Authority	**Signature of Authorized Officer**
AUSTRALIAN PATENT OFFICE	A HENDRICKSON

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US,A,4215702 (AYER) 5 August 1980 (05.08.80)	A US,A,4215702
A	US,A,4257426 (BAILEY) 24 March 1981 (24.03.81)	
A	GB,A,2218076 (BATES) 8 November 1989 (08.11,89)	

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim numbers ..., 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. ☐ Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4a

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consaquently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL APPLICATION NO. PCT/AU 92/00105

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Member	
US 4361155		
EP 279956	JP 63246145	US 4766908
US 3930492		

END OF ANNEX

29 April 2020

Examination report No. 1 for standard patent application

Griffith Hack
GPO Box 4164
Sydney NSW 2001
Australia

Your reference	P108089.AU
Application number	2016297849
Applicant name	Kurin, Inc.
Earliest priority date	24 July 2015

Final date for acceptance:	**29 April 2021**
Date of this report:	29 April 2020
Examination request date:	11 December 2019

Dear Griffith Hack,

Your application has been examined under *section 45 of the Patents Act 1990*. I consider that this application does not meet the requirements of the Act because there are issues with the application that are explained in the report details.

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 2020**.

NOTE: There is a current postponement of acceptance in place. If you overcome all other objections before the expiration of that postponement, the Commissioner will only accept the application at that time if you have filed a clear and unambiguous statement requesting the withdrawal of that postponement. Otherwise, a further adverse report will be issued.

Details of this patent application can be viewed on AusPat, our Australian patent search database.

Yours sincerely,

Morris Ark
Section: MXT - MIXED TECHNOLOGY
Phone: (612) 6210 8487

Report details

Basis of the report

In examining this application I have considered:

- the PCT pamphlet as originally filed

Summary of novelty, inventive step and patentable subject matter

	Satisfy requirements?	*Claim numbers*
Novelty/inventive step	**Yes**	NONE
	No	1-20
Patentable subject matter	**Yes**	1-20
	No	NONE

Detailed objections on issues that have been identified

Documents cited or considered relevant

D1 : WO 2011162772 A1 (CLEARVIEW PATIENT SAFETY TECHNOLOGIES, LLC et al.) 29 December 2011 [1]
Category: **X** Claims: 1-20

[1] Cited in WO 2017019552

Special categories of cited documents:

X: The claimed invention cannot be considered novel under *subsection 7(1)* in light of the document and/or cannot be considered to involve an inventive step under *subsection 7(2)* of the Act in light of the common general knowledge considered together with the document.

Novelty and inventive step

1 The invention defined in **claims 1, 8 and 17** are not novel (and do not involve an inventive step) when compared with the following prior art document **D1**.

Regarding **claim 1**, **D1** discloses a blood sequestration device (Fig. 15; item 10) comprising;

> an inlet port (100); an outlet port (330); a sequestration chamber connected with the inlet port (117), the sequestration chamber having a vent (160) comprising an air permeable blood barrier (Para [0042]); a sampling channel (130) having a proximal end connected with the inlet port and a distal end connected with the outlet port; and a housing (116) that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

Claims **8 and 17** define a blood sequestration device with a similar scope to claim 1, only differing by the additional features of a blood sampling pathway or blood sampling system

connected to said device. **D1** also discloses a blood sampling pathway or system connected to the blood sequestration device (Fig. 23; patient needle 184, connected to inlet 100).

Furthermore, appended **claims 2-7, 9-16, 18-20** are not considered to make any patentable contribution over the teachings of the cited document **D1** or are common general knowledge in the art or workshop improvements and which therefore cannot contribute to providing novelty or an inventive step. For example, **D1** discloses features of **claims 2, 11, 20** of the air permeable blood barrier sealing upon contact with blood (Para [0081], [0085]). Features of dependent **claim 3** are considered matters of workshop improvement over **D1**. It would be obvious to the person skilled in the art that a sequestration channel be implemented to improve transport of blood to the sequestration chamber.

END OF REPORT

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

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81541 München
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).

Europäisches Patentamt • European Patent Office • Office européen des brevets

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
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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
		DE 69523887 T2	29-08-2002
		EP 0725658 A1	14-08-1996
		JP H09504726 A	13-05-1997
		US 5947932 A	07-09-1999
		WO 9605875 A1	29-02-1996
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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	
US 3648684 A	14-03-1972	NONE	
EP 1665986 A1	07-06-2006	BR PI0505336 A	11-07-2006
		EP 1665986 A1	07-06-2006
		JP 4914601 B2	11-04-2012
		JP 2006150083 A	15-06-2006
		US 2006129064 A1	15-06-2006
US 4056101 A	01-11-1977	NONE	
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.

+++++

Notice of Reasons for Refusal

Application number: Japanese Patent Application No. 2020-118498
Date of Drafting: Reiwa 3(2021) August 2
Patent examiner: OKAZAKI, Jun 3330 2Q00
Representative/Applicant: MIYOSHI, Hidekazu (other trinominal)
Applied Provisions: Article 29 (2) (Inventive Step) Article 36 (6) (ii) (Clarity Requirement)

This application should be refused for the reason mentioned below. If the applicant has any opinion(s) against the reason, a written opinion should be submitted within 3 months from the date on which this notification was dispatched.

Reason

1. (Inventive step) The claimed invention(s) listed below of this patent application shall not be granted a patent under the provision of Patent Act Article 29 (2) for the reason that the claimed invention(s) could have easily been made by persons who have common knowledge in the technical field to which the claimed invention(s) pertains, on the basis of the invention(s) described in the distributed publication listed below or made available to the public through electric telecommunication lines in Japan or other foreign countries prior to the filing of the patent application.

2. (Clarity) This patent application does not fulfill the requirement of the provision of Patent Act Article 36(6)(ii) in terms of the item(s) listed below regarding the statement of the scope of claims.

Note (For the cited documents, please refer to the list of cited documents below.)
- Reason 1 (Inventive step)

- Claim 1-10

- Cited Document, etc. 1-2

- Remarks

[About Claim 1]
Are the blood isolation device which was connected to the patient needles (first needle 508;[0038] etc.) which it was a blood sample optimization system for optimizing the blood samples ([0020] etc.) brought together in Cited document 1 ([0019]-[0055], Fig.5-8) with blood collecting machines (sample vessels 506;[0038] etc.) (sample-procurement system;[0038] etc.), and were constituted for a patient's venipuncture in order to be able to take out the first portions of a patient's blood sample and the aforementioned blood samples ([0021] etc.) which contain a pollutant

at least, and the aforementioned patient needle, and was connected to the aforementioned blood collecting course between the sample needle (refer to suggestion of Fig.5 etc.) constituted so that the aforementioned blood collecting machine might be accepted in order to collect the second portion of the aforementioned blood sample as the blood collecting course constituted so that the aforementioned blood sample might be carried, and the aforementioned patient needle and the aforementioned sample needle, and are connected to the inlet ports (sterile input tubing 514;[0039] etc.) constituted so that the aforementioned blood sample might be accepted, and the aforementioned inlet port, and are an isolation chamber and it accepts the first portion of the aforementioned blood sample (Refer to / etc / Fig.5]), The isolation chamber (pre-sample reservoirs 504;[0038] etc.) constituted so that a pollutant might be included in the first portion of the aforementioned blood sample, Including a sampling channel, and (second sterile output tubing 518;[0038], Fig.5), etc. which were constituted so that it might have a proximal edge connected to the aforementioned inlet port and the second portion of the aforementioned blood sample might be accepted, the aforementioned isolation chamber, [the aforementioned sampling channel and the aforementioned inlet port] Enable the second portion of the aforementioned blood sample to bypass the aforementioned isolation chamber, are constituted so that the second portion of the aforementioned blood sample may be made to go to the aforementioned exit port, and, [the aforementioned exit port] Blood sample optimization system , containing ([0038] etc.) blood isolation devices constituted so that the second portion of the aforementioned blood sample may be discharged in the aforementioned blood collecting machine is described.

Cited document 2 ([0012]-[0013] etc.) has disclosed the technology , which constitutes the housing (needle tube base material 2) which stores and demarcates the technology, the port, isolation chamber, and flow path which constitute the isolation chamber which is an isolation chamber which has a vent containing the air permeability blood barrier (air permeability blood impermeable component 23) in a blood sample optimization system (blood collecting needle), and drives out the air in an isolation chamber through a vent.

An invention described in Cited documents 1-2 belongs to the same technical field of the blood collecting field.
In an invention described in Cited document 1, it is easy for a person skilled in the art to constitute by referring to the technology of the description to Cited document 2, so that the same air permeability blood barrier and housing as an invention related to the Claim 1 of this application may be provided.

[About Claims 2 and 4]
Refer to [0012]-[0013] of Cited document 2.

[About Claim 3]
It can be called design matter to arrange sealant to a sample needle.

[About Claim 5]
Refer to [0011] of Cited document 2.

[About Claim 6]
Refer to the Fig.5 of Cited document 1.

[About Claims 7-10]
Refer to the explanation as stated above including the description of Cited document 1-2.

- Reason 2 (Clarity)

- The description of Claims 1-10 Claims 1-10 is indefinite in respect of the following. Therefore, The claimed invention in Claims 1-10 is not clear.

(1) About the description of Claim 1
As for a description with "the first portions of a patient's blood sample and the aforementioned blood sample which contains a pollutant at least" of Claim 1, what "a pollutant is included for at least" is indefinite considering whether the "blood sample" is started and whether "the first portion of the aforementioned blood sample" is started as Japanese. In dependent claim -- the same .

(2) About the description of Claims 4 and 7
The description with "the portion of succession of the aforementioned blood sample" of Claims 4 and 7 is indefinite in whether what "follows" what kind of portion is specified. In dependent claim -- the same .

<The list of cited documents etc.>
1.The description of US Publication of Unexamined Patent Application No. 2008/0145933
2.JP 2001-000424A

Record of the result of prior art search
- Technical fields searched:

IPC
A61B 5/00 - 5/398
DB name

- Prior art documents: JP S 58 - 025146A

JP H 09-504726A
JP H 02-224742A
The description of US Publication of Unexamined Patent Application No. 2011/0306899

This record of the result of prior art search does not constitute the reasons for refusal.

<Suggestions in amending>
(1) When making amendment to the description or the scope of claims, the amended

parts should be underlined so as to be clearly identified (please refer to Note 6 and 7 of Form 13, Regulations under the Patent Act).
(2) Correction must be performed within the scope of the matter described in the The translation of a document written in foreign language (or the after Amendment Description by Correction of Erroneous Translation, a scope of the claim, or Drawings) of this application. In addition, for the evidence of the legality of each amendment, allege the legality in a written opinion with clear indication of the corresponding parts in the translation (or the description, scope of the claims or drawings after amendment by Written Correction of Mistranslation).
(3) One should make sure not to perform any corrections that invoke a violation against Patent Act Article 17-2(4) when amending the scope of claims.

Please contact the following contact, if there is any inquiries about the contents of this Notification of Reasons for Refusal or a request for an intervew with the examiner. When sending of a draft amendment etc. is wished by E-mail etc., please inform me of that by telephone.

The First Examination Department analysis diagnosis (medicine diagnosis) Okazaki * TEL.03-3581-1101 Extension 3291

A Director(p.p.), an examiner, and assistant examiner OKUMA, Yasuo -- * ▲ tearing -- ▼ and 9710 3330

拒絶理由通知書

特許出願の番号	特願２０２０-１１８４９８
起案日	令和　３年　８月　２日
特許庁審査官	岡▲さき▼　潤　　３３３０　２Ｑ００
特許出願人代理人	三好　秀和（ほか　３名）　様
適用条文	第２９条第２項（進歩性） 第３６条第６項第２号（明確性）

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．（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。

２．（明確性）この出願は、特許請求の範囲の記載が下記の点で、特許法第３６条第６項第２号に規定する要件を満たしていない。

記　　（引用文献等については引用文献等一覧参照）

●理由１（進歩性）について

・請求項　１-１０

・引用文献等　１-２

・備考

[請求項１について]

引用文献１（[0019]-[0055],図5-8）には、

採血器（sample vessels 506;[0038]等）によって集められる血液サンプル（[0020]等）を最適化するための血液サンプル最適化システム（sample-procurement system;[0038]等）であって、

患者の血液サンプル、少なくとも汚染物質を含む（[0021]等）前記血液サンプルの第１の部分を取り出せるようにするために患者の静脈穿刺用に構成された患者針（first needle 508;[0038]等）と、

前記患者針に接続され、前記血液サンプルを運ぶように構成された採血経路と（図5等参照）、
前記血液サンプルの第２の部分を集めるために前記採血器を受け入れるように構成されたサンプル針（図5等の示唆参照）と、
前記患者針と前記サンプル針との間の前記採血経路に接続された血液隔離装置であって、
前記血液サンプルを受け入れるように構成された入口ポート（sterile input tubing 514;[0039]等）と、
前記入口ポートに接続され、隔離チャンバであって、前記血液サンプルの第１の部分を受け入れ、前記血液サンプルの第１の部分に汚染物質を含むように構成された隔離チャンバ（pre-sample reservoirs 504;[0038]等）と、
前記入口ポートに接続される近位端を有し、前記血液サンプルの第２の部分を受け入れるように構成されたサンプリング流路と（second sterile output tubing 518;[0038],図5等）を含み、
前記隔離チャンバ、前記サンプリング流路及び前記入口ポートは、前記血液サンプルの第２の部分が前記隔離チャンバを迂回することを可能にし、前記血液サンプルの第２の部分を前記出口ポートに向かわせるように構成され、前記出口ポートは、前記血液サンプルの第２の部分を前記採血器に排出するように構成される（[0038]等）、血液隔離装置とを含む、血液サンプル最適化システム、
が記載されている。

引用文献２（[0012]-[0013]等）には、血液サンプル最適化システム（採血針）において、空気透過性血液バリア（空気透過性血液不透過性部材２３）を含む通気口を有する隔離チャンバであって、通気口を通して隔離チャンバ内の空気を追い出す隔離チャンバを構成する技術、ポート、隔離チャンバ及び流路を収容及び画定するハウジング（針管支持体２）を構成する技術、が開示されている。

引用文献１-２に記載のものは、採血分野という同一の技術分野に属する。
引用文献１に記載のものにおいて、引用文献２に記載の技術を参考として、本願の請求項１に係る発明と同様の空気透過性血液バリアとハウジングを具備するよう構成することは、当業者にとって容易である。

［請求項２，４について］
引用文献２の[0012]-[0013]を参照。

［請求項３について］
サンプル針に密封材を配置することは、設計的な事項といえる。

［請求項５について］

引用文献２の[0011]参照。

［請求項６について］
引用文献１の図5を参照。

［請求項７－１０について］
引用文献１－２の記載を含め既述の説示を参照。

●理由２（明確性）について
・請求項　１－１０
請求項１－１０の記載は、以下の点で不明確である。よって、請求項１－１０に係る発明は、明確でない。

（１）請求項１の記載について
請求項１の「患者の血液サンプル、少なくとも汚染物質を含む前記血液サンプルの第１の部分」との記載は、「少なくとも汚染物質を含む」ことが「血液サンプル」に係っているのか、「前記血液サンプルの第１の部分」に係っているのか、日本語として不明確である。引用項においても同様。

（２）請求項４，７の記載について
請求項４，７の「前記血液サンプルの後続の部分」との記載は、いかなる部分に「後続」するものを特定しているのか不明確である。引用項においても同様。

＜引用文献等一覧＞
１．米国特許出願公開第２００８／０１４５９３３号明細書
２．特開２００１-０００４２４号公報

＜先行技術文献調査結果の記録＞
・調査した分野　　ＩＰＣ　Ａ６１Ｂ　　５／００　－　５／３９８
ＤＢ名
・先行技術文献　　特開昭５８-０２５１４６号公報
特表平０９-５０４７２６号公報
特開平０２-２２４７４２号公報
米国特許出願公開第２０１１／０３０６８９９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、この出願の外国語書面の翻訳文（又は誤訳訂正書による補正後の明細書、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（又は誤訳訂正書による補正後の明細書、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。電子メール等で補正案等の送付を希望される場合は、その旨を電話でお知らせください。

審査第一部分析診断（医学診断）　岡崎　潤
ＴＥＬ．０３-３５８１-１１０１　内線３２９１

審査長／代理	審査官	審査官補
大熊　靖夫	岡▲さき▼	
９７１０	３３３０	

Reduction of the risk of bacterial contamination of blood components through diversion of the first part of the donation of blood and blood components

Giancarlo Maria Liumbruno[1,2], Liviana Catalano[1], Vanessa Piccinini[1], Simonetta Pupella[1], Giuliano Grazzini[1]

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Introduction

The level of safety of transfusion therapy is now very high thanks to the combination of serological methods and genomic amplification used to screen for transmissible diseases and the meticulous care with which repeat, voluntary, unpaid donors are selected[1-4].

The main risk of transfusion-related infectious diseases is currently that of bacterial sepsis[1,3-5]. The risk of bacterial contamination of blood components is, in fact, estimated to be about three orders of magnitude greater than that of post-transfusional HIV and HCV infections[5,6]; the risk of bacterial sepsis causes by the transfusion of platelets is more than two orders of magnitude greater than the risk of the same viral infections[5,6].

According to a study published in 2004[7], the year in which bacteriological screening tests for platelet units were introduced in the USA[3,8,9], the average prevalence of bacterial contamination in platelets from whole blood was 33.9/100,000 units, that of platelets from apheresis 51/100,000, while that of red cell concentrates was 2.6/100,000. The overall prevalence of bacterial contamination of units of cellular blood components was, therefore, about 1 in 3,000 donations (33.3/100,000)[7,10].

Table I reports the data on bacterial contamination of units of platelets and red blood cells derived from studies before 2003[11-19]. More recent estimates indicate that bacterial culture tests on units of platelets are positive, and confirmed as such, in about 1 in 5,000 units (20/100,000)[4]. The risk of receiving platelet concentrates contaminated by bacteria is, therefore, considerably higher than the risk of post-transfusion infection by HIV, HCV, HBV and HTLV[3,4].

Prior to the introduction of bacteriological screening tests[20], transfusion-related sepsis occurred after approximately 1 in 25,000 transfusions of platelet concentrates and 1 in 250,000 transfusions of red cells[5,7,20].

In the USA, where about 14 million units of red cells are transfused each year, in the period from 1976 to 1998, there were reports of 26 deaths due to bacterial contamination of this blood component, with an incidence, therefore, of just over one case per year[21,22]. More recently, still in the USA, analysis of data from 1998 to 2000 indicated that the incidence of fatal events was 1 case per 8,000,000 units of transfused red blood cells[23]. At the other end of the scale, the incidence of fatal events reported in New Zealand is 1 for every 104,000 units of transfused red cells[21].

According to North American studies, deaths following the transfusion of platelets are more frequent and occur after 1 in 50,000-500,000 transfusions[23,24].

Analysis of haemovigilance data from the United Kingdom, France and USA indicate that the mortality risk due to sepsis following transfusion of platelets is 1 case per 7,500-100,000 units transfused[21].

The contamination of platelets is easier and more common than that of red cells because of the storage temperature of platelets (20-24 °C), which favours the proliferation of bacteria, unlike the storage temperature of red cells, which is 2-6 °C[25,26]. Fresh-frozen plasma, precisely because of its storage conditions[25,26], is rarely contaminated by bacteria; on the other hand, this product can be contaminated during the thawing process in inadequately sterilised equipment[21].

The published mortality rates due to sepsis from bacterial contamination of transfused units of blood components vary in the different series: this is probably because of unrecognised and/or not reported cases and because of variations in the incidence in

Blood Transfus 2009; 7: 86-93 DOI 10.2450/2008.0026-08
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KUR-MAG-DE005075

Table I - Prevalence of bacterial contamination of cellular blood components recorded in studies before 2003

Type of blood component	Reference	Year of publication	Number of positive units	Number of units tested	Prevalence per 100,000 units
Platelets from whole blood	Barrett BB[11]	1993	1	4,272	23.4
	Yomtovian R[12]	1993	6	14,481	41.4
	Chiu EKW[13]	1994	10	21,503	46.5
	Blajchman MA[14]	1994	16	31,610	50.6
	Leiby DA[15]	1997	4	4,995	80.1
	Blajchman MA[16]	1997	7	10,065	69.5
Total			44	86,926	50.6
Platelets from apheresis	Blajchman MA[17]	1992	14	6,055	231.2
	Barrett BB[11]	1993	5	17,928	27.9
	Yomtovian R[12]	1993	0	2,476	0.0
	Dzieczkowski JS[18]	1995	1	5,197	19.2
	AuBuchon JP[19]	2002	1	2,678	37.3
Total			21	34,334	61.2
Red blood cell concentrates	Barrett BB[11]	1993	1	31,385	3.2
	Dzieczkowski JS[18]	1995	1	7,080	14.1
Total			2	38,465	5.2
Overall total			**67**	**159,725**	**41.9**

the context of different national epidemiological situations[21].

The aim of this review is to consider the scientific evidence supporting the efficacy of diversion of the first part of the blood collected in preventing bacterial contamination of blood components.

Source of contamination of blood components and prevention strategies

It is not always easy to identify the source of bacterial contamination of blood components. The contamination can be due to endogenous causes, such as asymptomatic bacteraemia in the donor, including transient episodes or due to exogenous causes, mainly related to contamination by transient or commensal bacterial flora present on the skin of the donor's arm or to contamination of the collection bags/kits and/or the blood component itself during the production process and/or storage[27,28]. In these latter cases, prevention is based on applying the principles of "good manufacturing practice", using sterile, closed collection systems and maintaining scrupulous hygiene of areas dedicated to the processing and storage of blood and blood components as well as the areas in which the materials used for the collection are stored.

Diversion of the first part of the blood collected is one of the interventions that can prevent the contamination of blood components caused by the introduction of skin bacteria into units of whole blood or blood components from apheresis at the time of venipuncture. Indeed, the major source of bacterial contamination is the donor's skin and disinfection, even if carried out very carefully thus reducing the bacterial load present on the superficial layers of the skin, cannot act on the deeper layers. The introduction of a needle through the skin to collect blood causes, in 65% of all cases[29], the passage of skin fragments containing live microbes or the movement of microbes from small skin flaps produced by the needle itself into the collection bags[30]. Furthermore, it is even more difficult to achieve satisfactory disinfection of a skin surface that has become irregular due to scars from previous donations[28].

The aim of diverting the first part of the blood collected into a collateral bag, used for the performance of tests of biological validation of the unit donated, is precisely that of preventing the initial flow of blood, containing microbes or skin fragments from the donor, from entering the collection bag and thus contaminating it[28,29,31,32].

Diversion of the first part of the blood

The diversion of the first 10-50 mL of donated blood, with the aim of preventing microbes or skin fragments from entering the collection bag, has been the object of

numerous studies from 1995 onwards[33-47].

Olthuis *et al.* were the first, in 1995, to demonstrate that the first 10 mL of blood, collected at the beginning of a plasmapheresis procedure with an open system, were more frequently contaminated by bacteria than were the subsequently collected 10 mL[34]; indeed, diversion of the first part of the donation guaranteed an 88% reduction in the percentage of bacterial contamination[28].

In the same year, using an experimental model, Figueroa showed that most of the bacteria (100 colony-forming units of *Staphylococcus aureus*) inoculated in the lumen of a collection needle entered the first 10 mL of fluid that it collected; this demonstrated, experimentally, that the diversion of the first 10 mL of blood collected could reduce the bacterial load of skin contaminants in the blood/blood component collected[35].

In 2000, Wagner *et al.*, also using an *in vitro* experimental model, demonstrated that diversion of the first 21-42 mL of physiological saline or whole blood reduced the load of colonies of *Staphylococcus aureus*, deliberately inoculated on the collection surface, by about 1 log[36]. This confirmed that a diversion system for the collection of samples of blood, before filling the collection bags, would be able to reduce the bacterial load in blood components subsequently produced from whole blood and, therefore, the incidence of sepsis due to cutaneous microbes.

In 2001, Cecile Bruneau's group in France published the results of a multicentre study[37] on new collection bags, specifically modified by the manufacturer (Maco Pharma, Tourcoing, France), which added two consecutive satellite bags, each containing 15 mL, to the collection line with the aim of comparing bacterial contamination between the first and second 15 mL of blood collected. The authors demonstrated that diversion of the first 15 mL reduced the bacterial contamination of the units of blood by 72% and that using the first 30 mL of blood to carry out the tests of biological validation of the units further reduced the potential bacterial load within the bags of whole blood.

Again in France, in 2002, Schneider's group obtained a 58% reduction in the contamination of platelet concentrates (PCs) from buffy coat (BC) pools by using diversion of the first part of the blood collected[38]; contemporaneously, in the Netherlands, Bos *et al.* obtained a 53% reduction of contamination of the same blood component[39].

In the same country, the use of blood bags supplied with diversion bags showed that the diversion of the first 20 mL of blood reduced the bacterial contamination of PCs from BC pools from 1% to 0.4% (- 60%)[40].

A subsequent multicentre, prospective clinical study, whose results were published in 2002 by Dirk de Korte's group from the Netherlands, demonstrated that the diversion of the first 10 mL of the donation enabled a statistically significant, 40% reduction in the percentage of contaminated whole blood units, compared to that of the standard collection without diversion[41]; consequently, there was also a statistically significant reduction (from 0.14% to 0.03% - $p<0.02$) in the frequency of staphylococcal contamination of units.

On the basis of these results in the Netherlands, since July 1, 2004, diversion of the first 20-30 mL of blood (used for validation tests of the units) has become obligatory for all whole blood and apheresis donations and this produced, on a national scale, a 59% reduction in bacterial contamination of PCs from BC pools already after 1 year[42].

In 2006, the same Dutch group published the results of another prospective, multicentre clinical study carried out between 2002 and 2003, in which they evaluated the effect of skin disinfection techniques, diversion bags, and bacterial detection tests on the contamination of more than 110,000 PCs from BC pools[43]. Diversion of the first 20-30 mL of blood was associated with a statistically significant reduction in the bacterial contamination of this blood component of 47% with the "old disinfection technique" and of 54% with the "new disinfection technique" (isopropylic alcohol 70%). Furthermore, the diversion caused a statistically significant reduction in contamination due to microbes of cutaneous origin.

More recent data from the same country, updated to 2007, but currently available only in abstract form, confirm the efficacy of the strategy adopted in 2004[44]; indeed, before diversion was obligatory, the rate of bacterial contamination among 127,797 PCs from BC pools was 0.90%, while the rate in 147,021 PCs produced after July 1, 2004, had fallen to 0.46% (- 49%). The strategy of diversion also caused:

a) a 35% reduction in the units transfused and found,

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subsequently, to be positive in culture tests;

b) a reduction (from 40% to 25%) of the frequency of contamination of red cell concentrates produced from the units from which the PCs from BC pools positive for bacterial contamination originated. The bacterial strains on which the diversion had the greatest effect were diphtheroids and coagulase-negative staphylococci.

A prospective study on units of whole blood, carried out in the United Kingdom and published in 2004 by McDonald, showed that diversion of the first 20 mL of blood produced a 47% reduction in bacterial contamination[45].

A statistically significant reduction ($p = 0.005$) in bacterial contamination of PCs from whole blood was also found in a Canadian study by Robillard[46], who analysed the data produced by the local haemovigilance system. In Canada the diversion of the first 40 mL of blood, introduced in February 2003, caused, in 2004, a 90% reduction in the bacterial contamination of PCs from whole blood; this result was confirmed by the data updated to the following year, in which no PCs, from either whole blood or apheresis, were found to be contaminated by bacteria[47].

In a study recently performed in the USA on bacterial contamination of platelets from apheresis[33], it was found that the bacterial contamination of PCs produced by single-needle cell separators was 47% lower than that of PCs produced by double-needle separators. The lower rate of bacterial contamination of the PCs produced by the former is explained by the different configuration of the two types of cell separators. In the double-needle separators, the sample for tests of biological validation is taken from the reinfusion line and there is not, therefore, diversion of the first amount of blood taken; in contrast, in the single-needle separators, the initial sample (40-50 mL) for haematological and biochemical investigations is taken from the collection line, thus preventing this blood from contaminating the collection kit and blood component produced.

Table II summarises the main studies on diversion, some of which are only available in abstract form, the amount of blood diverted and the percentage reduction in bacterial contamination obtained in the blood components under analysis.

Conclusions

Post-transfusion sepsis is the most common cause of death due to infectious agents[30,48].

According to data from SHOT (Serious Hazards Of Transfusion)[49], the haemovigilance system in the United Kingdom, in the period 1995-2006, there were 33 cases of post-transfusion bacterial sepsis, 29 of which (88%) were due to treatment with platelets (10 cases due to platelets from apheresis and 19 to platelets from pools) and four due to treatment with red cell concentrates. In the same period, there were no deaths due to post-transfusion infections with hepatitis viruses, HIV or HTLV-I, while eight deaths were caused by bacterial contamination of transfused

Table II - Reduction of the percentage of bacterial contamination of blood components achieved with different volumes of diversion in studies from 1995 to 2007

Reference	Year of publication	Country	Production procedure/ blood component analysed	Volume of diversion (mL)	Reduction of contamination of the blood components (%)
Olthuis H[34]	1995	The Netherlands	Plasmapheresis	10	88
Bruneau C[37]	2001	France	Whole blood	15 (+15)	72
Schneider T[38]	2002	France	PC from BC pools	Not stated	58
Bos H[39]	2002	The Netherlands	PC from BC pools	10	53
Yedema T[40]	2003	The Netherlands	PC from BC pools	20	60
de Korte D[41]	2002	The Netherlands	Whole blood	10	40
McDonald CP[45]	2004	United Kingdom	Whole blood	20	47
Robillard P[46]	2005	Canada	PC from whole blood	40	90
De Korte D[44]	2007	The Netherlands	PC from BC pools	20-30	49
Eder AF[33]	2007	USA	Platelets from apheresis	40-50	47

PC, platelet concentrates; BC, buffy coat.

platelets. This puts platelet transfusion-related sepsis alongside transfusion-related acute lung injury (TRALI) as the second most frequent cause of transfusion-related death, after post-transfusion graft-versus-host disease[48,49].

The frequency of clinical symptoms following transfusion of platelets contaminated by bacteria varies greatly; indeed, the reported range extends from a frequency of 1 case per 358 transfusions of platelets from whole blood[13], reported in a study from 1994, to the considerably lower value of 1 case per 73,000 transfusions of platelets from single donors[24], reported in a study from 2001. This latter result is completely in line with the findings of the American Red Cross[33] that, between 2004 and 2006, the residual risk of septic reactions to platelets from apheresis was 1 case per 74,807 units, and the residual risk of fatal reactions was 1 case per 498,711 units distributed.

This broad variability depends on the criteria and methods used to collect the data and is also influenced by the method used to produce the PC (from single units or pools, from BC or from platelet-rich plasma, or from apheresis) and whether strategies to divert the first part of the blood collected had been introduced[50].

The technique of diverting the first 20-40 mL of blood at the beginning of the donation of whole blood or blood components from apheresis is relatively simple and has no effect on the donor, since this is the quantity of blood that is normally taken to carry out the tests necessary for the biological validation of the unit donated.

The data from the studies analysed demonstrate the fundamental role that this modification to the collection process can have on reducing the rate of bacterial contamination of blood components: indeed, the percentage of contaminated blood components is decreased by 40-90%. The range in the reduction is probably due to differences in criteria for collecting and analysing the data and in the production processes of the blood components examined in the various studies.

In the United Kingdom, the introduction of diversion was already suggested in the SHOT report of 2002 as one of the strategies to use to reduce the risk of bacterial contamination of blood components[49]; in the same year, this measure was made obligatory in Germany[51] and other countries, including France, the Netherlands and Canada, subsequently adopted this modification of the production process of blood components[5,16,52], with manufacturers of blood bags and apheresis collection kits adapting their products to meet the circumstances. In Italy, the legislation on transfusion matters was recently integrated by Legislative Decree 208 of November 9, 2007[53]; this decree transposes Commission Directive 2005/62/EC of 30 September 2005, implementing Directive 2002/98/EC of the European Parliament and the Council as regards Community standards and specifications relating to a quality system for blood establishments, and sets out that "the procedures for collecting blood must minimise the risk of microbial contamination".

The frequency of bacterial contamination of platelets is influenced by the technique used to produce them[51]; the rate of contamination of platelets from single donors or from apheresis is significantly lower than that of PCs produced from pools. The predominant source of micro-organisms responsible for the contamination of PCs is the skin flora[51,54]. Most deaths are, however, caused by the transfusion of blood components contaminated by Gram-negative bacteria[23], predominantly of intestinal origin, responsible for asymptomatic bacteraemia in the donor, on which diversion, obviously, is not effective. The frequency of donations made during asymptomatic bacteraemia can be reduced by rigorously applying the selection criteria set out in the protocols for determining the suitability of donors of blood and blood components[55] and, during the selection process, encouraging donors to report any changes of health that occur in the period immediately after the donation[54].

Although the effect of diversion is limited to micro-organisms originating from the skin, such as coagulase-negative staphylococci, it is hoped that this strategy is applied extensively to both the collection of whole blood and apheresis collections[41,56,57].

In France[52], a statistically significant reduction in the rate of bacterial contamination of blood components was achieved through the combined action of a series of strategies aimed at preventing or reducing the initial contamination of the blood component (better skin disinfection techniques, care with regards to the personal hygiene of the staff collecting the donations, diversion, active reporting by donors of any changes in health after the donation), and the proliferation of microbes within it (meticulous control of the storage temperature of blood

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components, universal leucoreduction, separation of whole blood after 2-20 hours, transfusion of platelets stored for less than 3 days), as well as through constant improvement in scientific knowledge on the subject (production of guidelines on the management of post-transfusion bacterial infections and promotion of specific research on the subject). The implementation of these preventive measures at various stages of the production process led, at a national level, to a significant reduction in the risk of post-transfusion bacterial infection and provided results equivalent to those of other countries that privileged the use of diagnostic tests to detect bacterial contamination. The limitation of such diagnostic tests is the considerable percentage (about 50%) of false negative cultures at 24-48 hours[52,58,59]; these results are responsible for an estimated global residual risk of septic reactions of about 1/45,000 transfusions (2.2/100,000) and led, on January 29, 2008, to the premature interruption of the phase IV study, "PASSPORT" ("*Post-Approval Surveillance Study of Platelet Outcomes, Release Tested*")[60], the outcome of an agreement between Gambro BCT (Lakewood, CO, USA) and Fenwal Inc. (Lake Zurich, IL, USA). "PASSPORT" had the aim of validating the clinical use of platelets from apheresis produced by cell separators from two companies [Trima Accel, COBE Spectra (Gambro BCT) and AMICUS (Fenwal)], stored for up to 7 days and transfused after having been found to be negative for bacterial contamination according to a screening test (BacT/ALERT - bioMéricux SA, Marcy l'Etoile, France).

In conclusion, a global strategy of minimising post-transfusion bacterial infections must include the adoption of multiple preventive measures, such as those analysed in an article by George Andreau[52], as well as diagnostic tests and could also exploit pathogen inactivation methods, but remains dependent on appropriate use of transfusion therapy.

Key words: diversion volume, bacterial contamination, platelets, blood donation, blood component.

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Effects of skin disinfection method, deviation bag, and bacterial screening on clinical safety of platelet transfusions in the Netherlands

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BACKGROUND: Bacterial contamination of blood products is a great hazard for development of fatal transfusion reactions. Bacterial screening of platelet concentrates (PC) by aerobic and anaerobic culturing (BacT/ALERT, bioMérieux) was introduced in the Netherlands in October 2001.

STUDY DESIGN AND METHODS: In November 2002, a nationwide, uniform skin cleansing method was introduced with a double-swab disinfection with 70 percent isopropyl alcohol. One location routinely used an integrated diversion bag to collect the first 20 to 30 mL.

RESULTS: Over the calendar years 2002 and 2003, in total 113,093 PCs derived from pooled buffy coats were screened. After introduction of the new disinfection method, 0.85 percent were initially positive. This was a small reduction compared to the previous disinfection methods under which 0.95 percent were initially positive. The location with use of the diversion bag showed a significantly lower frequency of bacterial contamination, with 0.50 percent before and 0.37 percent after introduction of 70 percent isopropyl alcohol. In addition 8000 apheresis PCs were also screened, showing 24 initially positive samples (0.30%).

CONCLUSION: The use of the diversion bag and, to a lesser extent, the use of double swabs with 70 percent isopropyl alcohol, led to a reduction of contamination. As expected, predominant contamination with resident skin bacteria was reduced. The combination of diversion bag and new disinfection led to a frequency of initial positive results for pooled five-donor PCs, which is similar to that of single-donor apheresis PCs. Furthermore, the bacterial detection system and associated product recall procedures have been shown to be effective in preventing transfusion of contaminated PCs and/or related red cells, especially for rapidly growing bacteria.

Since the dramatic reduction of transfusion-transmitted viral infections though screening for various blood-borne viruses, transfusion-related bacterial infections have become one of the major risks of transfusion. Bacterial contamination is considered to be, after clerical errors, the second most common cause of death from transfusion, with mortality rates for platelet (PLT)-related sepsis ranging from 1 in 20,000 to 1 in 100,000 donor exposures.[1-3] In contrast, the current frequencies of virus transmission via blood components are estimated as 1 in 1,800,000 for hepatitis C virus, 1 in 220,000 for hepatitis B virus, and 1 in 2,300,000 for human immunodeficiency virus.[4,5] Therefore, additional screening of blood products for bacterial contamination is under consideration or has already been implemented in many countries, both in Europe and in North America.[6]

Because of their storage at room temperature, PLT products are most sensitive for bacterial contamination and thus a logical choice to start screening. In the Neth-

ABBREVIATIONS: CNS = coagulase-negative staphylococci; IPA = isopropyl alcohol; PC(s) = platelet concentrate(s); T5 = PCs prepared from pools of five buffy coats; TTBI = transfusion-transmitted bacterial infection.

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erlands, nationwide screening for bacterial contamination in 100 percent of PLT products was introduced at the end of 2001. All Dutch blood banks use the BacT/ALERT culturing system (bioMérieux [formerly Organon Teknika], Boxtel, the Netherlands), with a standardized protocol.

It has previously been shown that in the majority of positive cultures, bacterial contamination is a result of resident skin flora[7] most likely originating from the venipuncture plug.[8,9] Although hygienic precautions are taken to prevent contamination during collection, a further reduction of the number of products with bacterial contamination is desirable. To reduce the risk of contamination by skin flora two strategies can be used: 1) diversion of the first aliquot of the donation and 2) improvement of skin disinfection.

Regarding the first method we, as well as others, have previously shown that diversion of the first 10 mL of a whole-blood donation reduces the incidence of bacteria in the remaining whole-blood unit.[8,10,11] The effect of this diversion, however, on bacterial contamination of the final product, PLT concentrates (PCs) prepared from pooled buffy coats, has not yet been reported.

Considering skin disinfection, iodine is the most effective disinfectant. Because it is considered to be a donor-unfriendly agent, however, isopropyl alcohol (IPA) is the next best choice. McDonald and coworkers[12] have shown that improved skin disinfection methods drastically reduced the number of remaining bacteria on the phlebotomy puncture site—especially those methods with a double-swab method, with the best results for the combination of IPA and iodine. For this approach too, the final effect on bacterial contamination of buffy coat–derived PCs has not yet been reported.

From January 2002, at collection centers of the Sanquin Blood Bank Region Southeast (Nijmegen, the Netherlands), a collection system with an integrated diversion bag was used to divert the first 20 to 30 mL of the whole-blood donation. This volume was subsequently used for infection disease and immunohematology testing. All other collection centers of the Sanquin Blood Banks used standard whole-blood collection systems without a diversion bag. In October 2002, a standardized skin disinfection method, with 70 percent IPA in a double-swab method, was introduced in all the collection centers of the Sanquin Blood Banks (including Nijmegen). During the whole period all apheresis PCs were collected with a diversion pouch included in the system.

In this report we evaluate data on bacterial contamination in the Netherlands for all apheresis PCs and PCs prepared from pools of five buffy coats (T5), collected in 2002 and 2003. The large numbers enable us to make a reliable judgment of the effect of diversion and/or changed disinfection method on the final degree of bacterial contamination of PC.

MATERIALS AND METHODS

Blood collection with or without diversion

Whole blood was collected under standard blood banking conditions with either a four-bag top and bottom citrate phosphate dextrose (CPD)-saline adenine glucose mannitol (SAGM) red cell (RBC) inline filter system (Compoflex, Fresenius Hemocare, NPBI International, Emmer-Compascuum, the Netherlands) or a comparable system (Baxter PL146-CPD-70 mL 3-Optipure, Baxter, Utrecht, the Netherlands).

Sanquin Blood Bank Region Southeast (Nijmegen, the Netherlands) used a five-bag top and bottom CPD-SAGM RBC inline filter system (Compoflex, Fresenius Hemocare, NPBI International) including an integrated sample bag (T3941, Fresenius Hemocare), in which diversion of the first 20 to 30 mL of the donation was performed. After collection of the first volume, a clamp was set and the sample bag was sealed. Donation proceeded normally in the collection bag with CPD. All other collection centers collected blood for infectious diseases and immunohematology testing after donation was completed via a sampling site attached to the collection system.

Processing to PCs

Whole blood is processed similarly at all collection centers after collection, with rapid cooling to 20°C and overnight storage at this temperature.[13] Briefly, after a hard centrifugation of the whole blood, the buffy coats are collected. Five buffy coats (same blood group) are pooled and mixed with either 300 mL of plasma or additive solution (AS; PAS I, Baxter). The pooled buffy coats are centrifuged again (soft centrifugation) to produce T5 products. Preparation procedures for T5 varied slightly between regions, but these differences (type of leukodepletion filter and storage container) are not likely to cause variations in the degree of bacterial contamination.

The blood bank locations of Rotterdam (Region Southwest), Utrecht (Region Northwest), and Nijmegen (Region Southeast) used PAS II as AS in the T5 products; all other blood bank locations used plasma for pooling.

Skin disinfection

Before October 2002 skin disinfection was performed with various methods in the Sanquin collection centers, referred to as the "old skin disinfection method." Most centers (>95% of total collections) used a single swab method with 70 percent alcohol–0.5 percent chlorhexidine or 70 percent IPA, but some small centers used single swabs with iodine tincture, whereas one small center used a double-swab method with 70 percent alcohol–0.5 percent chlorhexidine. Because no differences were found between the various centers for the old methods,

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the data for the old methods have been pooled (with and without exclusion of the center with the diversion bag). Starting from October 2002, a uniform disinfection method was introduced nationwide with a 30-second spaced double-swab method with 70 percent IPA. Sanquin Blood Bank Region Southwest introduced this new disinfection method in October 2002, the Regions Northeast and Southeast did so in November 2002, and Region Northwest introduced it in January 2003.

Screening on bacterial contamination

For the screening on bacterial contamination, within 2 hours after preparation of a T5 (this is 16-22 hr after collection) or within 12 hours after collection of the apheresis product, both aerobic and anaerobic culture bottles were inoculated (approx. 7.5 mL per bottle; range, 5-10 mL). Inoculation was performed under aseptic conditions with a laminar airflow cabinet, as reported previously.[7]

Culture bottles were incubated at 35°C in the BacT/ALERT system until flagged positive or up to 7 days if negative (also in those cases were the corresponding bottle became positive). Positively flagged bottles were sent to regional reference laboratories for determination by plating the sample. PCs and RBCs related to an initially positive bottle were taken out of inventory or recalled. Corresponding RBCs, if available from stock or recall, were cultured in the BacT/ALERT (for 7 days; both aerobic and anaerobic bottle), and positively flagged bottles were also sent to the reference laboratories for determination.

Study design and statistical analysis

Both initial culture test results and data on the microbiologic determination have been included in analyses of the results over the complete calendar years 2002 and 2003. The results were used to test the effects of the new disinfection method and/or the diversion on the degree of contamination. The results of the center with the diversion bag were compared to the pooled results of all other centers not with the diversion bag.

Data showing a positive initial test, but without determination results, have been labeled as missing. If the determination test could not detect microorganisms, the initial test result has been labeled as negative determination culture.

Because the hypothesis was that the contamination degree would be decreased after introduction of diversion and/or new disinfection, differences in frequency of bacterial contamination between the (sub)groups were tested with a one-sided chi-square test unless indicated otherwise. Logistic regression was used to calculate the odds ratios (OR) for risk of bacterial contamination with the different methods (diversion and disinfection). Multivariate logistic regression was performed to correct for possible confounding effects, such as seasonal effects and AS.

All statistical analyses were performed with computer software (SPSS, version 11.0, SPSS Inc., Chicago, IL).

RESULTS

Number of contaminated products

In 2002 and 2003, a total of 122,907 PCs were tested in the BacT/ALERT system, with an aerobic and an anaerobic bottle per product, each inoculated with 7.5 mL of PC. The majority of these PCs were T5, but 1814 products were made by pooling three buffy coats, with an initially positive signal rate of 0.39 percent (n = 7). A total of 8000 apheresis PCs were tested, with 0.30 percent (n = 24) initially positive in the BacT/ALERT system. Because of their small numbers, the products made by pooling three buffy coats are left out of further analysis, and the apheresis products are presented as separate group, with limited data analyses, leaving 113,093 T5 products.

In approximately 10 percent of initially positive results, with some variation per region, no microorganism could be cultured from the positive bottle. Infrequently, however, a microorganism could be isolated from one of the associated RBCs (9 of 106). For a limited number of initially positive samples no information was reported regarding determination culture (these are labeled as missing), but for the large majority (98%) data on determination were available.

Effects of diversion and disinfection methods

In Table 1 the frequency of bacterial contamination for the different collection methods is shown. Diversion was associated with a significant reduction of bacterial contamination from 0.95 to 0.50 percent (chi-square test, $p = 0.002$) with the old skin disinfection method and from 0.85 to 0.37 percent (chi-square test, $p = 0.001$) when the new disinfection method was applied. For collections without diversion, the new skin disinfection method compared to the old methods resulted in a mild reduction in initially positive samples from 0.95 to 0.85 percent (chi-square test, $p = 0.049$). For collections with diversion, the new skin disinfection method compared to the old method also resulted in a reduction in initially positive samples from 0.50 to 0.37 percent (chi-square test, $p = 0.18$).

Calculated on initially positive samples, diversion resulted in an OR of 0.47 (95% CI, 0.35-0.63; $p < 0.001$) with univariate logistic regression. Multivariate logistic regression, with correction for disinfection method, time of screening (season), and AS resulted in an OR of 0.49 (95% CI, 0.36-0.67; $p = 0.003$).

For the new disinfection, the OR was 0.88 (95% CI, 0.77-1.00; $p = 0.05$) in univariate analysis and 0.87 (95% CI,

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TABLE 1. Degree of contamination in subsets of T5 products*

Collection method	No diversion	Diversion	Total
Old skin disinfections			
Total tested	42,582	4,362	46,944
Initially positive (%)	405 (0.95)	22 (0.50)	427 (0.91)
Positive determination culture (%)	373 (0.88)	18 (0.41)	391 (0.84)
Negative determination culture (%)	26 (0.06)	4 (0.09)	30 (0.06)
Missing subculture data	6	0	6
70 percent IPA skin disinfection			
Total tested	59,400	6,749	66,149
Initially positive (%)	505 (0.85)	25 (0.37)	530 (0.80)
Positive determination culture (%)	427 (0.72)	17 (0.25)	444 (0.67)
Negative determination culture (%)	68 (0.11)	8 (0.12)	76 (0.11)
Missing subculture data	10	0	10
Total test period			
Total tested	101,982	11,111	113,093
Initially positive (%)	910 (0.89)	47 (0.43)	957 (0.85)
Positive determination culture (%)	800 (0.78)	35 (0.32)	835 (0.74)
Negative determination culture (%)	94 (0.09)	12 (0.11)	106 (0.09)
Missing subculture data	16	0	16

* Absolute numbers, within parentheses: percentages of total tested.

0.76-0.99; p = 0.03) with multivariate analysis corrected for time of screening (season), AS, and diversion. Because of the study design, correction for the region was not possible, but no significant differences between the regions were found. Removing individual centers from the analysis did not alter any of the conclusions and only marginally affected estimated effect sizes and CIs.

The effects of the various interventions have been evaluated, either with the percentages of initially positive samples or with the percentage of positive samples resulting in a positive determination culture. The percentage of initially positive samples determines the effect of the interventions on the numbers of PCs and related RBCs blocked by the screening and thus the consequences for blood banking logistics. The positive determination cultures reflect the effect of the interventions on the final degree of bacterially contaminated PCs. The ORs were slightly lower (with lower p values) when calculated on the number of positive determination cultures, owing to the increase in negative determination cultures after introduction of diversion and/or the new disinfection method.

Plasma compared to AS

At three collection centers (Rotterdam in Region Southwest, Utrecht in Region Northwest, and Nijmegen in Region Southeast), T5 products were prepared in a mixture of PLT AS (PAS II, Baxter) and plasma (65:35 ratio, vol/vol; n = 35 812). We have compared the contamination in PAS II products without diversion with plasma products without diversion to evaluate the effect of AS on the degree of contamination.

The frequency of bacterial contamination was slightly reduced in PAS II PLT products (0.86%) compared to plasma products (0.91%; chi-square test, p = 0.44, not significant). This difference did not change after the introduction of the 70 percent IPA.

Determination results

Table 2 summarizes the different species found in the contaminated T5 products, with classification in some origin-related groups. The majority of detected microorganisms were skin bacteria, mainly diphtheroids or coagulase-negative staphylococci (CNS; and other Gram-positive cocci). The other bacteria belong either to the transient skin bacteria or to the gastrointestinal tract.

After diversion, contamination with skin flora (Table 2; both diphtheroids [chi-square test, p < 0.001] and the CNS plus group [chi-square test, p = 0.001]) was significantly reduced, whereas the other groups were not significantly reduced. The fact that no bacteria belonging to the gastrointestinal tract were found after diversion is probably due to their low frequency in combination with the relatively small numbers tested. The fraction of initially positive bottles with a negative determination culture was higher with diversion, although not significantly so (chi-square test, p = 0.36).

When comparing the old disinfection method with the new disinfection method (without diversion), a significant reduction of the CNS plus group was found (Table 2; chi-square test, p < 0.001), but no reduction of diphtheroids. Contamination with other bacteria was slightly reduced; however, this difference was significant only for *Staphylococcus aureus* (chi-square test, p = 0.02). As for diversion, an increase in the fraction with a negative determination culture was observed (chi-square test, p = 0.002).

Some significant differences in the type of microorganisms were detected between plasma and PAS II PLT

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TABLE 2. Determination of initially positive samples*

Variable	Old disinfection, no diversion	New disinfection, no diversion	Diversion (both disinfections)	Totals
Number of PCs tested	42,582	59,400	11,111	113,093
Initially positive bottles	405	505	47	957
Missing determination	6	10	0	16
Skin flora				
Diphtheroids†	160 (0.38)	230 (0.39)	18 (0.16)	408
CNS plus‡	153 (0.36)	119 (0.20)	12 (0.11)	284
S. aureus§	9 (0.02)	3 (0.005)	1 (0.01)	13
Transient skin flora				
Bacillus spp.‖	25 (0.06)	35 (0.06)	4 (0.04)	64
Gastrointestinal tract flora				
Gram-negative rods¶	8 (0.02)	9 (0.02)	0	17
Streptococci	5 (0.01)	1 (0.002)	0	6
Peptostreptococci	9 (0.02)	15 (0.03)	0	24
Residual group				
Others	4 (0.01)	15 (0.03)	0	19
No microorganism	26 (0.06)	68 (0.11)	12 (0.11)	106

* Values given as absolute numbers (percentage of total tested samples), with an additional column adding up absolute numbers.
† Diphtheroids include: *Propionibacterium* spp. (mainly acnes), *Corynebacterium* spp., and unspecified diphtheroid rods or Gram-positive rods (not spore forming).
‡ CNS plus include all coagulase-negative *Staphylococcus* subspecies (mainly epidermidis) and Gram-positive cocci (less than 10% of the total; aerococci [2]; micrococci [5], and unspecified [16]).
§ Although there are limited reports on *S. aureus* contamination originating from endogenous bacteremia in the donor.
‖ *Bacillus* spp. (roughly 50% *B. cereus*), including some unspecified spore formers (12).
¶ Various species, i.e., pseudomonas (1), brevundimonas (1), flavomonas (2), bacterioides spp. (4), salmonella (1), proteus vulgaris (1), and some unspecified (6 aerobic, 1 anaerobic).

products. Both *S. aureus* and Gram-negative rods had a significantly lower frequency in PAS II products (chi-square test, $p = 0.01$, two-sided). Moreover, the frequency of initially positive bottles with a negative determination culture was lower in PAS II (chi-square test, $p = 0.01$, two-sided). These differences might be explained by a lower initial load with bacteria, because less potentially contaminated whole blood–derived material is used.

Aerobic and anaerobic bottles

Table 3 shows the mean time until the aerobic and anaerobic bottles became positive, in relation to the determination result. In general, aerobic bottles became positive sooner than anaerobic bottles. From the positive aerobic bottles only 35 (11%) turned positive after 5 days, whereas from the positive anaerobic bottles 221 (35%) turned positive after 5 days. Except for diphtheroid (more particularly the *Propionibacterium* spp.) and peptostreptococci species, most bacteria did not show a preference for either the aerobic or the anaerobic bottles (Table 3). This is in agreement with the results of spiking studies by Brecher and colleagues[14] showing for most bacteria growth in both the aerobic and the anaerobic bottle. During the test period, only 46 positively flagged units were reported to become positive in both the aerobic and the anaerobic bottle. It must be kept in mind that every negative bottle (also in case the corresponding bottle became positive) was cultured for 7 days.

Apheresis products

Table 4 shows some details for the 8000 apheresis PCs, all collected with an apheresis set including a diversion pouch. Owing to small numbers, the 95 percent CIs overlap, and no significant differences were found between the old and new disinfection methods. As for the T5, the percentage of positively flagged bottles without microorganism in the determination culture was higher after introduction of the new disinfection method (chi-square test, $p = 0.26$). In the apheresis PCs in two cases a Gram-negative rod was detected (0.03%; an *Escherichia coli* and a *Bacteroides* spp.), in one case a *Bacillus* spp. (0.01%), and in two cases a *Streptococcus* (0.03%). In eight cases the bacteria belonged to the CNS plus group (0.1%), in three cases the bacteria belonged to the diphtheroids group (0.04%), and in seven cases a negative determination culture was obtained (0.09%). These frequencies were comparable to those found in the T5 products after diversion (Table 2), except for diphtheroids (0.04% vs. 0.16% in T5).

Follow-up procedures after positive flagging

PCs. For 790 (83% of total) positively flagged T5, data on recall procedures were available (Table 5). From these units, 386 (49%) units had to be recalled and 404 units were still at the blood bank. The majority (88%) of the recalled products had already been transfused and only 45 of the recalled products could be prevented from being transfused (Table 5). Positively flagged units, which were

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TABLE 3. Growth characteristics for different bacteria species

Variable	Total number of bottles	No data on time until positive	Both bottles positive	Aerobic bottle		Anaerobic bottle	
				Time until positive*	Number	Time until positive*	Number
Total	957	38	46	1.8	330	4.0	635
Skin flora							
Diphtheroids†	408	5	4	3.7	45	5.0	362
CNS plus‡	284	2	26	1.1	165	2.6	143
S. aureus§	13	0	0	0.9	6	1.3	7
Transient skin flora							
Bacillus spp.‖	64	1	7	1.7	41	2.1	29
Gastrointestinal tract flora							
Gram-negative rods¶	17	0	0	1.9	10	2.9	7
Streptococci	6	0	3	2.8	4	3.0	5
Peptostreptococci	24	1	0		0	3.9	23
Residual group							
Others	19		3	1.3	9	4.0	13
No microorganism	106	13	3	2.3	50	2.4	46
Missing determination	16	16					

* Mean time in days until positive signal with BacT/ALERT.
† Diphtheroids include: *Propionibacterium* spp. (mainly acnes), *Corynebacterium* spp., and unspecified diphtheroid rods or Gram-positive rods (not spore forming).
‡ CNS plus include all coagulase-negative *Staphylococcus* subspecies (mainly epidermidis) and Gram-positive cocci (less than 10% of the total; aerococci [2]; micrococci [5], and unspecified [16]).
§ Although there are limited reports on *S. aureus* contamination originating from endogenous bacteremia in the donor.
‖ *Bacillus* spp. (roughly 50% *B. cereus*), including some unspecified spore formers (12).
¶ Various species, i.e., pseudomonas (1), brevundimonas (1), flavomonas (2), bactericides spp. (4), salmonella (1), proteus vulgaris (1), and some unspecified (6 aerobic, 1 anaerobic).

TABLE 4. Degree of contamination in subsets of apheresis products*

Variable	Old skin disinfections	70% IPA skin disinfection	Total test period
Total number tested	3037	4963	8000
Initially positive (%)	7 (0.23)	17 (0.34)	24 (0.30)
Positive determination culture (%)	6 (0.20)	12 (0.24)	18 (0.23)
Negative determination culture (%)	1 (0.03)	5 (0.10)	6 (0.08)
Missing subculture	0	1	1

* Absolute numbers, within parentheses: percentages of total tested. All apheresis products were collected with a set with diversion pouch.

already transfused at the moment of detection, had a mean time until detection of 4.7 days, whereas for the units still in the blood bank the mean time until detection was 2.2 days. Of 345 units with a positive signal in the first 48 hours of culture, only 27 units had already been transfused.

Table 5 also shows the recall information in relation to the various microorganisms. For the rapidly growing bacteria, most of the PCs were still in the blood bank inventory or could successfully be recalled. The majority of already transfused PCs were contaminated with diphtheroids, mainly flagging positive between Day 4 and Day 7 of culture.

During this surveillance period, no severe clinical effects of units flagged positive after transfusion were reported to Sanquin or the Dutch hemovigilance system (Transfusion Reactions in Patients; TRIP). Over the entire period, there were 165 follow-up reports (for every case a report was asked, but only in 40% a response was received) of transfused products corresponding to cultures flagged positive after release. In two cases mild clinical symptoms (fever) were reported, but no direct relation with the PLT transfusion was established. During the same period, two cases of sepsis were reported after transfusion of PCs with a negative signal in the screening[15] (also after 7 days of culturing). In both cases *Bacillus cereus* was identified as the causative microorganism, but it remains unclear whether this microorganism could have entered the PC during preparation or storage, due to pinholes in the bag, or whether it was definitely a false-negative result of the screening system (present in the sample, but not resulting in a positive flagging of the culture).

Related RBCs. In case of a positive signal in the bacterial screening of a pooled PLT product, corresponding RBCs were cultured. Data on RBC recall and cultures were available for 94 percent (901/957) of the initially positive flagged T5 units. In 40 percent of these cases there was a positive signal from the BacT/ALERT for one of the RBC units. In 85 percent of positive RBC units, the same microorganism as in the corresponding PC was found (majority diphtheroids). In the majority of cases where the microorganism was of different species, it belonged to the same group. Only in 27 cases was the microorganism found in

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TABLE 5. Recall and transfusion details with respect to corresponding PCs and RBC units

	Corresponding PC units				Related RBC units			
Variable	Total number of PCs	Unknown*	Recall†	Transfused‡	Total number of RBC units	Unknown*	Recall†	Transfused‡
Total	957	167	386	341	4785	375	741	138
Skin flora								
Diphtheroids§	408	57	256	234	2040	76	553	113
CNS plus‖	284	54	57	42	1420	85	92	12
S. aureus¶	13	0	0	0	65	2	0	0
Transient skin flora								
Bacillus spp.**	64	10	16	12	320	15	28	2
Gastrointestinal tract flora								
Gram-negative rods††	17	0	3	3	85	25	2	1
Streptococci	6	1	1	1	30	0	1	0
Peptostreptococci	24	3	14	12	120	2	16	3
Residual group								
Others	19	3	11	9	95	0	6	1
No microorganism	106	23	28	28	530	90	43	6
Missing determination	16	16			80	80		

* No data on recall available.
† Recall of products already released to hospitals.
‡ Already transfused at time of recall.
§ Diphtheroids include: *Propionibacterium* spp. (mainly acnes), *Corynebacterium* spp., and unspecified diphtheroid rods or Gram-positive rods (not spore forming).
‖ CNS plus include all coagulase-negative *Staphylococcus* subspecies (mainly epidermidis) and Gram-positive cocci (less than 10% of the total; aerococci [2]; micrococci [5], and unspecified [16]).
¶ Although there are limited reports on *S. aureus* contamination originating from endogenous bacteremia in the donor.
** *Bacillus* spp. (roughly 50% *B. cereus*), including some unspecified spore formers (12).
†† Various species, i.e., pseudomonas (1), brevundimonas (1), flavomonas (2), bacterioides spp. (4), salmonella (1), proteus vulgaris (1), and some unspecified (6 aerobic, 1 anaerobic).

the RBCs totally unrelated to the organism as found in the PCs. This number included the 9 cases with no determination culture for the PC, whereas a microorganism could be isolated from one of the associated RBC units. The bacterial species in these cases were CNS plus (4), diphtheroids (4), and *Bacillus* spp. (1).

Of a total of 4505 RBC units (901 PCs each with 5 related RBC units), 741 RBC units had already been released and had to be recalled for culturing. The recall was successful in 68 percent of the cases. A total of 234 units were not available for culture, including 138 RBC units (relating to 99 PC units) that had already been transfused. For 69 of these 138 cases, one of the other related RBC units contained the same bacterium as found in the culture from the PC. From this it might be concluded that only in the remaining 69 cases possibly contaminated RBCs were transfused. These were mainly related to positive PLT cultures in which diphtheroids found (66/69). Because RBCs are stored at 4°C, however, it is not likely that these transfused RBCs contained harmful quantities of bacteria. This is supported by the fact that no transfusion reactions were reported for these units.

DISCUSSION

Based on the results of two calendar years (2002 and 2003) of bacterial screening of all PCs in the Netherlands, it can be concluded that interventions to reduce bacterial contamination were very effective, resulting in a reduction of initially positive cultures for pooled T5 products from 0.95 percent (no interventions) to 0.37 percent (two interventions: diversion and new skin disinfection). The 50 percent reduction in frequency upon diversion is very similar to that found in our previous whole-blood diversion study[10] and also corresponds with the reduction in contamination reported by McDonald and coworkers.[16] The double-swab 70 percent IPA disinfection method slightly enhanced the reducing effect on bacterial contamination of diversion, although this is of marginal significance and without synergy. The final frequency of 0.37 percent (95% CI, 0.24-0.55) positive cultures found for pooled T5 products after introduction of both diversion and new disinfection method is not significantly different from the 0.30 percent contamination rate for single donor apheresis PC (95% CI, 0.19-0.45), whereas the differentiation profile is also similar. This suggests that the relation between number of donor units and degree of bacterial contamination of the final PC, as described by Ness and colleagues,[1] no longer exists if special care is taken to avoid introduction of bacteria during collection. The finding that contamination is reduced to such a large extent by diversion has led to the introduction of the diversion pouch throughout the Netherlands, starting from July 2004.

Our current screening system for bacterial contamination of PC is highly sensitive by use of two bottles. The

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fact that in less than 5 percent of positively flagged units both bottles were positive suggests that positive units have an initial bacterial contamination around the lower detection limit of the culture system. Owing to the high sensitivity, the percentage of initially positive units is relatively high in our screening system compared to other reported rates of bacterial contamination. Most likely, this is due to the fact that other studies use only one culture bottle, with lower inoculation volumes and shorter culture times. Wagner and Robinette[17] showed that higher inoculation volumes lead to shorter detection times. Our results are very similar to those in Belgium, where a similar screening approach is used.[18,19] When reanalyzing our results according to the system used in Denmark, that is, only the aerobic bottle and 5 days of culture, our result of 0.4 percent initially positive for T5 (with double-swab disinfections and without diversion) is very comparable to the Danish results.[20] Also for apheresis units, the recalculated initially positive rate of 0.1 percent (only aerobic bottle, 5 days culturing) resembles the values reported by other groups[1] taken into account that our inoculated volume is larger.

The selectivity of a screening system should be as high as possible, because false-positive samples result in unnecessary recalls and false-negative samples result in possible transfusion of positive units. For some as yet unknown reason, the rate of negative determination cultures is increased after the introduction of interventions for disinfection and diversion. The fraction of negative determination cultures is 0.047 percent of total tested bottles (two per unit), which is in agreement with data from Belgium and Denmark.[18,20] This would result in a false-positive rate by system failure of about 1 of 2000 cultures. Given that in 9 percent of cases with a negative determination culture for PCs, one of the RBC units contained a microorganism, it remains questionable whether a negative determination culture really should be flagged false-positive. Another possibility would be that in some cases the microorganism still has growth capacity (positive signal in BacT/ALERT), but no colony-forming properties (negative determination culture). This possibility is not hypothetical, because experiments from our group showed that after UV-C illumination the survival of bacteria is much higher (about 1.5 log) when measured in liquid culture, compared to measurement of colony formation on solid media (unpublished results). Based on these results, we intend to implement a follow-up procedure for negative determination cultures, with additional attempts to obtain a subculture.

The effect of introducing a standardized double-swab 70 percent IPA disinfection method showed borderline significance in both univariate and multivariate statistical testing with respect to reduction of bacterial contamination. This is in contrast to literature results. McDonald and colleagues[16] reported a possible reduction of approximately 50 percent by the introduction of double-swab disinfection. These results, however, were obtained with a first swab with IPA and a second swab with iodine tincture, which might explain differences in the results. Lee and coworkers[21] recently also reported a significant reduction of the degree of bacterial contamination of PCs prepared from whole blood by the PLT-rich plasma method, as a result of a changed disinfection method. With respect to skin flora, however, as expected, our new disinfection method has a highly significant reducing effect on the CNS plus group, but no effect on diphtheroids. This can be explained by the fact that diphtheroids especially colonize the interior of the sebaceous glands[22] whereas Gram-positive cocci, including CNS, are more on the skin surface. Surface disinfection will therefore be less adequate to remove diphtheroids, whereas diversion will reduce all kind of skin flora, as found in our study.

The various bacteria species detected in 2 years of bacterial screening of PCs in the Netherlands are classified as skin flora, transient skin flora, or gastrointestinal tract flora, with some very rough subclassification. Within the skin flora, the relatively slowly growing diphtheroids (either anaerobic *Propionibacterium* or aerobic *Corynebacterium*) represent the largest group. These bacteria are usually not considered being a clinical hazard[14,23] but there are some reports describing transfusion-transmitted bacterial infection (TTBI) with *Propionibacterium*.[24,25] Diphtheroids also are among the Gram-positive bacteria that can colonize prosthetic valves and intravascular implants, causing infections that are difficult to treat.[26] Upon prolongation of storage time to 7 days or longer, and without a screening system able to detect these bacteria, one should be aware of transmission of slow-growing bacteria, such as *Propionibacterium* spp. This problem is currently not encountered, because PCs containing these bacteria are generally transfused before reaching the threshold for inducing TTBI in the recipient.

The second largest group are the Gram-positive cocci not being *S. aureus* (CNS plus). These commensal skin flora are not considered very pathogenic either. Gram-positive cocci, however, are a regular cause of TTBI[24,27] but seldom responsible for septic fatalities.[28] The small subgroup of *S. aureus* is the type of skin flora with a high clinical hazard profile[1] but all 13 cases found in our surveillance had a positive culture before the products were released.

The *Bacillus* spp. belongs to the transient skin flora and this group includes some not further determined spore formers. Owing to the etiology of infection (we are only considering transmission via transfusion), no further distinction was made between *B. cereus* (known from food poisoning) and other *Bacillus* spp. The new disinfection method has no effect on the frequency of this group, as expected, because spores are not inactivated by 70 percent IPA. Diversion is expected to result in a reduc-

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tion for spore formers, but the observed reduction is not significant, likely because of the low numbers. Because spore formers remain a risk to cause TTBI even with bacterial culturing in place, further research should be focused on improved disinfection also effective in inactivating spores.

Approximately 5 percent of all initial positive samples were determined as normally belonging to the gastrointestinal tract flora, although these bacteria can also be encountered as transient skin flora. The largest subgroup are the anaerobic *Peptostreptococci* spp. (associated with abdominal wound infections) and some *Streptococcus* spp., which are often reported in transfusion-associated sepsis.[26]

The group of Gram-negative rods is very heterogeneous, with *Bacteroides* spp. and *Salmonella* spp. highly likely to have come from the donor's blood circulation. The aerobic Gram-negative rods, although we did not fully determine the species in all cases, are most probably nonfermentative bacilli and are highly likely to have been introduced as transient skin flora. The Gram-negative rods are well known as causative agents for TTBI, especially those cases related to septic fatalities.[1,2,24,25,28] In our study most products positive for the presence of Gram-negative rods were prevented from entering the transfusion chain. In the single case with a transfused RBC unit, the culture turned positive after 5 days.

Among the remaining group, one remarkable microorganism is found, a *Nocordia* spp., well known as transient skin flora present in soil and causing pneumonia, especially in immunocompromised patients or in chronic lung disease.

Despite the absence of a quarantine period, in the Dutch practice more than 90 percent of the units that flagged positive within 2 days could be prevented from being transfused, including the majority of those contaminated with the more dangerous bacteria like Gram-negative bacteria, *B. cereus* and *S. aureus*. Ninety percent of units flagged positive after being released had a positive signal after more than 2 days of culturing. These units were mainly found to be contaminated with diphtheroids, especially *Propionibacterium* spp. and the majority of these units had already been transfused. During the period of the study, two mild transfusion reactions were reported due to transfusion of such units. In general, however, underreporting is noticed in hemovigilance systems, emphasizing the need for improvement. Extension of the storage period of PCs from 5 to 7 days allows for an initial quarantine period as proposed by Munksgaard and colleagues[20] but this will have a very limited impact on the number of PCs already transfused at the time of a positive culture.

In conclusion, it is shown that introduction of diversion and improvement of skin disinfection are effective in reducing the frequency of contaminated blood products. Still, the remaining risk is high enough to warrant screening for bacterial contamination. The screening system in place in the Netherlands proves to be successful in preventing the seriously contaminated PCs from entering the transfusion chain, a similar conclusion to that reported for Belgium[19] with a similar screening system.

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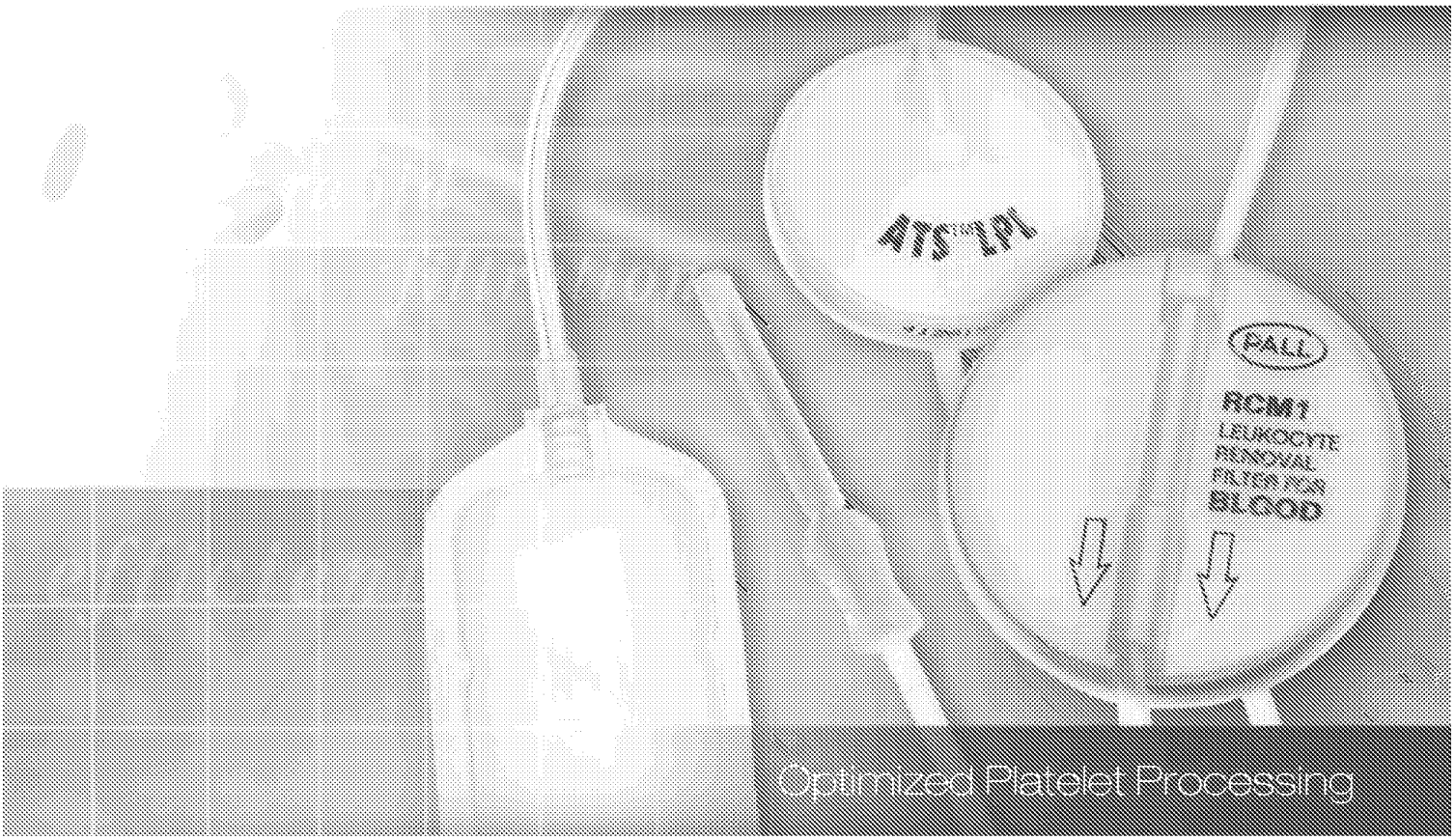
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Improving the Availability of Safer Whole Blood Derived Platelets

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.

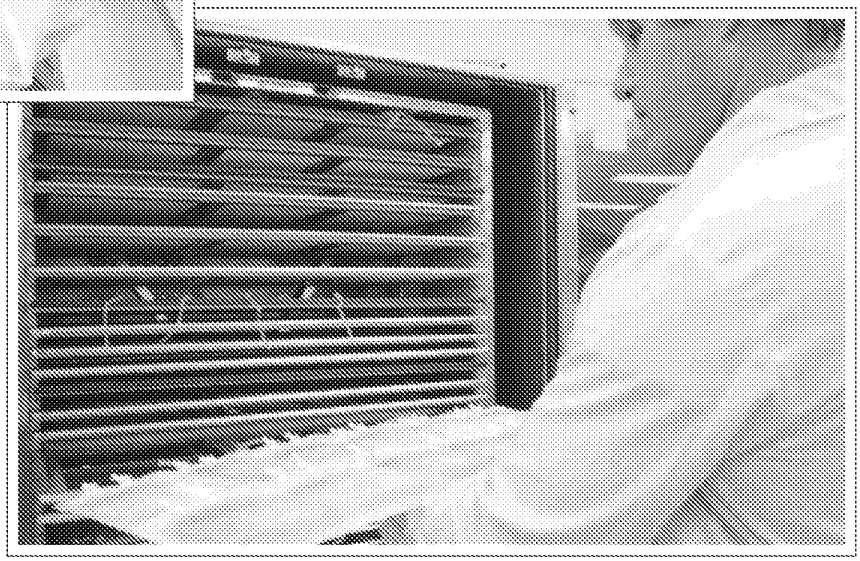
Leukotrap PL System produces leukocyte reduced platelets and plasma.

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- 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.*



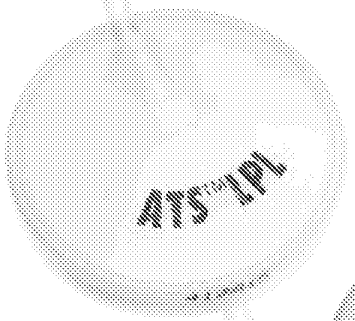
A Unique Combination of Technologies to Enhance Transfusion Safety and Operating Efficiency

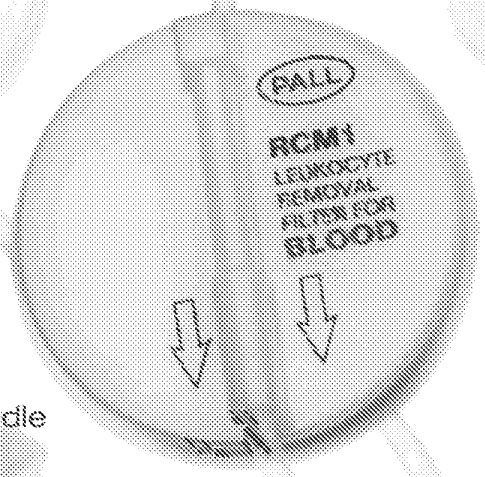
Proprietary CLX® Platelet Storage Container

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Ultra Thin Wall 16-Gauge Needle

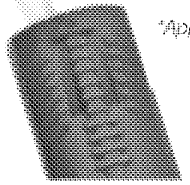
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- RBC recovery enhanced by auto-drainage.

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

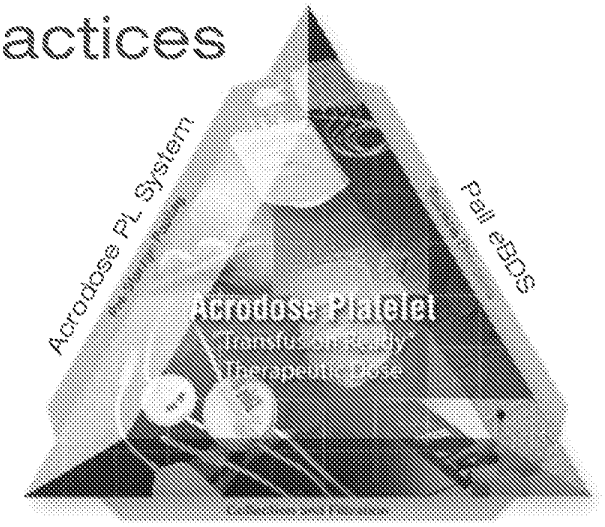
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A Synergy of Best Practices

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

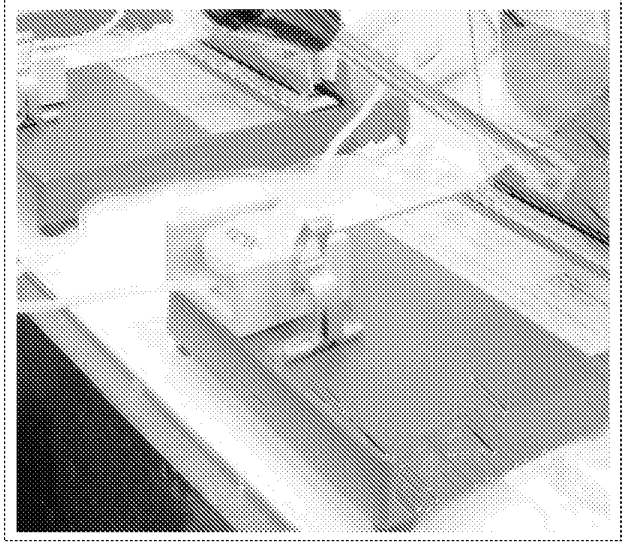
Collection and Filtration

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.

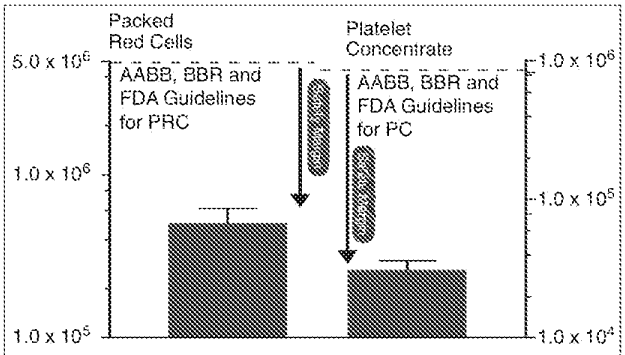
Pall eBDS and Pall Data



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

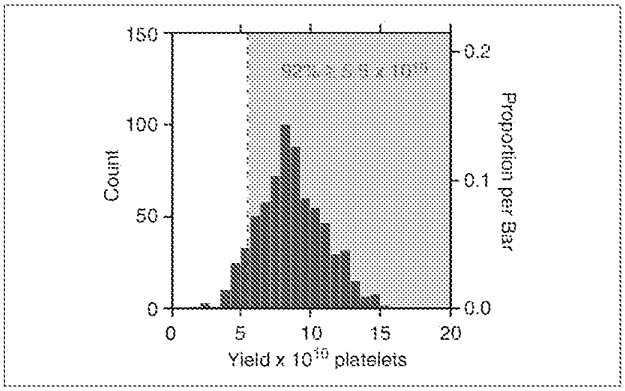


Figure 2

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}).

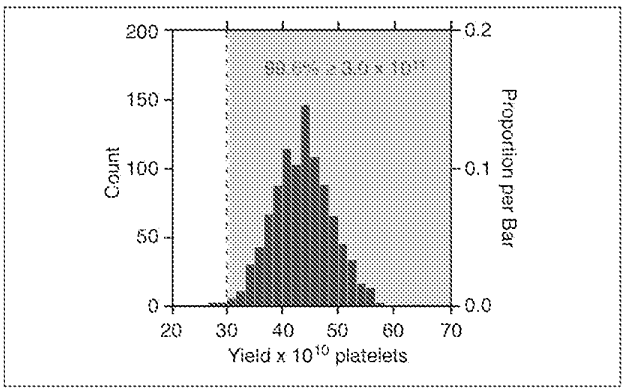


Figure 3

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.

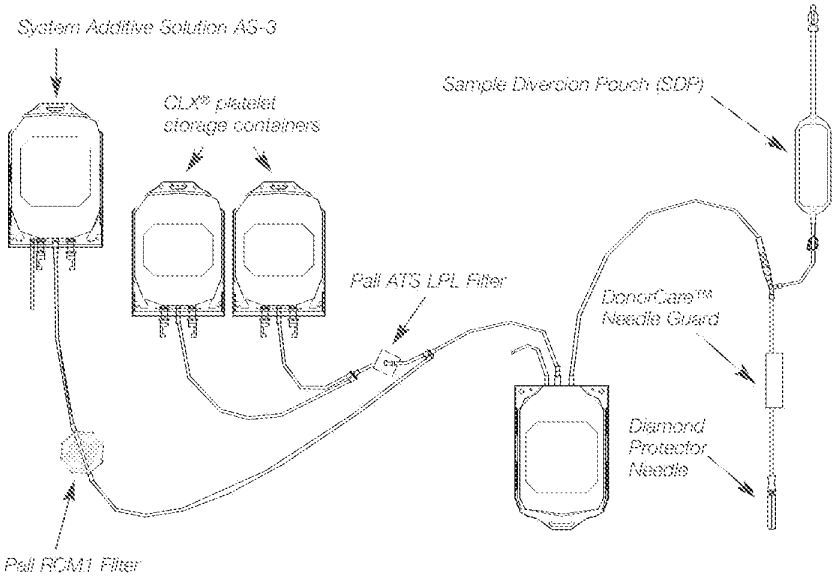
Mean platelet yield with a pool of 5 = 4.3 x 10^{11} with a standard deviation of 5.3 x 10^{10} platelets.

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

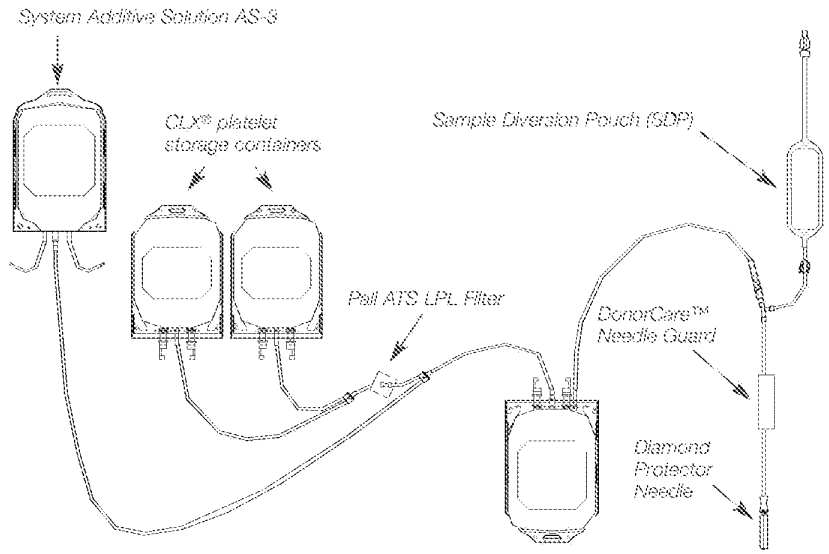


Ordering Information*

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

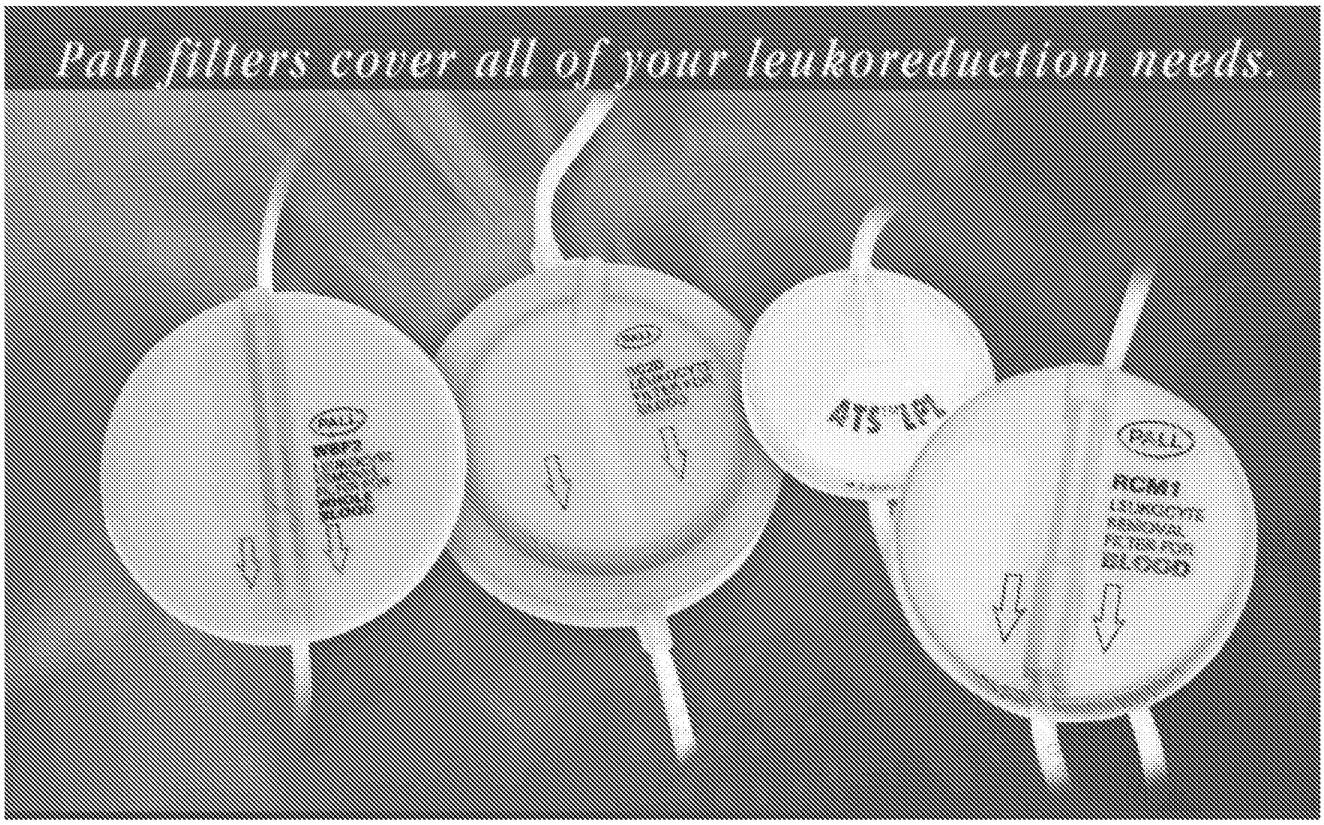


Ordering Information*

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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8 Standard 5.7.5.18 - Standards for Blood Banks and Transfusion Services, AABB 21st Edition, 2002.

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	First Named Inventor	Bobby E. Rogers
	Art Unit	
	Examiner Name	
	Attorney Docket Number	069366-0581370_KUR2C07US

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	50	20220304600		2022-09-29	HAMMER JEREMY	
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	Examiner Name	
	Attorney Docket Number	069366-0581370_KUR2C07US

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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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).

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☐ 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.

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

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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)	2024-09-27
Name/Print	Benjamin F. Hudson	Registration Number	71,474

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(Acta Anaesth. Belg., 2005, 56, 283-285)

New Closed IV Catheter System

A. VAN ZUNDERT

The insertion of peripheral intravenous (IV) lines is an extremely common procedure, practiced on approximately four out of five hospitalised patients. Issues are being raised concerning the hygienic aspects of the injection port of peripheral ported catheters (1, 2, 3).

Recently the choice of IV catheters has improved both patient care and the protection of caregivers.

We report here on our experience with IV catheters. In the past, our hospital used the BD Venflon™ (BD Infusion Therapy AB, Helsingborg, Sweden), followed by the BD Venflon Pro™. Recently we began using the BD Safelon Pro™ and most recently we have introduced the BD Nexiva™ (Fig. 1). The latter is a completely closed IV catheter system (Table 1).

A peripheral catheter is usually less than or equal to 7.5 cm in length, uses stainless steel needles and a plastic cannula, is limited to short-term or single-dose administration and should deliver therapy into peripheral veins without causing infection, leakage or extravasations. In the Netherlands, ported catheters are very popular, but its disadvantages include blood spilling and the risk of inadvertent prick accidents. An optimal peripheral IV catheter (Table 2) should reduce complications including phlebitis, thrombosis, haematoma formation at the puncture site as well as infiltration and rarely tissue necrosis. Additionally an ideal catheter should provide protection to the user against sharps injury and have advanced engineering to ensure ease of use (clearly visible and rapid flashback ; flexible and needle-less access ; and easy maintenance). Safety and comfort for the patient must be non-negotiable features.

Multi-lumen port access catheters provide many of the advantages of a central venous catheter. The inclusion of an additional port on the catheter itself (the 'ported' catheters used frequently in Europe), the attachment of a stopcock or, most cleverly, the use of an extension tubing (either attached or integral to the catheter) with multiple ports are current approaches to making peripheral catheters 'multi-access'.

The BD Nexiva™ integrated IV catheter system has many of these advanced features. It includes a safety IV catheter, an extension tubing with Y-connection or integrated stopcock and a BD Q-Syte™ needle-less access system. The Q-Syte™ can be accessed with Luer Lok (screw-on) or Luer Slip (tapered) syringes. The former may give a more secure connection. However the latter are perfectly acceptable : giving Luer Slip syringes a $^{1}/_{4}$ turn may ensure that no disconnection occurs. Regardless of the connector used, it is very important that the Q-Syte™ be cleaned with an antiseptic solution (and allowed to dry) before any device is inserted. The catheter itself is made of Vialon™ (BD Infusion Therapy, Sandy Utah, USA), biomaterial, a special designed medical grade polyurethane reducing phlebitis significantly (4, 5, 6). The two soft wings come with holes which allow for suturing, if needed. However, most peripheral catheter insertions require no suturing.

Not surprisingly, this integrated IV catheter system requires some modifications in insertion technique in comparison to the conventional IV catheter. Place the index finger on the push tab, the middle finger on the soft wing and thumb on the septum. The primary flashback is observed through the notch in the tip of the needle as soon as the needle tip enters the vein. While threading the catheter, secondary flashback is observed in the extension tubing. At this point the tourniquet is released. As long as the catheter is in the vein, there is continued blood flow in the extension tubing all the way to the vent plug where the blood stops. This avoids unnecessary blood contact. While withdrawing the needle from the catheter, the soft wings should be fixated by pressing a finger on one of them. Upon

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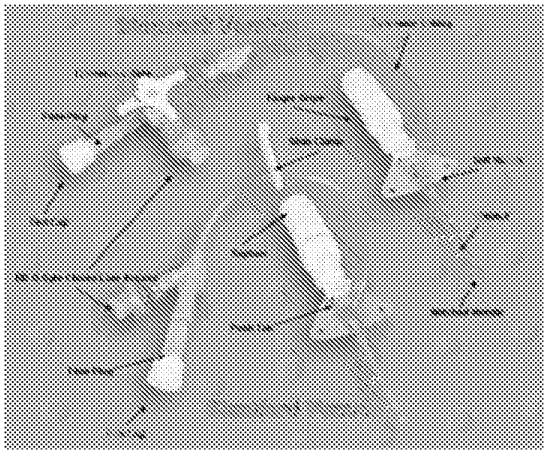


Fig. 1. — The new integrated completely closed IV catheter system (BD Nexiva™). Shown are two versions : the top one has a three-way valve to which the Q-Syte™ is attached ; the bottom one, with the Q-Syte™ closed Luer Lok access. Both devices have a flow plug for venting out the air during insertion. Advantages of both versions include avoidance of needlestick injuries and blood contact.

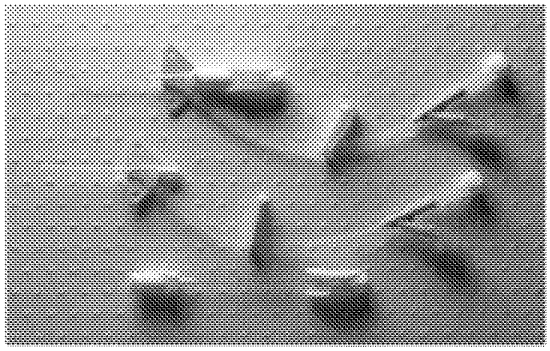


Fig. 2. — Non-activated (top) and activated (bottom) versions of the BD Nexiva™.
The white portion (catheter body) is used for gripping the device. Once inserted into the vein, the catheter body is withdrawn completely and the needle is automatically sheathed (see lower picture), thus protecting from accidental needle stick injuries.

Table 1

Characteristics of IV needles

	Ported IV cannula	Integrated valve	Needle tip protection	Integrated extension line
BD Venflon™	Yes	No	No	No
BD Venflon Pro™	Yes	No	No	No
BD Safelon Pro™	Yes	No	Yes	No
BD Nexiva™	No	Yes	Yes	Yes

Table 2

Advantages of new IV cannula over previous IV catheters

- rapid reliable blood flashback via notched needles
- reduced pain to patient*
- lower infection and thrombotic risks**
- simplicity in dressing, resistant to snagging
- needle-less access to ports
- more closed to bacterial entry
- reduced needlestick risk
- minimal blood exposure for the user

* a function of many factors including : the sharpness and geometry of the needle tip, the gauge of the catheter, the nature of the plastic in the catheter, the skill and speed of the inserter and the skill at preparing and distracting the patient.

** a function of many factors including : the catheter material, the agent and procedure used to prepare the skin, the drug injected, the post-insertion site care and the sterility of infusions given.

withdrawal, the needle tip is automatically shielded thus protecting the healthcare worker from needlestick injuries.

Once the needle is withdrawn and has been shielded it cannot be inserted into the cannula again. Furthermore, the hub, after needle withdrawal, cannot be accessed by any device (e.g. syringe, tubing, plug). At this point, the extension line has to be clamped before removing the vent plug and either connecting the infusion line or flushing and attaching the white cap. The three-way stopcock version (Fig. 1) does not have a clamp. The valve serves this function.

Our experience with the new BD Nexiva™ integrated IV catheter system is limited to hundred insertions ; but so far it has been positive. We have found that the grip on the catheter is designed in such a way as to make vein access quite easy. Confirmation that one is in, is provided via a clear primary flashback. Patients seem to experience less pain due to its sharp needle. Once withdrawn, the needle tip is covered automatically thus protecting the patient and the caregiver from needlestick injuries. The flat soft wings are simple to dress with Tegaderm™ (3M Health Care, St. Paul, USA). An IV line can be attached immediately to the side port without need for additional extension tubing or administration sets. Instead of a 'ported' access, the BD Nexiva™ has a BD Q-Syte™ access. This is a

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needle-less valve containing silicone and can also be used to attach another IV line, administer medication or blood withdrawal. There are additional convenience features. The flat profile of the BD Nexiva™ IV catheter allows dressing to cover it smoothly without wrinkling or binding up. Therefore it is less likely to catch on objects in the environment.

There are two features of BD Nexiva™ that could be improved. In few occasions, secondary flashback (via extension line) stops too early, leaving a gap in the tubing containing air. This can be solved by aspirating the remaining air from the tubing. The BD Q-Syte™ is not a one-way valve, so that backflow is possible if a syringe is attached. The BD Nexiva™ stopcock version solves this issue.

In conclusion, our experience with the BD Nexiva™ peripheral IV catheter indicates that it provides better IV access to peripheral veins, with less pain to patients and with rapid and clearly visible primary and secondary flashback of blood. By having all the add-ons (valve, extension tube, stopcock) already integrated into the device, infection risk should be reduced. Above all this IV cannula prevents needlestick and blood exposure, which is a dramatic improvement in an era where risks of infections are increasingly due to blood exposure.

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KUR-MAG-DE003908

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.

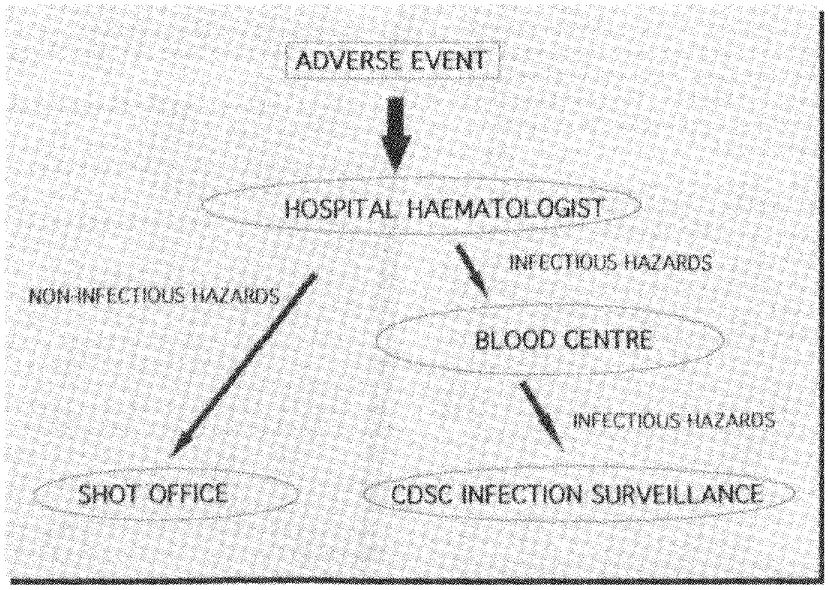
Risks of transfusion and new approaches to reducing the risks

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)



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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/bbf2). 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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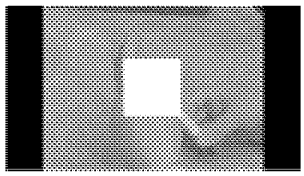
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DEVICE AND METHOD FOR PREPARING BLOOD

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Abstract not available for DE10134913 (A1)
Abstract of corresponding document: WO03008012 (A2)

The invention relates to a preparation device (100) for treating suspension samples, especially for preparing blood cryobanks. Said device comprises an arrangement of at least two containers for receiving suspension samples, sample parts and/or additives. Said containers are formed as chambers (13 to 15, 90) having fixed walls and are arranged in a fixed manner in relation to each other. A transfer device comprising at least one connecting line (22) is provided, by which means the chambers (13 to 15) can be interconnected.

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DESCRIPTION DE10134913C2

[0001]

13 The invention relates to a device for sample preparation, in particular a device for handling and treating blood samples, such as. B. for separating blood samples by centrifugation and for modifying blood samples by additives in preparation for cryopreservation of the blood samples, as well as a preparation station and a method for blood preparation, in particular for preparing blood samples for cryopreservation.

[0002]

21 It is known, for the cryopreservation of blood samples, to first prepare a blood unit from a blood donation for the state ready for freezing. The preparation comprises in particular firstly a separation of the blood donation into an erythrocyte suspension which is to be cryopreserved and residual components and secondly the addition of a cryoadditive to the erythrocyte suspension. In conventional methods, blood samples are handled using flexible blood bags, as illustrated schematically in FIG. A blood donation is provided in a first blood bag 1' and centrifuged. After centrifugation, the blood donation is separated into the sediment and the supernatant (plasma). If necessary, the supernatant is drawn off into a waste container 4'. The erythrocyte suspension is transferred into another blood bag 2', to which a cryo-additive is added to provide the preserved product ready for freezing. The illustrated use of blood bags, described for example in DE 298 05 538 and WO 00/38762, has the following disadvantages.

[0003]

35 A major problem relates to the handling of the blood bags.

36 Since the blood bags do not have a fixed shape, careful handling of the blood bags must be provided, in particular to preserve the phase boundary after centrifugation. In the conventional

systems mentioned, devices for holding and transporting the blood bags are provided. However, these devices can only be automated to a very limited extent. The devices must be loaded manually and the operation must be continuously monitored. Furthermore, in the conventional devices, the blood bags are connected to one another via flexible hoses. To separate the erythrocyte suspension and supernatant, the phase boundary on the blood bag or tube must be detected. Due to the flexibility of the respective containers, there is a risk of incorrect detection and thus a malfunction during preparation.

[0004]

48 Further disadvantages result from sterility problems when handling the blood bags.

49 The hose connections must be connected to the blood bags in a sterile manner and separated and sealed after the respective process step. In each step of the preparation, complex precautions must be taken to maintain the sterility and freedom from pyrogens of the blood samples.

[0005]

56 The conventional blood bag preparation is also problematic because of the risk of mix-ups.

57 If a blood bag is mixed up during preparation or cross-contamination occurs between blood bags, the consequences for the recipient of the blood donation can be devastating. Extensive safety measures have to be implemented in conventional systems to rule out the risk of confusion.

[0006]

64 Another disadvantage of the technique described in WO 00/38762 is its specific tailoring to stem cell preparation.

66 When separating stem cells from biological fluid samples, only a very small amount of stem cells has to be separated from the samples. This allows for the use of special centrifugation techniques and less sensitivity to the use of blood bags.

[0007]

72 In modern medicine and in civil protection there is an interest in enlarged blood banks with a wide range of different blood types.

74 Automating the preparation of the canned goods is necessary for the production of modern blood banks. Because of the need for automation, the applicability of conventional preparation devices is limited.

[0008]

80 The problems illustrated in handling blood samples are not unique to the preparation of preserves for cryopreservation.

82 A corresponding need for sterile, automated and safe sample handling also exists when processing biological cell suspensions for therapeutic purposes.

[0009]

87 The object of the invention is to provide an improved device for the preparation of suspended biological samples, with which the disadvantages of conventional systems are overcome and which is particularly suitable for automated and safe handling of a large number of samples.

90 Furthermore, an improved system for the preparation of cryopreserves such.

91 B. cryopreserved blood can be created, as well as a new method for handling biological suspended samples, which can be automated and carried out safely in particular.

[0010]

96 These objects are achieved with a preparation device, a preparation station and a method having the features according to patent claims 1, 9 and 11.

98 Advantageous embodiments and applications of the invention result from the dependent claims.

[0011]

102 The basic idea of the invention is to provide a preparation device that has at least two containers for receiving the suspension samples to be treated, the containers, in contrast to conventional systems, being formed by chambers with fixed walls that are positioned stationary relative to one another.

106 The chambers are connected to one another via line connections that can be actuated individually or are equipped with connecting pieces for the optional formation of line connections between the chambers.

109 According to a first embodiment, the preparation device according to the invention is formed by an integral structure in which the chambers are formed in a chamber body, at one end of which the line connections can be attached or adjusted.

112 According to a second embodiment, the preparation device comprises a framework into which the chambers can be inserted individually.

114 The connection pieces of the individual chambers are all on one (e.g.

115 B. lower) side of the rack arranged.

116 Depending on requirements, the connecting pieces, which are initially sealed with a septum, are opened and connected in pairs via line connections.

118 According to a third embodiment, the design with individual chambers is such that the framework is equipped with a valve plate with line connections via which the individual chambers can be connected in pairs.

121 The design of the preparation device as an integral structure or as a frame structure with at

least two chambers has the advantages that the preparation device represents an object that can be safely gripped and manipulated within the scope of an automated process sequence and that the sample handling, in particular the independent pre-filling of the chambers, the treatment of samples in the chambers and the transfer of the samples between the chambers, is simplified.

127 When using the preparation device according to the invention for the production of blood samples for cryopreservation, at least three chambers are preferably provided.

[0012]

132 According to said first embodiment of the invention, the chambers are preferably formed in the form of right circular cylinders in a plastic body, at one end of which is attached a valve plate which contains at least one line connection for coupling two chambers each.

135 The construction with an integral plastic body has the advantage that the preparation device can be manufactured as a disposable product, so that problems with sterility and mix-ups can be ruled out.

138 A further advantage is the high stability of the preparation device, particularly during centrifugation processes.

[0013]

143 The second and third embodiments of the invention mentioned each represent a modular structure.

145 The chambers can be used as disposable products.

146 An additional advantage is the relatively low weight of the frame construction.

[0014]

150 The transfer of samples between the chambers is preferably effected by hydrostatic pressure applied as gas pressure or preferably with plungers located in each chamber.

152 Alternatively, it is possible to transfer the pressure with a mechanically actuated piston (e.g.

153 B. with a connecting rod rod).

154 In this configuration, the chambers of the preparation device according to the invention form piston pressure generators, which are set up both to receive the respective samples and to transfer the samples to adjacent chambers.

[0015]

160 According to a further preferred embodiment, the preparation device, in particular the chambers as the main components, consists at least partially of a transparent plastic material.

162 If non-transparent material is used, the chambers preferably have at least one transparent window for optical detection.

164 A reliable and reproducible optical detection of sample properties, in particular the position of the phase boundary after centrifugation, is made possible.

[0016]

169 The invention also relates to a preparation station that is equipped with the preparation device according to the invention and also has a pressure device for transferring samples between the chambers, a detector device for measuring sample properties in the chambers and an actuating device for selectively coupling chambers.

[0017]

176 The invention also relates to a method for the preparation of suspensions containing biologically relevant components, such as e.g.

178 B. cells, cell components or macromolecules, using the preparation device according to the invention.

180 The method is characterized in particular by the fact that all preparation steps are carried out with the entire preparation device, which contains different chambers for receiving samples at different stages of preparation.

[0018]

186 The invention has the following advantages for sample preparation, particularly for the manufacture of cryopreserved blood.

188 The preparation process is designed to increase productivity in canning, i. H. to achieve the highest possible canning throughput, can be automated, while at the same time increasing the production quality and maintaining it independently of the manual skills of an operator.

191 A blood unit produced according to the invention already experiences an increase in quality through the use of the preparation device, without the preparation becoming significantly more expensive.

[0019]

197 The preparation device according to the invention is completely closed off from the outside during the preparation procedure.

199 It only comes into contact with the environment once during filling and emptying.

200 For example, the pre-treatment of a preserve is absolutely sterile until it is ready for freezing.

201 Advantageously, the opening, connecting and closing of bags and connecting tubes according to the conventional systems is avoided.

203 The suspension sample does not leave the preparation device during the preparation steps.

204 A mix-up e.g.

205 B. blood from different donors or contamination by foreign blood or microorganisms are

excluded.

207 The identity of the donor blood is guaranteed.

208 The preparation process is greatly accelerated, since work steps that may be necessary several times in conventional systems can be completely eliminated according to the invention.

210 Partial or complete sample loss or contamination of the working environment, including the laboratory staff, through leaking tube connections are ruled out with the preparation device according to the invention.

[0020]

216 The preparation device according to the invention forms a solid container which, in comparison with conventionally used blood bags, enables the device and the valves and/or nozzles attached to it to be gripped and manipulated in a defined and reproducible manner.

219 There is no need to grip or position and clamp connecting hoses if the at least one connecting line is integrated into the preparation device and thus enables the individual chambers to be connected repeatedly and reproducibly over the shortest possible route.

222 The short distances and the choice of a suitable cross-section for the respective connecting line allow the transfer time for transferring samples between the chambers to be optimized.

224 The construction of the device enables a defined positioning of the at least one connecting line.

225 Accidental connection of currently non-cooperating chambers is excluded.

226 Deformation or squeezing of the chambers is avoided according to the invention.

227 a z.

228 B. set by centrifugation phase separation of sample components can not be blurred by a gripping process.

[0021]

233 The fixed and preferably symmetrical arrangement of the chambers in a preparation device according to the invention enables rapid and defined positioning of the chamber of interest in a preparation system, independently of the process step.

236 All sensors and actuators are automatically positioned correctly.

237 Increased, error-free throughput is achieved.

238 For example, with a preparation device according to the invention, around three times as many cryopreserves can be prepared per unit of time.

240 The preparation device allows a free choice of material and dimensioning of the outer shape of the chamber arrangement.

242 Advantageously, the device can be readily used with conventional centrifuge equipment.

[0022]

246 By manufacturing the preparation device from inexpensive plastic materials, large numbers of the device can be manufactured using injection molding or extrusion techniques.

248 This is advantageous for the use according to the invention of the solidly walled chambers as disposable products.

[0023]

253 The following additional advantages result in particular in the preparation of blood samples.

254 When using the preparation device according to the invention, there is no significant additional effort for blood donation services.

256 No multiple bag systems are required.

257 The preparation device can be coupled directly to a simple donation bag (single blood bag).

258 The supernatant (plasma and buffy coat) which in conventional methods ends up in the waste or can only be obtained with great effort is available according to the invention as an additional end product if required.

261 The preparation device also provides advantages when filling freezing bags after preparation.

262 When docked to the preparation device, a filled freezing bag can be vented in a simple and sterile manner with this device by subjecting the respective chamber to negative pressure.

[0024]

267 Further advantages and details of the invention result from the following description of the accompanying drawings.

269 Show it:

[0025]

273 1 shows a schematic phantom view of an embodiment of a preparation device according to the invention in a partially expanded state,

[0026]

278 FIG. 2 shows an illustration of the integration of the preparation device according to FIG. 1 into a device for the production of blood reserves,

[0027]

283 3 shows an enlarged partial view of a chamber end of the preparation device according to FIG. 1,

[0028]

288 4 illustration of a modified embodiment of a preparation device according to the invention,

[0029]

292 5 shows a schematic sectional view of a single chamber used according to the invention, and

[0030]

296 6 shows an illustration of a conventional preparation technique (prior art).

[0031]

300 1 shows an embodiment of a preparation device 100 according to the invention in a schematic phantom view.

302 The preparation device 100 comprises a chamber body 10, in which three chambers for receiving suspension samples are formed, a transmission device 20, consisting of a valve plate 22 and at least one connecting line 22, a stamp device 30 with several pressure stamps 31 to 33 and a cover plate 40, which upper end of the chamber body 10 forms.

306 The chamber body 10 is integrally formed of a transparent plastic material (e.g.

307 B. PMMA, cycloolefin copolymers, polyamide, polycarbonate, PCHP, polyester or polysulfone).

308 It has the external shape of a right circular cylinder with a flat upper side 11 and a flat lower side 12.

310 In the interior of the chamber body 10, the three cylindrical chambers 13, 14 and 15 for receiving samples are formed.

312 At the upper end of the chamber body 10, the chambers open out freely into the top 11.

313 At the lower end, each chamber has a taper 16 with a connecting piece 17, as illustrated in FIG. 3 on an enlarged scale.

315 The connecting piece 17 opens into the underside 12 of the chamber body 10.

[0032]

319 For use in the preparation of blood samples, the preparation device 100 has, for example, a diameter of approximately 18 to 20 cm, the height of the chamber body 10 being approximately 10 to 12 cm and the chambers 13 to 15 each having an internal diameter of approximately 6 to own 8 cm.

323 A chamber preferably has a volume in the range 400 ml to 600 ml.

324 The chambers 13 to 15 are preferably distributed symmetrically relative to the axis of the chamber body 10 .

[0033]

329 The transfer device 20 is set up to transfer samples between the chambers 13 to 15 .

330 The valve plate 21 is rotatably attached to the bottom 12 of the chamber body 10 .

331 The connecting line 22, which forms an overflow channel, is integrated into the valve plate 21,

which is also made of plastic material.

333 Sealing rings made of an elastic material (e.g.

334 B. PTFE) attached.

335 In addition to the sealing function, the sealing rings (not shown) can also serve as latching devices.

337 Upon rotation of the connecting plate 21, the sealing rings snap into place at the desired positions of the connecting pieces or the mouth of the connecting pipe 22 when these are straightly aligned with one another.

[0034]

343 The valve plate 21 has a valve function since liquid is generally only ever pumped in one direction from one chamber to the adjacent chamber.

345 To rule out incorrect operation, a device for forced specification of a specific direction of rotation and/or a repeat lock can be provided on the valve plate 21 or on the chamber body 10 .

348 This device includes, for example, teeth that prevent reverse rotation and/or an additional locking aid.

[0035]

353 The structure of the valve plate 21 can be modified depending on the application (see FIG. 4).

354 Several connecting lines can be provided.

355 The at least one connecting line can be equipped with a blocking or valve device.

356 Additional through-openings for charging the chambers can preferably be provided in the valve plate.

358 However, loading can also take place from the top.

[0036]

362 Pressure is applied to the samples to transport the samples between the chambers.

363 The sample is transferred via the overflow channel in the valve plate 21 under the effect of an overpressure in the chamber from which the transfer originates.

365 The transfer pressure is applied with a pressure device which is part of the preparation station (see FIG. 2) in which the preparation device according to the invention is preferably used.

367 According to an advantageous embodiment of the invention, the pressure is transmitted using a stamp device 30 which has a pressure stamp 31 to 33 in each of the chambers 13 to 15 .

369 The plunger 31 to 33 consist of plastic bodies z.

370 B. in the form of a cylinder, which are fitted in a form-fitting manner into the respective chamber.

372 Each plunger has at least one circumferential sealing lip, which seals any gaps that may occur between the plungers and the inner walls of the chamber.

374 The sealing lips prevent the piston from passing through the liquid samples when pressure is applied.
376 The pistons with the sealing lips are made of a plastic material (e.g.
377 e.g. PTFE).
378 The use of the plungers 31 to 33 in the chambers has the advantage that when the preparation device 100 moves, a sample movement in the chambers is prevented when the plungers are respectively placed on the liquids.
381 After a centrifugation, the phase boundary between the fractions is advantageously avoided.

[0037]

385 According to a preferred embodiment, the plungers 31 to 33 can each have a central bore (shown in dashed lines) with a closure (e.g.
387 B. a septum).
388 This allows access to the samples or supplemental liquids in the chambers from the top of the device 100.

[0038]

393 According to a modified embodiment of the invention, the use of the plunger can also be dispensed with.
395 In this case, the transfer pressure is applied directly to the liquid surface in the respective chamber.
397 In this design, the upper ends of the chambers are preferably equipped with a sterile filter insert at the top, which is only suitable for the sterile pressure medium used (e.g.
399 B. air, inert gas) is permeable.
400 The structure without a plunger has the advantages of an increased internal volume and a simplified structure of the chambers and thus cost savings.

[0039]

405 The upper cover plate 40 serves to close off the preparation device 100.
406 It is fixedly mounted on the chamber body 10 and has through openings or ports 41 aligned with the upper ends of the chambers 13-15, respectively.
408 The connecting pieces 41 serve to connect individual chambers or all chambers at the same time to the pressure device and/or charging devices.

[0040]

413 The process sequence for producing a blood cryopreservation using a preparation device according to the invention is explained below with reference to FIG.
415 FIG. 2 shows the preparation device 100 analogous to the representation according to FIG. 1 in

combination with parts of the preparation station.

[0041]

420 The components of the preparation device 100 are provided with the same reference symbols as in FIG. 1 .

[0042]

425 The preparation station includes, in particular, the printing device 50, a detector device 60, an actuating device 70 and a control device 80.

427 The pressure device 50 preferably comprises a pressure generator 51 with a motor 52 and a pump part 53.

429 Alternatively, the pressure device 50 comprises a lever device with a connecting rod.

430 The mechanical power transmission has the advantage that the positioning of the plunger can be done with increased precision.

432 According to alternative embodiments of the invention, the pressure generator can also be supplied by a pressure source (e.g.

434 B. compressed gas cylinder) are formed with a control valve.

[0043]

438 The detector device 60 comprises, in particular, at least one light-sensitive element 61 for detecting the phase boundary.

440 Depending on the application, the light-sensitive element 61 can be equipped with filter devices (not shown).

442 A plurality of light-sensitive elements can also be arranged corresponding to the positions of the chambers.

444 Depending on the application, other detectors for detecting sample properties can also be provided, as are known from analytics (e.g.

446 B. spectrophotometer, resistivity meter for density determination).

447 The chambers can also each have a scale extending over their length for optical control of the filling level, the position of the plunger or the position of the phase boundary.

449 The detectors can also be attached to other components of the preparation device, e.g.

450 B. be provided on a connecting line in the valve plate.

[0044]

454 To adjust the valve plate 21 explained above, the adjusting device 70 comprises an actuating element 71 and a servomotor 72.

456 The actuating element 71 has the form of a plate with at least one projection 73 which cooperates with at least one corresponding recess (not shown) on the underside of the valve

plate 21.

459 The projection 73 engages in the recess and rotates the valve plate 21 into the desired position when the servomotor 72 is actuated, so that one chamber can be opened or emptied, two chambers are connected via the connecting line 22 or all three chambers are closed.

[0045]

465 The control device 80 is connected to the components 50, 60 and 70 of the preparation system.

466 Depending on the operating state and the detector signal supplied by the detector device 60, the pressure generator 50 and the actuating device 70 are actuated in the following manner.

468 In the case of semi-automatic or manual operation, the corresponding steps are at least partially carried out by an operator.

[0046]

473 In a starting state, the chambers of the preparation device 100 according to the invention are loaded as follows.

475 In the first chamber 13 there is a blood donation.

476 The blood donation is poured into the first chamber 13 from a donor bag, which may be carried out with the application of a supporting negative pressure.

478 The second chamber 14 is filled with a wash solution.

479 A cryoadditive is located in the third chamber 15 .

480 In the starting state, the first chamber 13 is completely filled, while the remaining chambers 14, 15 are only partially filled.

482 There is as much free volume in these chambers as is required to take over the erythrocyte suspension after centrifugation (see below).

484 After the starting state (all closed), the valve plate 21 is set in such a way that, for example, the first and second chambers 13, 14 are connected.

486 Advantageously, there is essentially no liquid exchange via the connecting line despite the connection in the pressure-free state.

[0047]

491 In a first preparation step, the chamber body with the filled chambers is centrifuged using a centrifugation device.

493 The centrifugation device (not shown) has the design of a large centrifuge known per se with individual centrifuge buckets in which a large number of preparation devices can be centrifuged at the same time.

496 During centrifugation, the blood donation is only separated into fractions.

497 The plungers 31 to 33 are not shifted.

498 The chambers are sealed during centrifugation.

[0048]

502 The state of the preparation device after centrifugation is shown in FIG.

503 In the first chamber 13, the formed fractions of the blood donation with the erythrocyte sediment 1 of the so-called

505 "Buffy Coat" layer 2 and the plasma supernatant 3 illustrated.

506 Depending on the operation, the erythrocyte sediment 1 comprises a volume proportion of approx. 45% of the chamber 13.

508 The volume fraction depends in particular on the centrifugation speed.

509 A higher speed results in a higher packing density of the erythrocytes and thus a lower volume fraction.

511 The “buffy coat” layer 2 is a greyish-colored coating containing thrombocytes and leukocytes, which forms between the deep red erythrocyte sediment 1 and the bright red plasma supernatant 3 after centrifugation.

[0049]

517 After the centrifugation, the preparation device 100 is inserted into the preparation station.

518 The valve plate 21 is rotated between the first and second chambers 13, 14 in the passage direction.

520 This is done manually, e.g.

521 B. with a knob wrench or with the adjusting device 70 (see above).

522 The first chamber 13 is pressurized.

523 Under the action of hydrostatic or mechanical pressure, the plunger 31 moves downwards and the plunger 32 moves upwards.

525 The separated blood donation is transferred to the second chamber 14 .

526 This preparation step is terminated as soon as the detector device 60 arranged at the lower end of the first chamber 13 detects the "buffy coat" layer 2 .

528 In this state it is ensured that only erythrocyte sediment is still present in the narrowed area 16 (see FIG. 3) and the connecting line.

530 When the buffy coat layer 2 has been detected, the print transfer is stopped.

531 Then the valve plate is brought into the closed position.

532 This occurs either immediately upon detection of the layer 2 or with a time delay, so that concentrate residues from the narrowed area 16 can still get into the connecting line.

[0050]

537 The erythrocytes transferred to the second chamber 14 mix with the washing solution.

538 The washing solution includes, for example, physiological saline.

539 Another centrifugation follows, as a result of which the treated erythrocytes again collect as a concentrate in the lower part of the second chamber 14, while the remaining washing solution forms the supernatant.

[0051]

545 In a further preparation step, the washed erythrocyte sediment is transferred to the third chamber 15 analogously to the manner described.

547 For this purpose, the valve plate 21 is rotated in such a way that the connecting line 22 is arranged between the second and third chambers 14 , 15 .

549 In addition, the pressure distributor 56 is adjusted accordingly.

550 The pressure transmission is in turn controlled as a function of the detector signal from the detector device 60 .

552 A further sensor (not shown) can be provided on the second chamber 14 .

553 Alternatively, it is possible to rotate the preparation device 100 towards the sensor 61 so that the phase boundary in the second chamber 14 can be detected.

[0052]

558 After the washed erythrocyte sediment has been transferred to the third chamber 15, it is mixed with the cryoadditive there.

560 The additives known per se are used as cryoadditive.

561 For example, the cryoadditive comprises a solution of water-soluble starch derivative.

[0053]

565 After the washed erythrocytes have been transferred to the third chamber 15 and mixed with the cryoadditive, the cryopreserve is ready to be frozen.

567 This is followed by the transfer to the container selected depending on the application, e.g.

568 B. a cryobag in which the freezing process takes place.

569 After completion of the preparation, the plasma supernatant is advantageously present in the first chamber 13 as a donor-specific residual product.

571 Depending on the application, the plasma can be used for other purposes.

[0054]

575 Details of a design of the preparation device according to the invention that is modified compared to FIG. 1 are shown in FIG.

577 The differences relate to the design of the valve plate 21.

578 The lower side 12 of the chamber body 10 with the chambers 13 to 15 is illustrated in the top partial image of FIG.

580 Each chamber has an inlet and outlet opening in the form of a connecting piece 17 (see FIG. 3).

582 An O-ring seal 18 is provided on each connecting piece 17 .

583 In the middle of the chamber body 10, corresponding to the cylinder axis, there is a threaded

hole 19 for fastening the valve plate 21.

[0055]

588 In the middle part of Fig. 4, the valve plate 21 is shown individually.

589 In this design, two connecting lines (or overflow channels) 22, 23 are provided, which are arranged in such a way that two chambers can be connected to one of the connecting lines 22 or 23, while the other connecting line 22 or 23 is closed.

592 The use of two connecting lines has the advantage of shorter adjustment paths when setting the chamber connections in the individual preparation steps.

594 Three inlet and outlet bores 24 are provided in the valve plate, which are arranged in such a way that when one of the inlet and outlet bores 24 is aligned with one of the connecting pieces 17, the other connecting pieces remain closed.

[0056]

600 The valve plate 21 has a circumferential O-ring 25 which provides an additional seal against the underside 12 of the chamber body 10.

602 The reference number 26 refers to the axis of rotation and the bearing of the valve plate 21.

[0057]

606 In the lower partial image of FIG. 4, the valve plate 21 and the underside 12 of the chamber body 10 are shown in the assembled state.

608 If the valve plate 21 is turned to the left from the state shown, the chambers 13 and 14 are first connected to the connecting line 22 and the chambers 14 and 15 are connected via the connecting line 23 as the adjustment continues.

611 The two preparation steps explained above can thus be carried out with a short travel distance.

[0058]

615 The embodiment of the invention illustrated in FIGS. 1 to 4 can be modified in many ways depending on the task at hand.

617 For example, further chambers for accommodating further additives can be provided in the chamber body in order to carry out further preparation steps.

619 Instead of the 120° arrangement, the chambers can also be arranged differently in the chamber body or a frame (see below).

621 Depending on the application, the chambers can be loaded from the top or bottom.

622 This is preferably done using tubing or pipetting systems.

623 According to a preferred embodiment of the invention, the inlet openings of the chambers are adapted to the outer diameter of standardized liquid pipettes or tube adapters, so that they can be easily attached and operated for loading.

626 Depending on the application, the size of the preparation device can be scaled as desired.
627 The transmission device with the valve plate can be replaced by a fixed arrangement of several connecting lines with valves that can be actuated.

[0059]
632 Additional gripping or fastening devices for handling the chamber body and/or for use in a centrifuge can be provided on the outside of the chamber body.

[0060]
637 According to the invention, the chamber body with the integrated chambers can be replaced by an arrangement of individual chambers in a frame.
639 This configuration has advantages with regard to separate filling of the individual chambers before composition for the preparation device and disposal of the chambers after use.
641 Any suitable structure can be used as the framework, into which the chambers can be inserted in a fixed manner in accordance with the desired arrangement and which has sufficient stability during centrifugation.
644 Depending on the design of the chambers, the structure of the frame is adjusted.

[0061]
648 If ready-made plunger syringes with suitable plunger diameters are used as chambers, then the frame has recesses to accommodate the syringe plunger.
650 If the individual chambers are formed by straight tubular bodies, the recesses in the framework are adjusted accordingly.
652 If necessary, conically preformed chamber floors are provided on the floor of the framework, as illustrated in FIG.

[0062]
657 5 shows a single chamber in a schematic sectional view.
658 Two or more such individual chambers (e.g.
659 B. according to the above design three individual chambers) are provided on a frame (not shown).
661 The single chamber 90 comprises a chamber wall 91 in the shape of a right circular cylinder and a tapered portion 92 which rests in a correspondingly shaped support base 93 which is part of the framework.
664 Inside the single chamber 90 is the plunger (see above).
665 In this configuration, the pressure ram is not cylindrical, but is designed as a ram plate 94 with a sealing ring 97 running around it on the outside.
667 The stamp plate 94 consists of PMMA, for example. The sealing ring 97 is a z.

668 B. made of PTFE molded part that is pulled positively over the outer edge of the stamp plate 94.

670 The cross section of the sealing ring 97 has a U-shape, the open ends of which form two sealing lips.

672 This shape ensures that the sealing lips lie tightly against the chamber wall.

673 The upper side of the individual chamber 90 is closed with a cover plate 95, which has a passage opening 96 for the passage of the pressure medium.

[0063]

678 The individual chamber 90 has, for example, a volume of 470 ml with a diameter of approx. 80 mm, a length of the chamber wall 91 of approx. 110 mm and a height of the support base 93 of approx. 30 mm.

681 The partial area 92 delimits a partial volume of approximately 30 ml.

[0064]

685 In a method according to the invention for blood preparation, the following single-chamber centrifugation can be provided in deviation from the centrifugation of the entire preparation device explained above.

688 The individual chamber of interest (e.g.

689 B. according to FIG. 5) removed from the frame and centrifuged separately.

690 Before or after centrifugation, the individual chamber is arranged in the frame for carrying out the remaining steps of sample preparation.

692 This method is particularly advantageous if no suitable centrifuge is available for centrifugation.

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CLAIMS DE10134913C2

1.

13 Preparation device (100) for the treatment of suspension samples, in particular for the preparation of cryopreserved blood, with an arrangement of at least two containers for receiving the suspension samples, sample parts and/or additives, characterized in that the containers as chambers (13 to 15, 90) are formed with solid walls and are arranged stationary relative to each other and a transmission device (20) is provided with at least one connecting line (22) via which the chambers (13 to 15) can be connected to one another.

2.

22 Preparation device according to Claim 1, characterized in that the chambers (13 to 15) are formed in a one-piece chamber body (10).

3.

27 Preparation device according to Claim 1, characterized in that the chambers (90) are detachably fastened as individual chambers in a framework.

4.

32 Preparation device according to one of the preceding claims, characterized in that the walls of the chambers or the chamber bodies (10) consist of a transparent material.

5.

37 Preparation device according to one of the preceding claims 1 or 2, characterized in that the

chambers (13 to 15) have the shape of straight hollow cylinders which run from an upper side (11) to an underside (12) of the chamber body (10), with the underside (12) of each chamber (13 to 15) has a connecting piece (17) to which one end of the at least one connecting line (22) can be connected.

6.

45 Preparation device according to one of the preceding claims, characterized in that a pressure plunger (31 to 33) is provided in each chamber.

7.

50 Preparation device according to Claim 6, characterized in that each pressure plunger (31 to 33) has a circumferential sealing lip.

8.

55 Preparation device according to one of the preceding claims, characterized in that the transmission device (20) is formed by a valve plate (21) in which at least one connecting line (22) is integrated, the valve plate (21) being rotatably arranged.

9.

61 Preparation station for the preparation of suspension samples, having: at least one preparation device (100) according to one of the preceding claims, a pressure device (50) which is set up to generate an overpressure or underpressure in one of the chambers (13 to 15), a detector device (60) for detecting a phase boundary in one of the chambers (13 to 15), an actuating device (70) which has an actuating element (71) with which the transmission device (20) can be adjusted in such a way that two chambers each via the at least one connecting line (22) and a control device which is connected to the printing device (50), the detector device (60) and the actuating device (70) and for actuating the printing device (50) and the actuating device (70) as a function of a detector signal from the detector device (60) is established.

10.

73 Preparation station according to Claim 9, characterized in that the pressure device (50) has a pneumatic pressure generator or a mechanical pressure generator with connecting rods.

11.

78 Method for preparing suspension samples or cryopreserved blood using a preparation device (100) according to one of Claims 1 to 8, characterized in that a treatment of a sample in at least

one of the chambers (13 to 15, 90) and a transfer at least part of the sample between two chambers.

12.

Method according to Claim 11, characterized in that the sample treatment comprises centrifugation of the sample and/or treatment of the sample with additives.

13.

Method according to Claim 12, characterized in that the entire preparation device (100) or an individual chamber (90) is centrifuged during the centrifugation of the sample.

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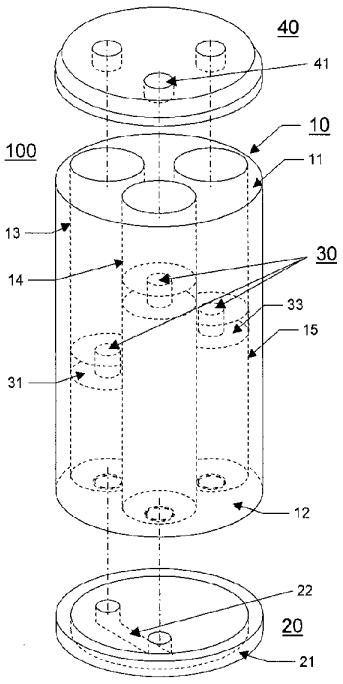
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DE 298 05 538 U1
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(54) Vorrichtung und Verfahren zur Blutpräparation

(57) Präparationsvorrichtung (100) zur Behandlung von Suspensionsproben, insbesondere zur Präparation von Blut-Kryokonserven, mit einer Anordnung von mindestens zwei Behältnissen zur Aufnahme der Suspensionsproben, von Probenteilen und/oder von Zusatzstoffen, dadurch gekennzeichnet, dass die Behältnisse als Kammern (13 bis 15, 90) mit festen Wänden gebildet und relativ zueinander ortsfest angeordnet sind und eine Übertragungseinrichtung (20) mit mindestens einer Verbindungsleitung (22) vorgesehen ist, über die die Kammern (13 bis 15) miteinander verbindbar sind.



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Beschreibung

[0001] Die Erfindung betrifft eine Vorrichtung zur Probenpräparation, insbesondere eine Vorrichtung zur Handhabung und Behandlung von Blutproben, wie z. B. zum Trennen von Blutproben durch Zentrifugation und zur Modifizierung von Blutproben durch Zusatzstoffe zur Vorbereitung einer Kryokonservierung der Blutproben sowie eine Präparationsstation und ein Verfahren zur Blutpräparation, insbesondere zur Vorbereitung von Blutproben für die Kryokonservierung.

[0002] Es ist bekannt, zur Kryokonservierung von Blutproben zunächst aus einer Blutspende eine Blutkonserve für den einfrierfertigen Zustand zu präparieren. Die Präparation umfasst insbesondere erstens eine Auftrennung der Blutspende in eine Erythrozytensuspension, die kryokonserviert werden soll, und Restbestandteile und zweitens den Zusatz eines Kryoadditives zur Erythrozytensuspension. Bei herkömmlichen Verfahren erfolgt die Handhabung der Blutproben unter Verwendung von flexiblen Blutbeuteln, wie es schematisch in **Fig.** 6 illustriert ist. Eine Blutspende wird in einem ersten Blutbeutel **1'** bereitgestellt und zentrifugiert. Nach dem Zentrifugieren ist die Blutspende in das Sediment und den Überstand (Plasma) getrennt. Der Überstand wird ggf. in einen Abfallbehälter **4'** abgezogen. Die Erythrozytensuspension wird in einen weiteren Blutbeutel **2'** umgefüllt, dem zur Bereitstellung der einfrierfertigen Konserve ein Kryoadditiv zugesetzt wird. Die illustrierte Verwendung von Blutbeuteln, die bspw. in DE 298 05 538 und WO 00/38762 beschrieben wird, besitzt die folgenden Nachteile.

[0003] Ein Hauptproblem betrifft die Handhabung der Blutbeutel. Da die Blutbeutel keine feste Form besitzen, muss insbesondere zur Erhaltung der Phasengrenze nach der Zentrifugation ein schonender Umgang mit den Blutbeuteln vorgesehen sein. Bei den genannten herkömmlichen Systemen sind zwar Vorrichtungen zur Halterung und zum Transport der Blutbeutel vorgesehen. Diese Vorrichtungen sind jedoch nur sehr eingeschränkt automatisierbar. Es müssen eine manuelle Beschickung der Vorrichtungen und eine laufende Überwachung des Betriebes erfolgen. Des Weiteren sind die Blutbeutel bei den herkömmlichen Vorrichtungen über flexible Schläuche miteinander verbunden. Zur Trennung von Erythrozytensuspension und Überstand muss die Phasengrenze am Blutbeutel oder am Schlauch detektiert werden. Wegen der Flexibilität der jeweiligen Behältnisse besteht das Risiko einer Fehldetektion und damit einer Fehlfunktion bei der Präparation.

[0004] Weitere Nachteile ergeben sich aus Sterilitätsproblemen beim Umgang mit den Blutbeuteln. Die Schlauchverbindungen müssen steril an die Blutbeutel angeschlossen und nach dem jeweiligen Verfahrensschritt abgetrennt und verschweißt werden. Bei jedem Präparationsschritt müssen aufwendige Vorkehrungen zur Erhaltung der Sterilität und Pyrogenfreiheit der Blutproben getroffen werden.

[0005] Die herkömmliche Blutbeutelpräparation ist auch wegen der Verwechslungsgefahr problematisch. Wenn während der Präparation ein Blutbeutel verwechselt wird oder eine Kreuzkontamination zwischen Blutbeuteln auftritt, so kann dies verheerende Folgen für den Empfänger der Blutspende haben. Zum Ausschluss der Verwechslungsgefahr müssen bei herkömmlichen Systemen aufwendige Sicherheitsmaßnahmen realisiert werden.

[0006] Ein weiterer Nachteil der in WO 00/38762 beschriebenen Technik besteht in deren spezifischen Zuschnitt auf die Stammzellenpräparation. Bei der Trennung von Stammzellen aus biologischen Flüssigkeitsproben ist lediglich ein sehr geringer Stammzellengehalt aus den Proben abzutrennen. Dies ermöglicht den Einsatz spezieller Zentrifugationstechniken und eine geringere Empfindlichkeit in Bezug auf die Verwendung von Blutbeuteln.

[0007] In der modernen Medizin und im Katastrophenschutz besteht ein Interesse an vergrößerten Blutbanken mit einem breiten Spektrum verschiedenster Bluttypen. Zur Herstellung moderner Blutbanken ist eine Automatisierung der Konservenpräparation erforderlich. Wegen des Automatisierungsbedarfes ist die Anwendbarkeit herkömmlicher Präparationsvorrichtungen eingeschränkt.

[0008] Die illustrierten Probleme bei der Handhabung von Blutproben bestehen nicht nur bei der Vorbereitung von Konserven für die Kryokonservierung. Ein entsprechender Bedarf nach steriler, automatisierter und sicherer Probenhandhabung besteht auch bei der Bearbeitung von biologischen Zellsuspensionen für therapeutische Zwecke.

[0009] Die Aufgabe der Erfindung ist es, eine verbesserte Vorrichtung zur Präparation suspendierter biologischer Proben bereitzustellen, mit der die Nachteile herkömmlicher Systeme überwunden werden und die insbesondere für eine automatisierbare und sichere Handhabung einer Vielzahl von Proben geeignet ist. Ferner soll ein verbessertes System zur Präparation von Kryokonserven, wie z. B. Blut-Kryokonserven geschaffen werden sowie ein neuartiges Verfahren zur Handhabung biologischer suspendierter Proben, das insbesondere automatisierbar und sicher durchführbar ist.

[0010] Diese Aufgaben werden mit einer Präparationsvorrichtung, eine Präparationsstation und einem Verfahren mit den Merkmalen gemäß den Patentansprüchen 1, 9 und 11 gelöst. Vorteilhafte Ausführungsformen und Anwendungen der Erfindung ergeben sich aus den abhängigen Ansprüchen.

[0011] Die Grundidee der Erfindung ist es, eine Präparationsvorrichtung bereitzustellen, die mindestens zwei Behältnisse zur Aufnahme der zu behandelnden Suspensionsproben aufweist, wobei die Behältnisse im Unterschied zu herkömmlichen Systemen durch relativ zueinander ortsfest positionierte Kammern mit festen Wänden gebildet werden. Die Kammern sind über einzeln betätigbare Leitungsverbindungen miteinander verbunden oder mit Anschlussstücken zur optionalen Ausbildung von Leitungsverbindungen zwischen den Kammern ausgestattet. Die erfindungsgemäße Präparationsvorrichtung ist gemäß einer ersten Ausführungsform durch einen integralen Aufbau gebildet, bei dem die Kammern in einem Kammerkörper geformt sind, an dessen einem Ende die Leitungsverbindungen ansetzbar oder einstellbar sind. Gemäß einer zweiten Ausführungsform umfasst die Präparationsvorrichtung ein Rahmengestell, in das die Kammern einzeln einsetzbar sind. Die Anschlussstücke der einzelnen Kammern sind sämtlich auf einer (z. B. unteren) Seite des Rahmengestells angeordnet. Je nach Bedarf werden die zunächst mit einem Septum verschlossenen Anschlussstücke geöffnet und über Leitungsverbindungen paarweise in Verbindung gebracht. Die Gestaltung mit einzelnen Kammern ist gemäß einer dritten Ausführungsform derart ausgebildet, dass das Rahmengestell mit einer Ventilplatte mit Leitungsverbindungen ausgestattet ist, über die die einzelnen Kammern paarweise verbunden werden können. Die Ausbildung der Präparationsvorrichtung als integraler Aufbau oder als Gestellaufbau mit mindestens zwei Kammern besitzt die Vorteile, dass die Präparationsvorrichtung im Rahmen eines automatisierten Verfahrensablaufes einen sicher greif- und manipulierbaren Gegenstand darstellt und dass die Probenhandhabung, insbesondere die unabhängige Vorbefüllung der Kammern, die Behandlung von Proben in den Kammern und die Überführung der Proben zwischen den Kammern, vereinfacht wird. Bei Anwendung der erfindungsgemäßen Präparationsvorrichtung zur Herstellung von Blutproben für die Kryokonservierung sind

vorzugsweise mindestens drei Kammern vorgesehen.

[0012] Gemäß der genannten ersten Ausführungsform der Erfindung sind die Kammern vorzugsweise in Form von geraden Kreiszylindern in einem Kunststoffkörper gebildet, an dessen einem Ende eine Ventilplatte angebracht ist, die mindestens eine Leitungsverbindung zur Kopplung von jeweils zwei Kammern enthält. Der Aufbau mit einem integralen Kunststoffkörper besitzt den Vorteil, dass die Präparationsvorrichtung als Einwegprodukt herstellbar ist, so dass Sterilitäts- und Verwechslungsprobleme ausgeschlossen werden können. Als weiterer Vorteil ergibt sich eine hohe Stabilität der Präparationsvorrichtung insbesondere bei Zentrifugationsvorgängen.

[0013] Die genannten zweiten und dritten Ausführungsformen der Erfindung stellen jeweils einen modularen Aufbau dar. Die Kammern können als Einwegprodukte verwendet werden. Als zusätzlicher Vorteil ergibt sich beim Rahmenaufbau ein relativ geringes Gewicht.

[0014] Die Übertragung von Proben zwischen den Kammern erfolgt vorzugsweise durch einen hydrostatischen Druck, der als Gasdruck oder vorzugsweise mit Druckstempeln ausgeübt wird, die jeweils in den Kammern angeordnet sind. Alternativ ist es möglich, den Druck mit einem mechanisch betätigbaren Kolben zu übertragen (z. B. mit einem Pleuelgestänge). Die Kammern der erfindungsgemäßen Präparationsvorrichtung bilden bei dieser Gestaltung Kolben-Druckerzeuger, die sowohl zur Aufnahme der jeweiligen Proben als auch zur Übertragung der Proben in benachbarte Kammern eingerichtet sind.

[0015] Gemäß einer weiteren bevorzugten Gestaltung besteht die Präparationsvorrichtung, insbesondere die Kammern als Hauptkomponenten, zumindest teilweise aus einem transparenten Kunststoffmaterial. Bei Verwendung von nicht-transparentem Material besitzen die Kammern vorzugsweise mindestens ein transparentes Fenster zur optischen Detektion. Es wird eine zuverlässige und reproduzierbare optische Detektion von Probeneigenschaften, insbesondere der Lage der Phasengrenze nach einer Zentrifugation, ermöglicht.

[0016] Gegenstand der Erfindung ist auch eine Präparationsstation, die mit der erfindungsgemäßen Präparationsvorrichtung ausgestattet ist und des Weiteren eine Druckeinrichtung zur Probenübertragung zwischen den Kammern, eine Detektoreinrichtung zur Messung von Probeneigenschaften in den Kammern und eine Stelleinrichtung zur selektiven Kopplung von Kammern aufweist.

[0017] Gegenstand der Erfindung ist auch ein Verfahren zur Präparation von Suspensionen, die biologisch relevante Komponenten, wie z. B. Zellen, Zellbestandteile oder Makromoleküle, enthalten, unter Verwendung der erfindungsgemäßen Präparationsvorrichtung. Das Verfahren zeichnet sich insbesondere dadurch aus, dass alle Präparationsschritte mit der gesamten Präparationsvorrichtung durchgeführt werden, die verschiedene Kammern zur Aufnahme von Proben in verschiedenen Präparationsstadien enthält.

[0018] Die Erfindung besitzt die folgenden Vorteile für die Probenpräparation, insbesondere für die Herstellung von Blut-Kryokonserven. Der Präparationsprozess ist zur Erhöhung der Produktivität bei der Konservenherstellung, d. h. zur Erzielung eines möglichst hohen Konservendurchsatzes, automatisierbar, wobei gleichzeitig die Herstellungsqualität gesteigert und unabhängig von der Handfertigkeit eines Bedieners aufrechterhalten wird. Eine erfindungsgemäß hergestellte Blutkonserve erfährt bereits durch die Verwendung der Präparationsvorrichtung eine Qualitätssteigerung, ohne dass die Präparation wesentlich verteuert wird.

[0019] Die erfindungsgemäße Präparationsvorrichtung ist während der Präparationsprozedur nach außen hin absolut abgeschlossen. Sie tritt lediglich einmalig jeweils beim Befüllen und beim Entleeren in Kontakt mit der Umgebung. Beispielsweise erfolgt die Vorbehandlung einer Konserve bis zum Erlangen des einfrierfertigen Zustandes absolut steril. Vorteilhafterweise wird das Öffnen, Verbinden und Verschließen von Beuteln und Verbindungsschläuchen entsprechend den herkömmlichen Systemen vermieden. Die Suspensionsprobe verlässt während der Präparationsschritte nicht die Präparationsvorrichtung. Eine Verwechslung z. B. von Blut verschiedener Spender oder eine Kontamination durch Fremdblut oder Mikroorganismen sind ausgeschlossen. Die Identität des Spenderblutes ist garantiert. Der Präparationsvorgang wird stark beschleunigt, da Arbeitsschritte, die bei herkömmlichen Systemen ggf. mehrfach notwendig sind, erfindungsgemäß vollständig entfallen können. Ein teilweiser oder vollständiger Probenverlust oder eine Kontamination der Arbeitsumgebung einschließlich des Laborpersonals durch undichte Schlauchverbindungen werden bei der erfindungsgemäßen Präparationsvorrichtung ausgeschlossen.

[0020] Die erfindungsgemäße Präparationsvorrichtung bildet ein festes Behältnis, das im Vergleich mit herkömmlich verwendeten Blutbeuteln ein definiertes und reproduzierbares Greifen und Handhaben der Vorrichtung und der an dieser angebrachten Ventile und/oder Stutzen ermöglicht. Das Greifen oder Positionieren und Klemmen von Verbindungsschläuchen entfällt, wenn die mindestens eine Verbindungsleitung in die Präparationsvorrichtung integriert ist und somit ein reproduzierbares und mehrfaches Verbinden der einzelnen Kammern auf kürzestem Weg ermöglicht. Durch die kurzen Wege und die Wahl eines geeigneten Querschnittes der jeweiligen Verbindungsleitung lässt sich die Transferzeit zur Übertragung von Proben zwischen den Kammern optimieren. Der Aufbau der Vorrichtung ermöglicht ein definiertes Positionieren der mindestens einen Verbindungsleitung. Ein versehentliches Verbinden von aktuell nicht kooperierenden Kammern wird ausgeschlossen. Ein Deformieren oder Quetschen der Kammern wird erfindungsgemäß vermieden. Eine z. B. durch Zentrifugation eingestellte Phasentrennung von Probenbestandteilen kann durch einen Greifvorgang nicht verwischt werden.

[0021] Die feste und vorzugsweise symmetrische Anordnung der Kammern in einer erfindungsgemäßen Präparationsvorrichtung ermöglicht ein schnelles und definiertes Positionieren der jeweils interessierenden Kammer in einem Präparationssystem unabhängig vom Verfahrensschritt. Alle Sensoren und Aktoren sind automatisch korrekt positioniert. Es wird ein erhöhter, fehlerfreier Durchsatz erzielt. Beispielsweise lassen sich mit einer erfindungsgemäß Präparationsvorrichtung rund dreifach mehr Kryokonserven pro Zeiteinheit präparieren. Die Präparationsvorrichtung ermöglicht eine freie Materialwahl und Dimensionierung der Außenform der Kammeranordnung. Vorteilhafterweise kann die Vorrichtung ohne Weiteres mit herkömmlichen Zentrifugiereinrichtungen verwendet werden.

[0022] Durch die Herstellung der Präparationsvorrichtung aus kostengünstigen Kunststoffmaterialien können große Stückzahlen der Vorrichtung in Spritzgieß- oder Extrusionstechniken hergestellt werden. Dies ist für die erfindungsgemäße Verwendung der fest bewandeten Kammern als Einwegprodukte von Vorteil.

[0023] Insbesondere bei der Präparation von Blutproben ergeben sich zusätzlich die folgenden Vorteile. Für Blutspendedienste entsteht bei Einsatz der erfindungsgemäßen Präparationsvorrichtung kein wesentlicher Zusatzaufwand. Es werden keine Mehrfachbeutelsysteme erforderlich. Die Präparationsvorrichtung kann direkt mit einem einfachen Spendebeutel (Einfachblutbeutel) gekoppelt werden. Der

bei herkömmlichen Verfahren ggf. in den Abfall gelangende oder nur mit großem Aufwand gewinnbare Überstand (Plasma und "Buffy Coat") steht erfindungsgemäß bei Bedarf als zusätzliches Endprodukt zur Verfügung. Die Präparationsvorrichtung liefert auch Vorteile bei der nach der Präparation vorgesehenen Befüllung von Einfrierbeuteln. Ein befüllter Einfrierbeutel kann im angedockten Zustand an der Präparationsvorrichtung mit dieser einfach und steril entlüftet werden, in dem die jeweilige Kammer mit einem Unterdruck beaufschlagt wird.

[0024] Weitere Vorteile und Einzelheiten der Erfindung ergeben sich aus der folgenden Beschreibung der beigefügten Zeichnungen. Es zeigen:

[0025] **Fig.** 1 eine schematische Phantomansicht einer Ausführungsform einer erfindungsgemäßen Präparationsvorrichtung in teilweise auseinander gezogenem Zustand,

[0026] **Fig.** 2 eine Illustration der Einbindung der Präparationsvorrichtung gemäß **Fig.** 1 in eine Vorrichtung zur Herstellung von Blutkonserven,

[0027] **Fig.** 3 eine vergrößerte Teilansicht eines Kammerendes der Präparationsvorrichtung gemäß **Fig.** 1,

[0028] **Fig.** 4 Illustration einer abgewandelten Ausführungsform einer erfindungsgemäßen Präparationsvorrichtung,

[0029] **Fig.** 5 eine schematische Schnittansicht einer erfindungsgemäß verwendeten Einzelkammer, und

[0030] **Fig.** 6 eine Illustration einer herkömmlichen Präparationstechnik (Stand der Technik).

[0031] In **Fig.** 1 ist eine Ausführungsform einer erfindungsgemäßen Präparationsvorrichtung **100** in schematischer Phantomansicht dargestellt. Die Präparationsvorrichtung **100** umfasst einen Kammerkörper **10**, in dem drei Kammern zur Aufnahme von Suspensionsproben gebildet sind, eine Übertragungseinrichtung **20**, bestehend aus einer Ventilplatte **22** und mindestens einer Verbindungsleitung **22**, eine Stempeleinrichtung **30** mit mehreren Druckstempeln **31** bis **33** und eine Deckplatte **40**, die den oberen Abschluss des Kammerkörpers **10** bildet. Der Kammerkörper **10** ist einstückig aus einem transparenten Kunststoffmaterial (z. B. PMMA, Cycloolefin-Copolymere, Polyamid, Polycarbonat, PCHP, Polyester oder Polysulfone) geformt. Er besitzt die äußere Form eines geraden Kreiszylinders mit einer ebenen Oberseite **11** und einer ebenen Unterseite **12**. Im Inneren des Kammerkörpers **10** sind die drei zylinderförmigen Kammern **13**, **14** und **15** zur Probenaufnahme gebildet. Am oberen Ende des Kammerkörpers **10** münden die Kammern frei in die Oberseite **11**. Am unteren Ende besitzt jede Kammer eine Verjüngung **16** mit einem Anschlussstutzen **17**, wie es vergrößert in **Fig.** 3 illustriert ist. Der Anschlussstutzen **17** mündet jeweils in die Unterseite **12** des Kammerköpers **10**.

[0032] Zur Anwendung bei der Präparation von Blutproben besitzt die Präparationsvorrichtung **100** bspw. einen Durchmesser von ca. 18 bis 20 cm, wobei die Höhe des Kammerkörpers **10** ca. 10 bis 12 cm beträgt und die Kammern **13** bis **15** jeweils einen Innendurchmesser von ca. 6 bis 8 cm besitzen. Eine Kammer besitzt vorzugsweise ein Volumen im Bereich von 400 ml bis 600 ml. Die Kammern **13** bis **15** sind vorzugsweise relativ zur Achse des Kammerkörpers **10** symmetrisch verteilt angeordnet.

[0033] Die Übertragungseinrichtung **20** ist zur Übertragung von Proben zwischen den Kammern **13** bis **15** eingerichtet. Die Ventilplatte **21** ist drehbar an der Unterseite **12** des Kammerkörpers **10** befestigt. In die ebenfalls aus Kunststoffmaterial hergestellte Ventilplatte **21** ist die Verbindungsleitung **22** integriert, die einen Überströmkanal bildet. An den Mündungen der Verbindungsleitungen **22** auf der inneren Seite der Verbindungsplatte **21**, die an die Unterseite **12** des Kammerkörpers **10** angrenzt, oder an den Anschlussstutzen **17** der einzelnen Kammern (siehe **Fig.** 3) sind Dichtungsringe aus einem elastischen Material (z. B. PTFE) angebracht. Neben der Dichtfunktion können die Dichtungsringe (nicht dargestellt) auch als Rasteinrichtungen dienen. Bei Drehung der Verbindungsplatte **21** rasten die Dichtungsringe an den gewünschten Positionen der Anschlussstutzen oder der Mündung der Verbindungsleitung **22** ein, wenn diese gerade zueinander ausgerichtet sind.

[0034] Die Ventilplatte **21** besitzt eine Ventilfunktion, da in der Regel Flüssigkeit immer nur in einer Richtung von einer Kammer zur benachbarten Kammer gepumpt wird. Zum Ausschluss einer Fehlbedienung kann an der Ventilplatte **21** oder am Kammerkörper **10** eine Vorrichtung zur erzwungenen Vorgabe einer bestimmten Drehrichtung und/oder eine Wiederholsperre vorgesehen sein. Diese Vorrichtung umfasst bspw. eine Verzahnung, die eine Rückwärtsdrehung ausschließt, und/oder eine zusätzliche Arretierhilfe.

[0035] Der Aufbau der Ventilplatte **21** kann anwendungsabhängig abgewandelt werden (siehe **Fig.** 4). Es können mehrere Verbindungsleitungen vorgesehen sein. Die mindestens eine Verbindungsleitung kann mit einer Sperr- oder Ventileinrichtung ausgestattet sein. In der Ventilplatte können vorzugsweise zusätzliche Durchgangsöffnungen zur Beschickung der Kammern vorgesehen sein. Die Beschickung kann aber auch von der oberen Seite her erfolgen.

[0036] Zum Probentransport zwischen den Kammern werden die Proben mit einem Druck beaufschlagt. Unter der Wirkung eines Überdruckes in der Kammer, von der die Übertragung ausgeht, wird die Probe über den Überströmkanal in der Ventilplatte **21** übertragen. Der Übertragungsdruck wird mit einer Druckeinrichtung aufgebracht, die Teil der Präparationsstation (siehe **Fig.** 2) ist, in der die erfindungsgemäße Präparationsvorrichtung vorzugsweise verwendet wird. Gemäß einer vorteilhaften Ausführungsform der Erfindung wird der Druck mit einer Stempeleinrichtung **30** übertragen, die in den Kammern **13** bis **15** jeweils einen Druckstempel **31** bis **33** aufweist. Die Druckstempel **31** bis **33** bestehen aus Kunststoffkörpern z. B. in Zylinderform, die formschlüssig in die jeweilige Kammer eingepasst sind. Jeder Druckstempel weist mindestens eine umlaufende Dichtlippe auf, die ggf. auftretende Spalte zwischen den Druckstempeln und den Kammerinnenwänden abdichtet. Die Dichtlippen verhindern ein Durchlauf des Kolbens durch die flüssigen Proben bei Druckbeaufschlagung. Die Kolben mit den Dichtlippen bestehen aus einem Kunststoffmaterial (z. B. PTFE). Der Einsatz der Druckstempel **31** bis **33** in den Kammern besitzt den Vorteil, dass bei einer Bewegung der Präparationsvorrichtung **100** eine Probenbewegung in den Kammern verhindert wird, wenn die Druckstempel jeweils auf den Flüssigkeiten aufgesetzt sind. Nach einer Zentrifugation wird vorteilhafterweise eine Aufhebung der Phasengrenze zwischen den Fraktionen vermieden.

[0037] Die Druckstempel **31** bis **33** können gemäß einer bevorzugten Ausführungsform jeweils eine zentralen Bohrung (gestrichelt eingezeichnet) mit einem Verschluss (z. B. einem Septum) aufweisen. Dies ermöglicht einen Zugriff zu den Proben oder Zusatzflüssigkeiten in den Kammern von der Oberseite der Vorrichtung **100** her.

[0038] Gemäß einer abgewandelten Ausführungsform der Erfindung kann auf die Verwendung der Druckstempel auch verzichtet werden. In diesem Fall wird der Übertragungsdruck direkt auf die Flüssigkeitsoberfläche in der jeweiligen Kammer gegeben. Bei dieser Gestaltung sind die oberen Enden der Kammern an der Oberseite vorzugsweise mit einem Sterilfiltereinsatz ausgestattet, der nur für das jeweilig verwendete sterile Druckmedium (z. B. Luft, inertes Gas) durchlässig ist. Der Aufbau ohne Druckstempel besitzt die

Vorteile eines vergrößerten Innenvolumens und vereinfachten Aufbaus der Kammern und damit einer Kostenersparnis.

[0039] Die obere Deckplatte **40** dient dem Abschluss der Präparationsvorrichtung **100**. Sie ist fest auf dem Kammerkörper **10** angebracht und besitzt Durchtrittöffnungen oder Anschlussstutzen **41**, die jeweils mit den oberen Enden der Kammern **13** bis **15** ausgerichtet sind. Die Anschlussstutzen **41** dienen der Verbindung von einzelnen oder gleichzeitig allen Kammern mit der Druckeinrichtung und/oder Beschickungseinrichtungen.

[0040] Der Verfahrensablauf zur Herstellung einer Blut-Kryokonserve unter Verwendung einer erfindungsgemäßen Präparationsvorrichtung wird im Folgenden unter Bezug auf **Fig.** 2 erläutert. **Fig.** 2 zeigt die Präparationsvorrichtung **100** analog zur Darstellung gemäß **Fig.** 1 in Kombination mit Teilen der Präparationsstation.

[0041] Die Komponenten der Präparationsvorrichtung **100** sind mit den gleichen Bezugszeichen wie in **Fig.** 1 versehen.

[0042] Zur Präparationsstation gehören insbesondere die Druckeinrichtung **50**, eine Detektoreinrichtung **60**, eine Stelleinrichtung **70** und eine Steuereinrichtung **80**. Die Druckeinrichtung **50** umfasst vorzugsweise einen Druckerzeuger **51** mit einem Motor **52** und einem Pumpenteil **53**. Alternativ umfasst die Druckeinrichtung **50** eine Hebeleinrichtung mit einer Pleuelstange. Die mechanische Kraftübertragung besitzt den Vorteil, dass die Positionierung der Druckstempel mit einer erhöhten Präzision erfolgen kann. Gemäß alternativen Ausführungsformen der Erfindung kann der Druckerzeuger auch durch eine Druckquelle (z. B. Druckgasflasche) mit einem Regelventil gebildet werden.

[0043] Die Detektoreinrichtung **60** umfasst insbesondere mindestens ein lichtempfindliches Element **61** zur Erkennung der Phasengrenze. Das lichtempfindliche Element **61** kann anwendungsabhängig mit (nicht dargestellten) Filtereinrichtungen ausgestattet sein. Es können auch mehrere lichtempfindliche Elemente entsprechend den Positionen der Kammern angeordnet sein. Anwendungsabhängig können auch andere Detektoren zur Erfassung von Probeneigenschaften vorgesehen sein, wie sie an sich aus der Analytik bekannt sind (z. B. Spektralphotometer, Widerstandsmesser zur Dichtebestimmung). Die Kammern können auch eine sich jeweils über ihre Länge erstreckende Skalierung zur optischen Kontrolle des Füllstandes, der Position der Druckstempel oder der Position der Phasengrenze aufweisen. Die Detektoren können ferner an anderen Komponenten der Präparationsvorrichtung, z. B. an einer Verbindungsleitung in der Ventilplatte, vorgesehen sein.

[0044] Zur Verstellung der oben erläuterten Ventilplatte **21** umfasst die Stelleinrichtung **70** ein Betätigungselement **71** und einen Stellmotor **72**. Das Betätigungselement **71** besitzt die Form einer Platte mit mindestens einem Vorsprung **73**, der mit mindestens einer entsprechenden Ausnehmung (nicht dargestellt) auf der Unterseite der Ventilplatte **21** zusammenwirkt. Der Vorsprung **73** greift in die Ausnehmung ein und verdreht die Ventilplatte **21** bei Betätigung des Stellmotors **72** in die gewünschte Position, so dass jeweils eine Kammer geöffnet oder geleert werden kann, jeweils zwei Kammern über die Verbindungsleitung **22** verbunden sind oder alle drei Kammern verschlossen sind.

[0045] Die Steuereinrichtung **80** ist mit den Komponenten **50**, **60** und **70** des Präparationssystems verbunden. Je nach Betriebszustand und dem von der Detektoreinrichtung **60** gelieferten Detektorsignal werden in der folgenden Weise der Druckerzeuger **50** und die Stelleinrichtung **70** betätigt. Bei halbautomatischem oder manuellem Betrieb werden die entsprechenden Schritte zumindest teilweise durch einen Bediener durchgeführt.

[0046] In einem Startzustand sind die Kammern der erfindungsgemäßen Präparationsvorrichtung **100** wie folgt beschickt. In der ersten Kammer **13** befindet sich eine Blutspende. Die Blutspende wird aus einem Spenderbeutel in die erste Kammer **13** gefüllt, was ggf. unter Ausübung eines unterstützenden Unterdruckes erfolgt. Die zweite Kammer **14** ist mit einer Waschlösung gefüllt. In der dritten Kammer **15** befindet sich ein Kryoadditiv. Im Startzustand ist die erste Kammer **13** vollständig gefüllt, während die übrigen Kammern **14**, **15** lediglich teilweise befüllt sind. In diesen Kammern ist so viel Volumen frei, wie es zur Übernahme der Erythrozytensuspension nach der Zentrifugation (siehe unten) erforderlich ist. Die Ventilplatte **21** wird nach dem Startzustand (alle verschlossen) so eingestellt, dass bspw. die erste und zweite Kammer **13**, **14** verbunden sind. Vorteilhafterweise ist trotz der Verbindung im druckfreien Zustand über die Verbindungsleitung im Wesentlichen kein Flüssigkeitsaustausch gegeben.

[0047] In einem ersten Präparationsschritt wird der Kammerkörper mit den befüllten Kammern mit einer Zentrifugationseinrichtung zentrifugiert. Die (nicht dargestellte) Zentrifugationseinrichtung besitzt die Bauform einer an sich bekannten Großzentrifuge mit einzelnen Zentrifugenbechern, in denen eine Vielzahl von Präparationsvorrichtungen gleichzeitig zentrifugiert werden können. Während der Zentrifugation erfolgt lediglich die Auftrennung der Blutspende in die Fraktionen. Eine Verschiebung der Druckstempel **31** bis **33** erfolgt nicht. Während der Zentrifugation sind die Kammern verschlossen.

[0048] Der Zustand der Präparationsvorrichtung nach der Zentrifugation ist in **Fig.** 2 dargestellt. In der ersten Kammer **13** sind die gebildeten Fraktionen der Blutspende mit dem Erythrozytensediment **1** der sog. "Buffy Coat"-Schicht **2** und dem Plasmaüberstand **3** illustriert. Das Erythrozytensediment **1** umfasst betriebsabhängig einen Volumenanteil von ca. 45% der Kammer **13**. Der Volumenanteil hängt insbesondere von der Zentrifugationsgeschwindigkeit ab. Bei einer höheren Geschwindigkeit ergibt sich eine höhere Packungsdichte der Erythrozyten und damit ein geringerer Volumenanteil. Die "Buffy-Coat"-Schicht **2** ist ein thrombozyten- und leukozytenhaltiger Belag mit einer gräulichen Färbung, der sich nach der Zentrifugation zwischen den tiefroten Erythrozytensediment **1** und dem hellroten Plasmaüberstand **3** ausbildet.

[0049] Nach der Zentrifugation wird die Präparationsvorrichtung **100** in die Präparationsstation eingesetzt. Die Ventilplatte **21** wird in Durchlassrichtung zwischen die erste und zweite Kammer **13**, **14** gedreht. Dies erfolgt manuell, z. B. mit einem Noppenschlüssel oder mit der Stelleinrichtung **70** (siehe oben). Die erste Kammer **13** wird mit einem Überdruck beaufschlagt. Unter der hydrostatischen oder mechanischen Druckeinwirkung bewegen sich der Druckstempel **31** nach unten und der Druckstempel **32** nach oben. Die aufgetrennte Blutspende wird in die zweite Kammer **14** übertragen. Dieser Präparationsschritt wird beendet, sobald die am unteren Ende der ersten Kammer **13** angeordnete Detektoreinrichtung **60** die "Buffy Coat"-Schicht **2** erfasst. In diesem Zustand ist sichergestellt, dass in dem verjüngtem Bereich **16** (siehe **Fig.** 3) und der Verbindungsleitung noch ausschließlich Erythrozytensediment vorhanden ist. Wenn die "Buffy Coat"-Schicht **2** erfasst worden ist, wird die Druckübertragung gestoppt. Danach wird die Ventilplatte in Verschlussstellung gebracht. Dies erfolgt entweder unmittelbar bei Detektion der Schicht **2** oder zeitlich verzögert, so dass Konzentratreste aus dem verjüngten Bereich **16** noch in die Verbindungsleitung gelangen können.

[0050] Die in die zweite Kammer **14** übertragenen Erythrozyten vermengen sich mit der Waschlösung. Die Wasch-

lösung umfasst bspw. physiologische Kochsalzlösung. Es folgt eine weitere Zentrifugation, in deren Ergebnis sich die behandelten Erythrozyten als Konzentrat wiederum im unteren Teil der zweiten Kammer **14** sammeln, während die übrige Waschlösung den Überstand bildet.

[0051] In einem weiteren Präparationsschritt wird analog zu der beschriebenen Weise das gewaschene Erythrozytensediment in die dritte Kammer **15** übertragen. Hierzu wird die Ventilplatte **21** so verdreht, dass die Verbindungsleitung **22** zwischen der zweiten und dritten Kammer **14**, **15** angeordnet ist. Außerdem wird der Druckverteiler **56** entsprechend verstellt. Die Druckübertragung wird wiederum in Abhängigkeit vom Detektorsignal der Detektoreinrichtung **60** gesteuert. Es kann an der zweiten Kammer **14** ein weiterer Sensor (nicht dargestellt) vorgesehen sein. Alternativ ist es möglich, die Präparationsvorrichtung **100** zu dem Sensor **61** hin zu verdrehen, so dass die Phasengrenze in der zweiten Kammer **14** erfasst werden kann.

[0052] Nach Übertragung des gewaschenen Erythrozytensedimentes in die dritte Kammer **15** erfolgt dort die Vermengung mit dem Kryoadditiv. Als Kryoadditiv werden die an sich bekannten Zusatzstoffe verwendet. Das Kryoadditiv umfasst bspw. eine Lösung aus wasserlöslichem Stärkederivat.

[0053] Nach Übertragung der gewaschenen Erythrozyten in die dritte Kammer **15** und Vermengung mit dem Kryoadditiv ist die Kryokonserve einfrierfertig. Es folgt die Übertragung in den anwendungsabhängig gewählten Behälter, z. B. einen Kryobeutel, in dem der Einfriervorgang erfolgt. Vorteilhafterweise ist nach Abschluss der Präparation in der ersten Kammer **13** der Plasmaüberstand als spenderspezifisches Restprodukt vorhanden. Anwendungsabhängig kann das Plasma einer weiteren Verwendung zugeführt werden.

[0054] Einzelheiten einer gegenüber **Fig.** 1 abgewandelten Gestaltung der erfindungsgemäßen Präparationsvorrichtung sind in **Fig.** 4 dargestellt. Die Unterschiede beziehen sich auf die Ausbildung der Ventilplatte **21**. Im obersten Teilbild von **Fig.** 4 ist die Unterseite **12** des Kammerkörpers **10** mit den Kammern **13** bis **15** illustriert. Jede Kammer besitzt eine Ein- und Auslassöffnung in Form eines Anschlussstutzens **17** (siehe **Fig.** 3). An jedem Anschlussstutzen **17** ist ein O-Dichtring **18** vorgesehen. In der Mitte des Kammerkörpers **10** befindet sich entsprechend der Zylinderachse eine Gewindebohrung **19** zur Befestigung der Ventilplatte **21**.

[0055] Im mittleren Teilbild von **Fig.** 4 ist die Ventilplatte **21** einzeln dargestellt. Bei dieser Gestaltung sind zwei Verbindungsleitungen (oder Überströmkanäle) **22**, **23** vorgesehen, die so angeordnet sind, dass mit einer der Verbindungsleitungen **22** oder **23** jeweils zwei Kammern verbunden werden können, während die jeweils andere Verbindungsleitung **22** oder **23** verschlossen ist. Die Verwendung von zwei Verbindungsleitungen besitzt den Vorteil geringerer Verstellwege bei der Einstellung der Kammerverbindungen bei den einzelnen Präparationsschritten. In der Ventilplatte sind drei Ein- und Auslassbohrungen **24** vorgesehen, die so angeordnet sind, dass wenn eine der Ein- und Auslassbohrungen **24** mit einem der Anschlussstutzen **17** ausgerichtet ist, die anderen Anschlussstutzen jeweils verschlossen bleiben.

[0056] Die Ventilplatte **21** besitzt einen umlaufenden O-Dichtring **25**, der eine zusätzliche Dichtung gegenüber der Unterseite **12** des Kammerkörpers **10** bereitstellt. Das Bezugszeichen **26** bezieht sich auf die Drehachse und das Lager der Ventilplatte **21**.

[0057] Im unteren Teilbild von **Fig.** 4 ist die Ventilplatte **21** und die Unterseite **12** des Kammerkörpers **10** im zusammenmontierten Zustand dargestellt. Wird die Ventilplatte **21** vom dargestellten Zustand nach links gedreht, so werden zunächst mit der Verbindungsleitung **22** die Kammern **13** und **14** verbunden und bei der weiteren Verstellung werden die Kammern **14** und **15** über die Verbindungsleitung **23** verbunden. Damit können mit einem kurzen Stellweg die beiden oben erläuterten Präparationsschritte ausgeführt werden.

[0058] Die in den **Fig.** 1 bis 4 illustrierte Ausführungsform der Erfindung kann je nach Aufgabenstellung vielfältig modifiziert werden. So können bspw. zur Durchführung weiterer Präparationsschritte im Kammerkörper weitere Kammern zur Aufnahme weiterer Zusatzstoffe vorgesehen sein. Anstelle der 120°-Anordnung können die Kammern auch anderweitig im Kammerkörper oder einem Rahmengestell (siehe unten) angeordnet werden. Die Beschickung der Kammern kann anwendungsabhängig von der Ober- oder Unterseite her erfolgen. Dies erfolgt vorzugsweise unter Verwendung von Schlauch- oder Pipettiersystemen. Gemäß einer bevorzugten Gestaltung der Erfindung sind die Einlassöffnungen der Kammern gerade an die Außendurchmesser von standardisierten Flüssigkeitspipetten oder Schlauchadapter angepasst, so dass diese zur Beschickung einfach angesetzt und betätigt werden können. Die Präparationsvorrichtung kann anwendungsabhängig in ihrer Größe beliebig skaliert werden. Die Übertragungseinrichtung mit der Ventilplatte kann durch eine fest eingestellte Anordnung mehrerer Verbindungsleitungen mit betätigbaren Ventilen ersetzt werden.

[0059] An der Außenseite des Kammerkörpers können zusätzliche Greif- oder Befestigungseinrichtungen zur Handhabung des Kammerkörpers und/oder zum Einsatz in eine Zentrifuge vorgesehen sein.

[0060] Der Kammerkörper mit den integrierten Kammern kann erfindungsgemäß durch eine Anordnung einzelner Kammern in einem Rahmengestell ersetzt werden. Diese Gestaltung besitzt Vorteile in Bezug auf eine separate Befüllung der einzelnen Kammern vor der Zusammensetzung zur Präparationsvorrichtung und die Entsorgung der Kammern nach Verwendung. Als Rahmengestell kann jede geeignete Struktur verwendet werden, in die die Kammern entsprechend der gewünschten Anordnung fixiert einsetzbar sind und die eine genügende Stabilität bei der Zentrifugation besitzt. Je nach der Gestaltung der Kammern ist die Struktur des Rahmengestells angepasst.

[0061] Werden als Kammern fertige Kolbenspritzen mit geeigneten Kolbendurchmessern verwendet, so besitzt das Rahmengestell Ausnehmungen zur Aufnahme der Spritzenkolben. Wenn die Einzelkammern durch gerade Rohrkörper gebildet sind, werden die Ausnehmungen des Rahmengestells entsprechend angepasst. Am Boden des Rahmengestells sind ggf. konisch vorgeformte Kammerböden vorgesehen, wie dies in **Fig.** 5 illustriert ist.

[0062] **Fig.** 5 zeigt eine Einzelkammer in schematischer Schnittansicht. Zwei oder mehr derartige Einzelkammern (z. B. entsprechend der obigen Gestaltung drei Einzelkammern) sind an einem Rahmengestell (nicht dargestellt) vorgesehen. Die Einzelkammer **90** umfasst eine Kammerwand **91** in Form eines geraden Kreiszylinders und einen sich verjüngenden Teilbereich **92**, der in einem entsprechend geformten Stützsockel **93** ruht, der Teil des Rahmengestells ist. Im Inneren der Einzelkammer **90** befindet sich der Druckstempel (siehe oben). Der Druckstempel ist bei dieser Gestaltung nicht zylinderförmig, sondern als Stempelplatte **94** mit einem außen umlaufenden Dichtring **97** ausgebildet. Die Stempelplatte **94** besteht beispielsweise aus PMMA. Der Dichtring **97** ist ein z. B. aus PTFE bestehendes Formteil, das formschlüssig über den äußeren Rand der Stempelplatte **94** gezogen ist. Der Querschnitt des Dichtringes **97** besitzt eine U-Form, deren offenen Enden zwei Dichtlippen bilden.

Durch diese Formgebung wird ein dichtendes Anlegen der Dichtlippen an die Kammerwand sicherstellt. Die Oberseite der Einzelkammer **90** ist mit einer Deckplatte **95** verschlossen, die eine Durchtrittsöffnung **96** zum Durchlass des Druckmediums aufweist.

[0063] Die Einzelkammer **90** besitzt bspw. ein Volumen von 470 ml bei einem Durchmesser von ca. 80 mm, einer Länge der Kammerwand **91** von ca. 110 mm und einer Höhe des Stützsockels **93** von ca. 30 mm. Der Teilbereich **92** grenzt ein Teilvolumen von ca. 30 ml ab.

[0064] Bei einem erfindungsgemäßen Verfahren zur Blutpräparation kann abweichend von der oben erläuterten Zentrifugation der gesamten Präparationsvorrichtung die folgende Einzelkammerzentrifugation vorgesehen sein. Dabei wird die jeweils interessierende Einzelkammer (z. B. gemäß **Fig.** 5) aus dem Rahmengestell entnommen und separat zentrifugiert. Vor oder nach der Zentrifugation ist die Einzelkammer im Rahmengestell zur Durchführung der übrigen Schritte der Probenpräparation angeordnet. Dieses Verfahren ist besonders vorteilhaft, falls zur Zentrifugation keine passende Zentrifuge zur Verfügung steht.

Patentansprüche

1. Präparationsvorrichtung (**100**) zur Behandlung von Suspensionsproben, insbesondere zur Präparation von Blut-Kryokonserven, mit einer Anordnung von mindestens zwei Behältnissen zur Aufnahme der Suspensionsproben, von Probenteilen und/oder von Zusatzstoffen, **dadurch gekennzeichnet**, dass die Behältnisse als Kammern (**13** bis **15**, **90**) mit festen Wänden gebildet und relativ zueinander ortsfest angeordnet sind und eine Übertragungseinrichtung (**20**) mit mindestens einer Verbindungsleitung (**22**) vorgesehen ist, über die die Kammern (**13** bis **15**) miteinander verbindbar sind.

2. Präparationsvorrichtung nach Anspruch 1, dadurch gekennzeichnet, dass die Kammern (**13** bis **15**) in einem einstückigen Kammerkörper (**10**) gebildet sind.

3. Präparationsvorrichtung nach Anspruch 1, dadurch gekennzeichnet, dass die Kammern (**90**) als Einzelkammern lösbar in einem Rahmengestell befestigt sind.

4. Präparationsvorrichtung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, dass die Wände der Kammern oder der Kammerkörper (**10**) aus einem transparenten Material bestehen.

5. Präparationsvorrichtung nach einem der vorhergehenden Ansprüche 1 oder 2, dadurch gekennzeichnet, dass die Kammern (**13** bis **15**) die Gestalt gerader Hohlzylinder besitzen, die von einer Oberseite (**11**) bis zu einer Unterseite (**12**) des Kammerkörpers (**10**) verlaufen, wobei an der Unterseite (**12**) jede Kammer (**13** bis **15**) einen Anschlussstutzen (**17**) aufweist, mit dem jeweils ein Ende der mindestens einen Verbindungsleitung (**22**) verbunden werden kann.

6. Präparationsvorrichtung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, dass in jeder Kammer ein Druckstempel (**31** bis **33**) vorgesehen ist.

7. Präparationsvorrichtung nach Anspruch 6, dadurch gekennzeichnet, dass jeder Druckstempel (**31** bis **33**) eine umlaufende Dichtlippe aufweist.

8. Präparationsvorrichtung nach einem der vorhergehenden Ansprüche, dadurch gekennzeichnet, dass die Übertragungseinrichtung (**20**) durch eine Ventilplatte (**21**) gebildet ist, in der mindestens eine Verbindungsleitung (**22**) integriert ist, wobei die Ventilplatte (**21**) verdrehbar angeordnet ist.

9. Präparationsstation zur Präparation von Suspensionsproben, mit:
mindestens einer Präparationsvorrichtung (**100**) nach einem der vorhergehenden Ansprüche,
einer Druckeinrichtung (**50**), die zur Erzeugung eines Über- oder Unterdruckes in einer der Kammern (**13** bis **15**) eingerichtet ist,
einer Detektoreinrichtung (**60**) zur Erkennung einer Phasengrenze in einer der Kammern (**13** bis **15**),
einer Stelleinrichtung (**70**), die ein Betätigungselement (**71**) aufweist, mit dem die Übertragungseinrichtung (**20**) derart einstellbar ist, dass jeweils zwei Kammern über die mindestens eine Verbindungsleitung (**22**) verbunden sind, und
einer Steuereinrichtung, die mit der Druckeinrichtung (**50**), der Detektoreinrichtung (**60**) und der Stelleinrichtung (**70**) verbunden und zur Betätigung der Druckeinrichtung (**50**) und der Stelleinrichtung (**70**) in Abhängigkeit von einem Detektorsignal der Detektoreinrichtung (**60**) eingerichtet ist.

10. Präparationsstation nach Anspruch 9, dadurch gekennzeichnet, dass die Druckeinrichtung (**50**) einen pneumatischen Druckerzeuger oder einen mechanischen Druckerzeuger mit Pleuelstangen aufweist.

11. Verfahren zum Präparieren von Suspensionsproben oder von Blut-Kryokonserven unter Verwendung einer Präparationsvorrichtung (**100**) nach einem der Ansprüche 1 bis 8, dadurch gekennzeichnet, dass abwechselnd eine Behandlung einer Probe in mindestens einer der Kammern (**13** bis **15**, **90**) und eine Übertragung mindestens eines Teils der Probe zwischen zwei Kammern erfolgt.

12. Verfahren nach Anspruch 11, dadurch gekennzeichnet, dass die Probenbehandlung eine Zentrifugation der Probe und/oder eine Behandlung der Probe mit Zusatzstoffen umfasst.

13. Verfahren nach Anspruch 12, dadurch gekennzeichnet, dass bei der Zentifugation der Probe die gesamte Präparationsvorrichtung (**100**) oder eine Einzelkammer (**90**) zentrifugiert wird.

Hierzu 5 Seite(n) Zeichnungen

Nummer: **DE 101 34 913 C2**
Int. Cl.[7]: **A 61 M 1/00**
Veröffentlichungstag: 26. Juni 2003

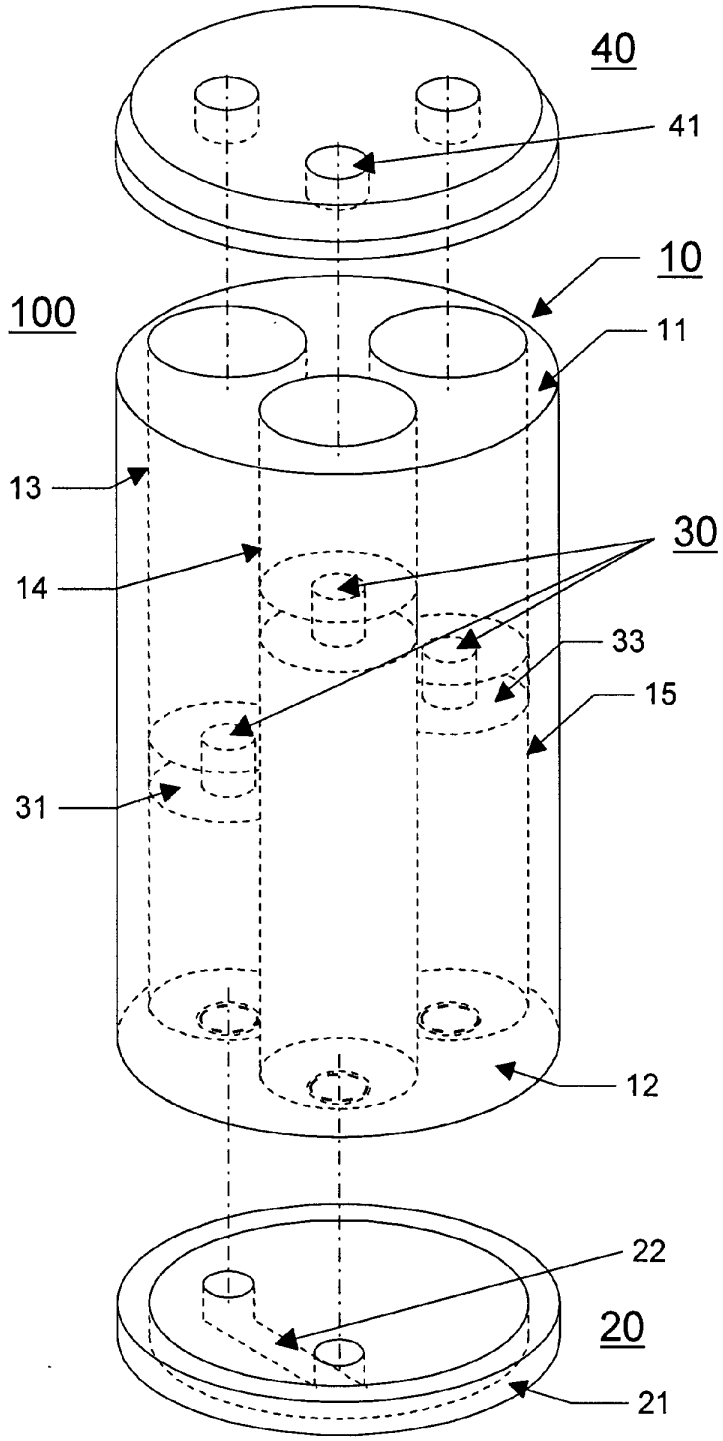


Fig. 1

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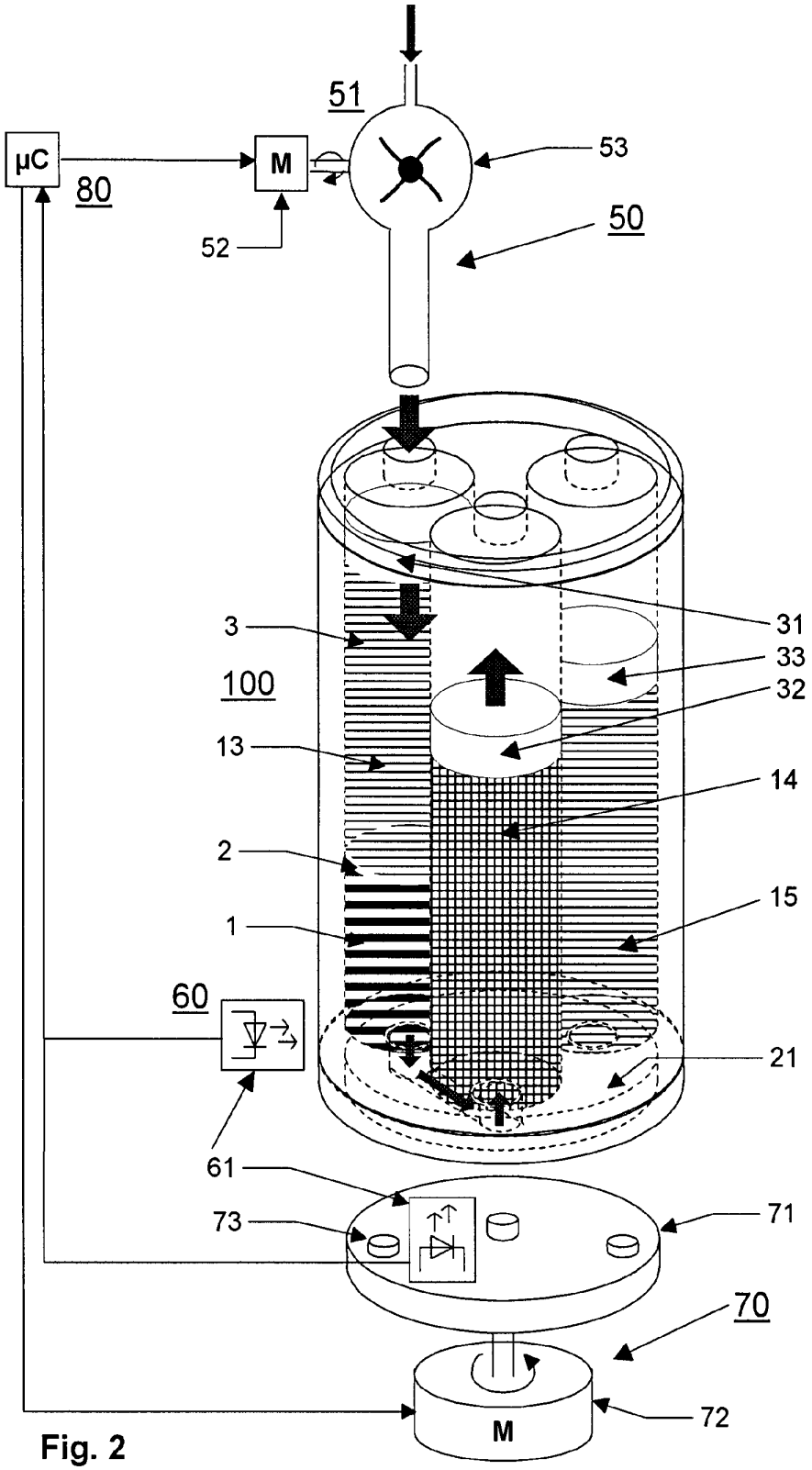


Fig. 2

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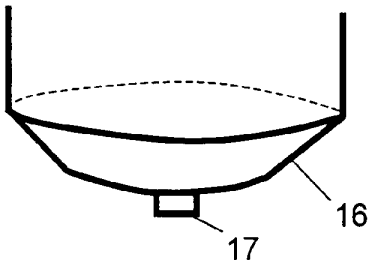


Fig. 3

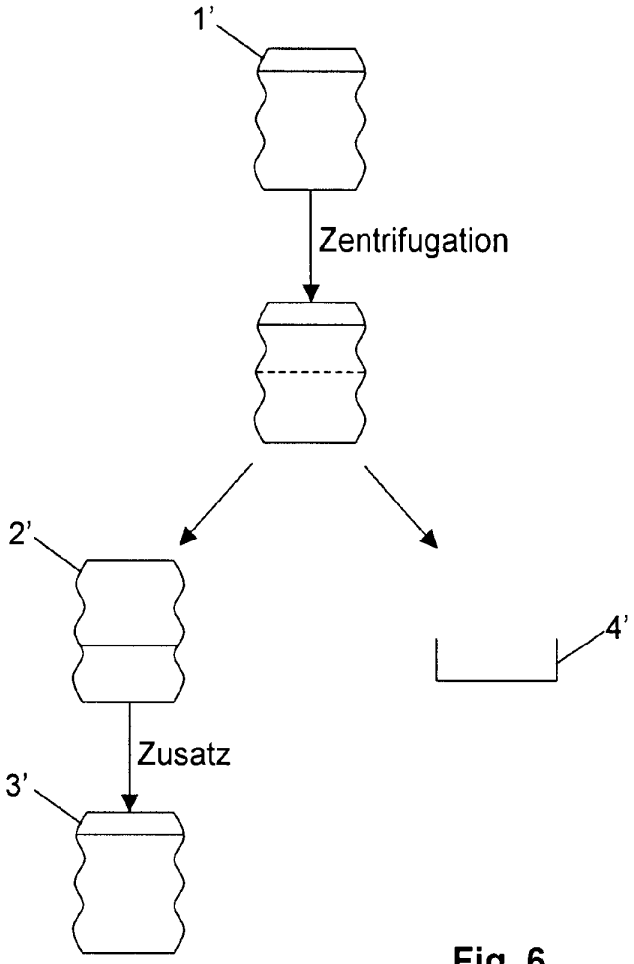
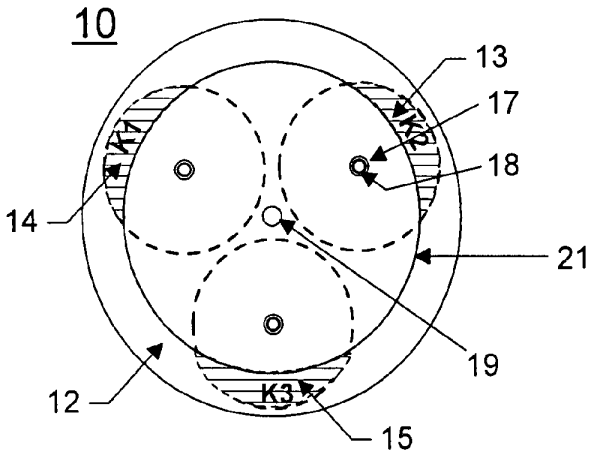
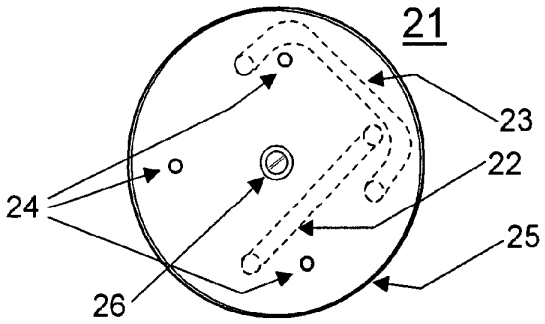


Fig. 6
(Stand der Technik)

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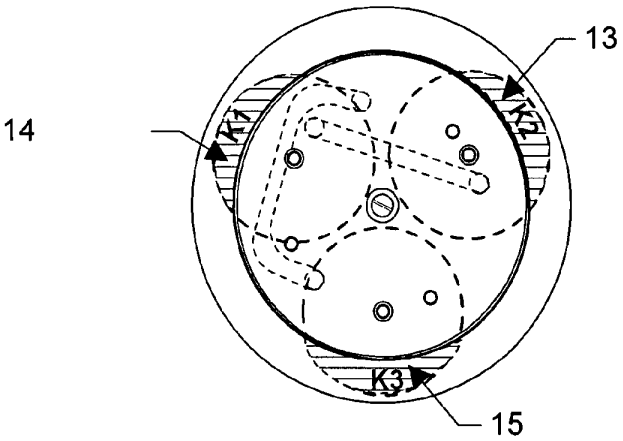


Fig. 4

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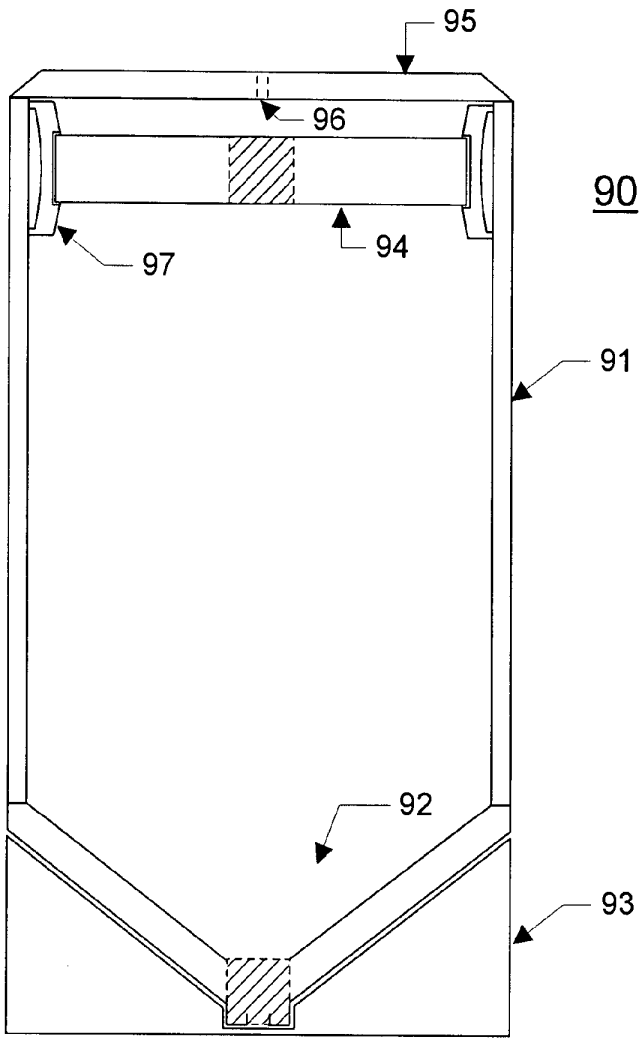


Fig. 5

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

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

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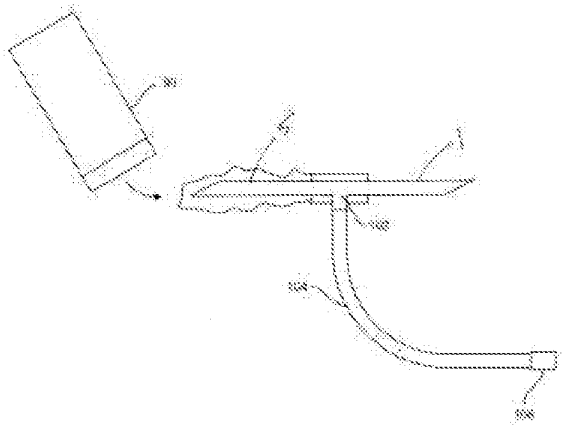
Application number: CA20162993646 20160722 Global Dossier

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

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Abstract of CA2993646 (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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(71) Demandeur/Applicant:
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(74) Agent: BRION RAFFOUL

(54) Titre : SYSTEME D'OPTIMISATION D'ECHANTILLON DE SANG ET DISPOSITIF ET PROCEDE DE SEQUESTRATION DE CONTAMINANTS DU SANG

(54) Title: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

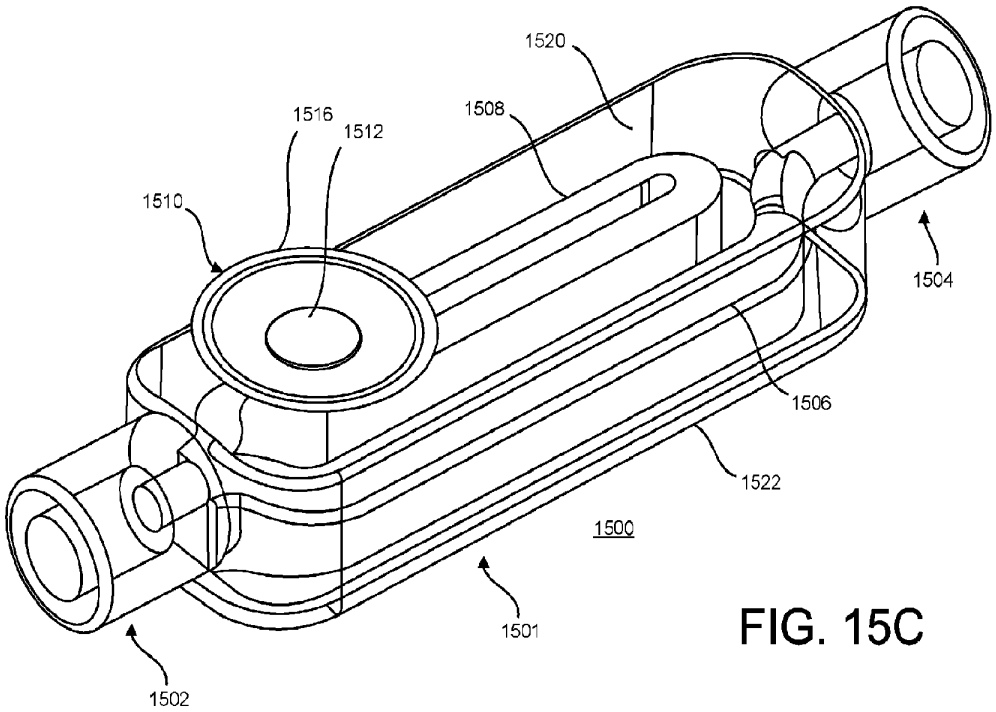


FIG. 15C

(57) Abrégé/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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(74) Agents: **CLEARY, James, P.** et al.; Mintz Levin Cohn Ferris Glovsky And Popeo, P.C., 3580 Carmel Mountain Road, Suite 300, San Diego, CA 92130-6768 (US).

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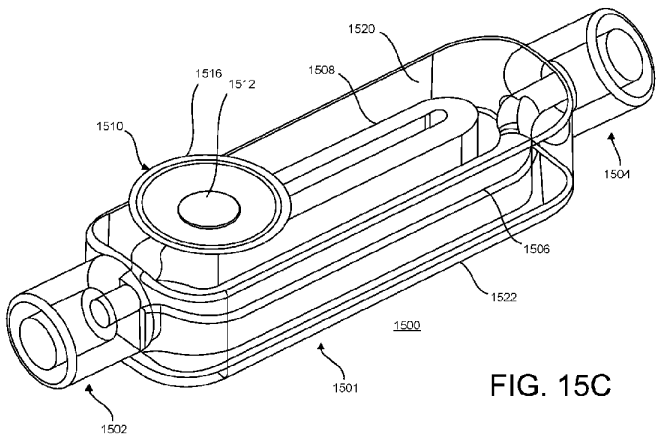


FIG. 15C

(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.

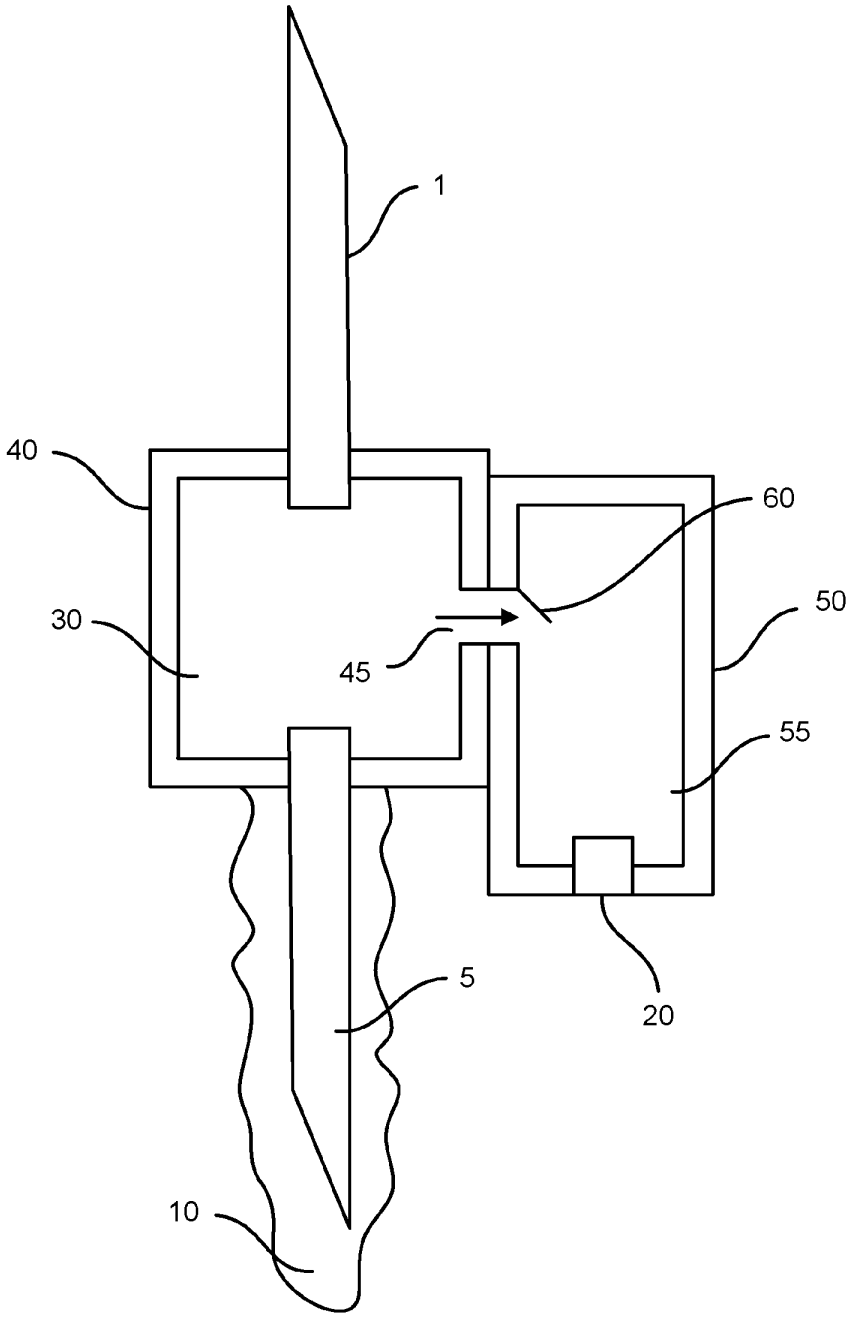


FIG. 1

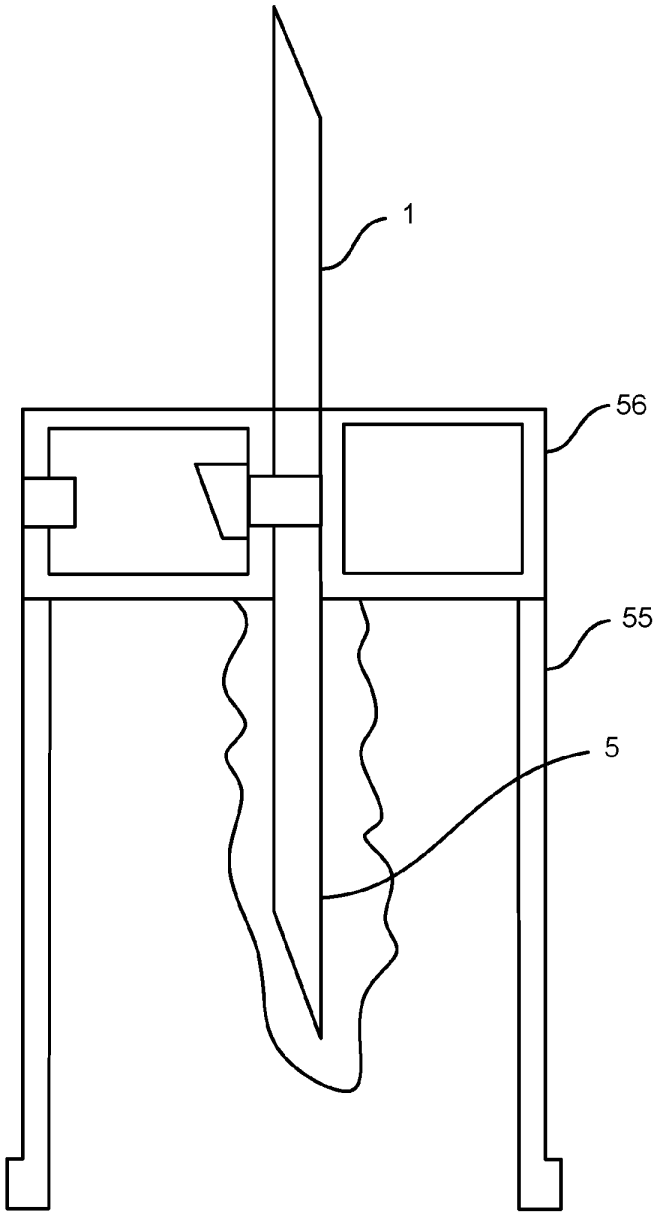


FIG. 2

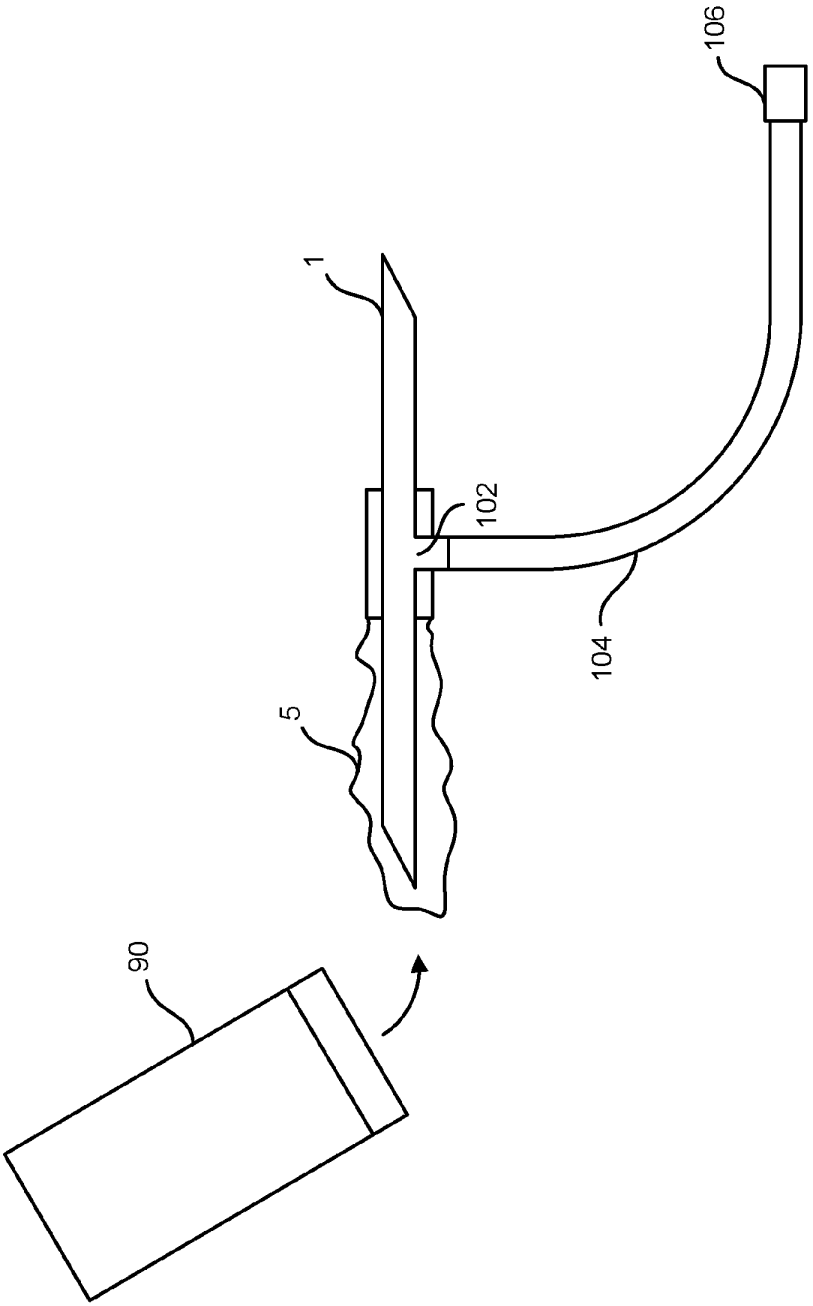


FIG. 3

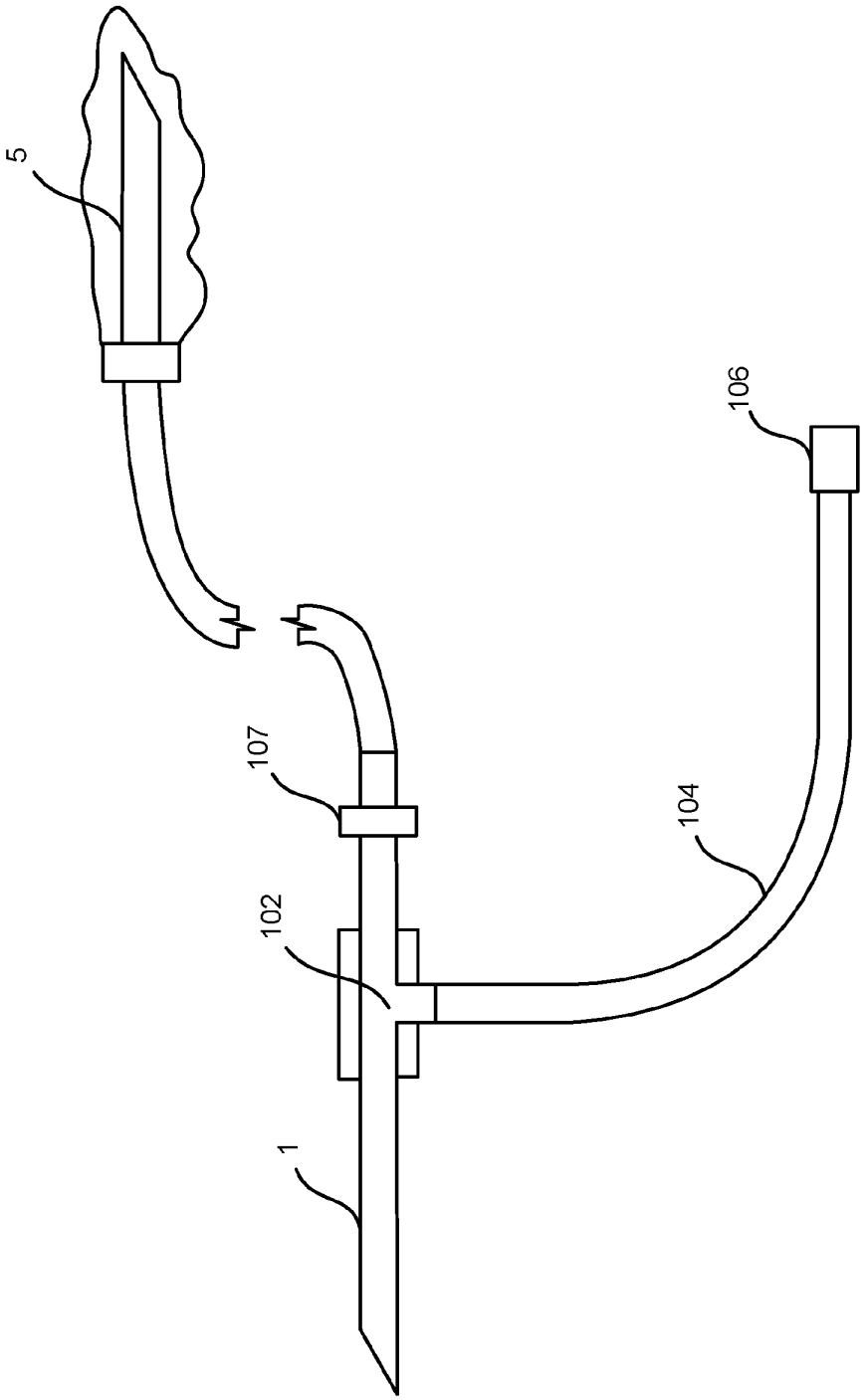


FIG. 4

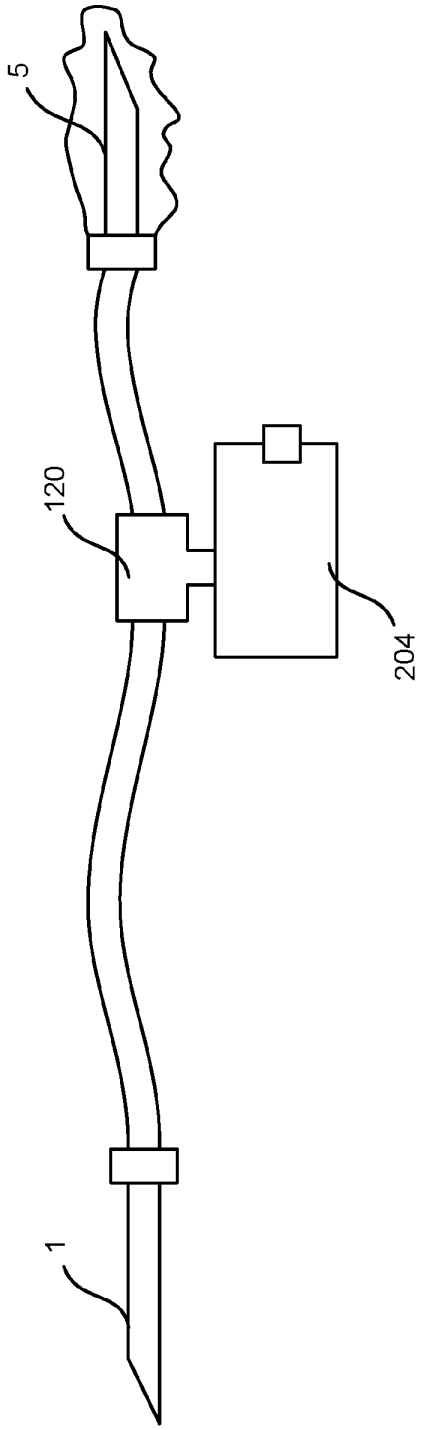


FIG. 5

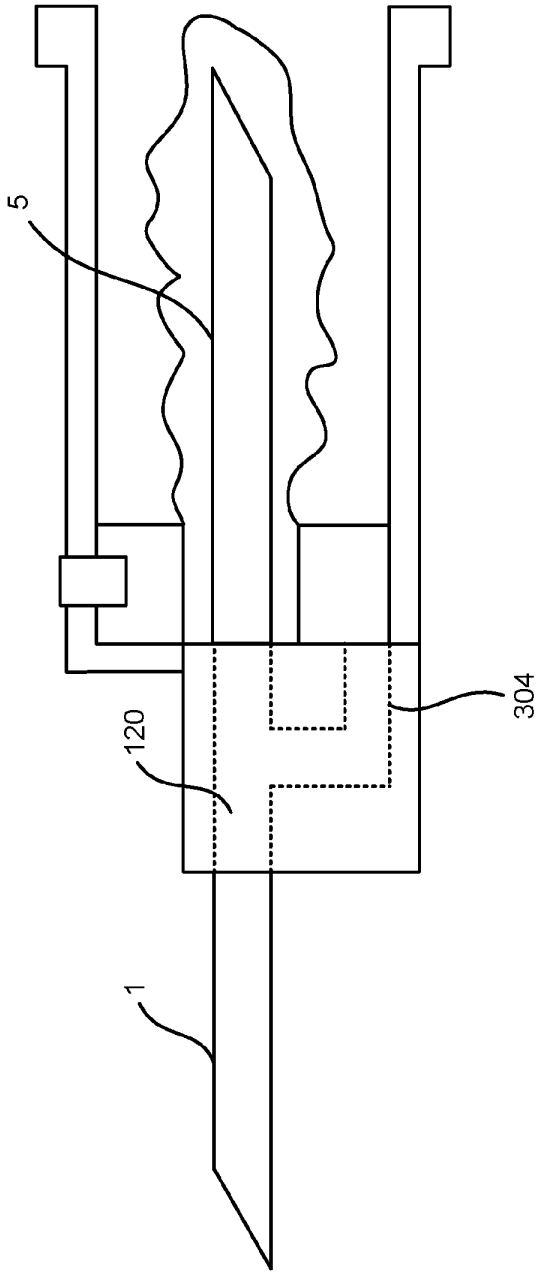


FIG. 6

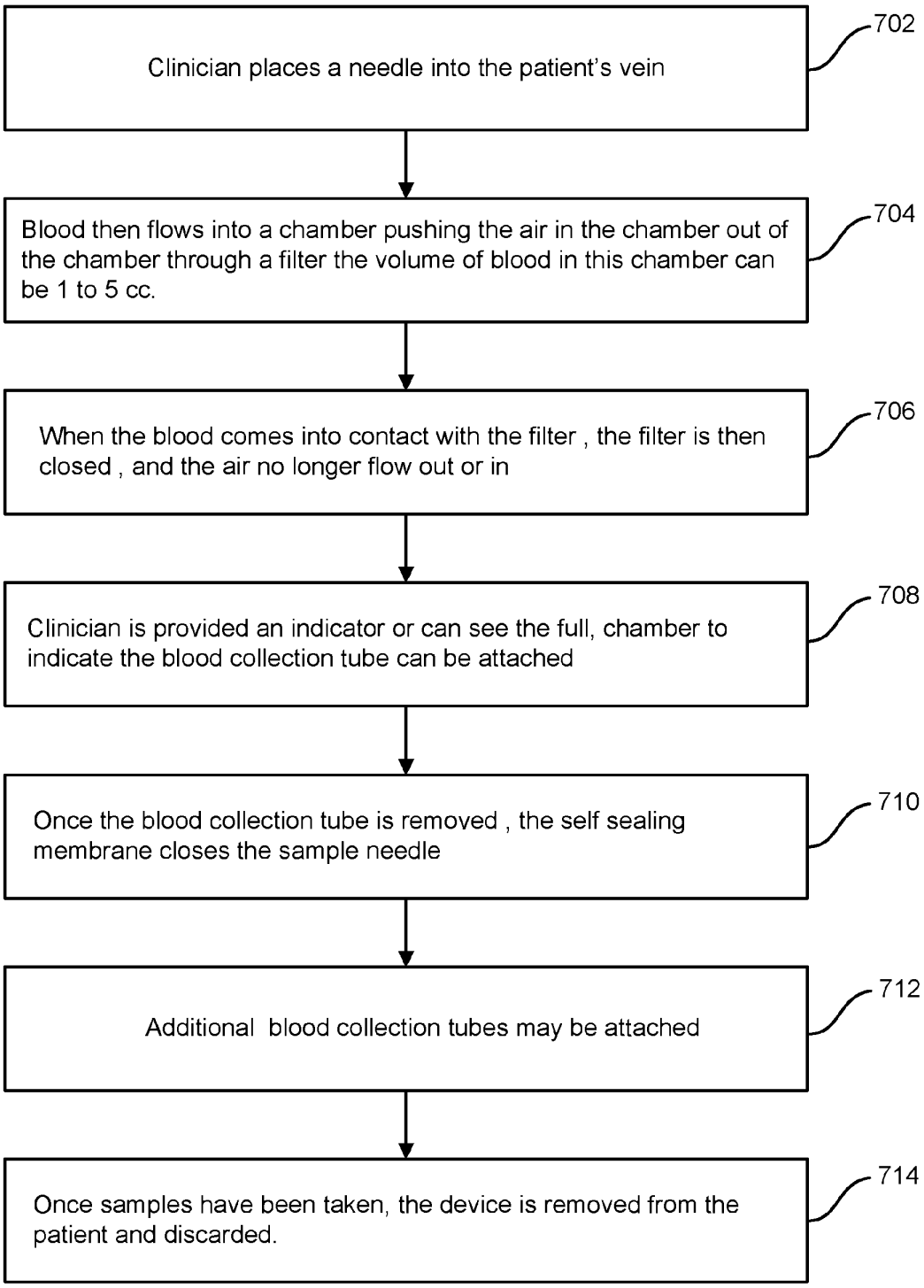

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air 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

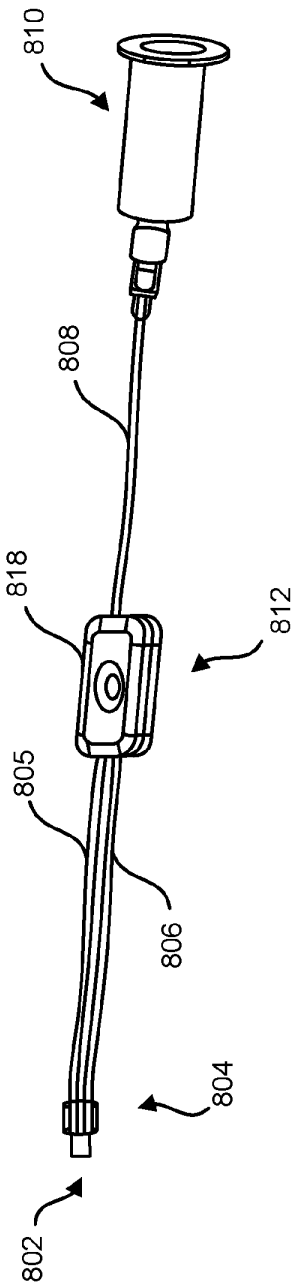


FIG. 8A

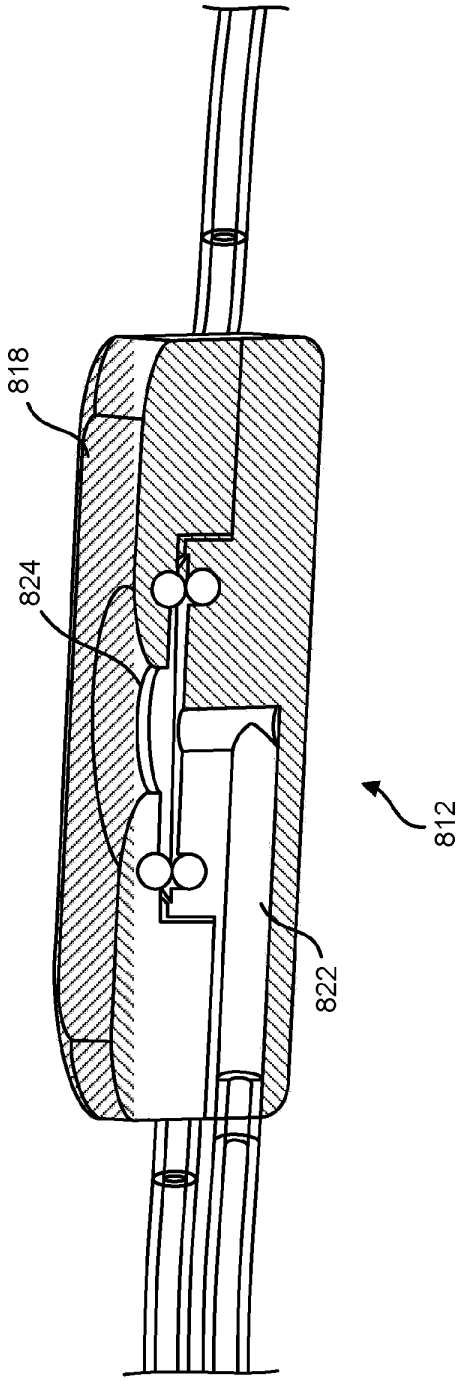


FIG. 8B

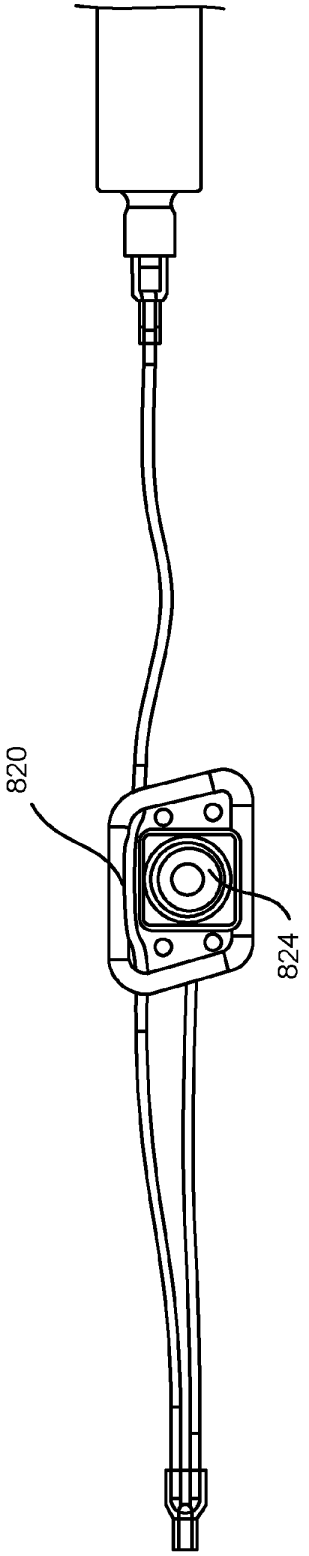


FIG. 8C

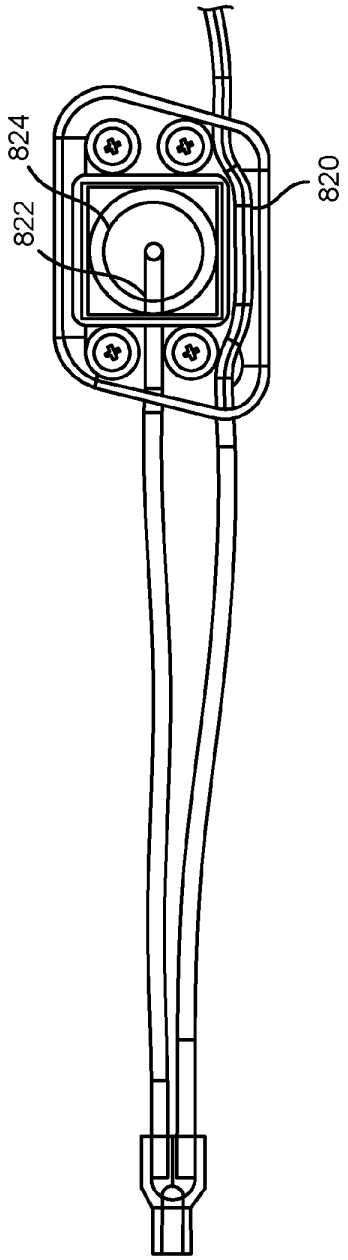


FIG. 8D

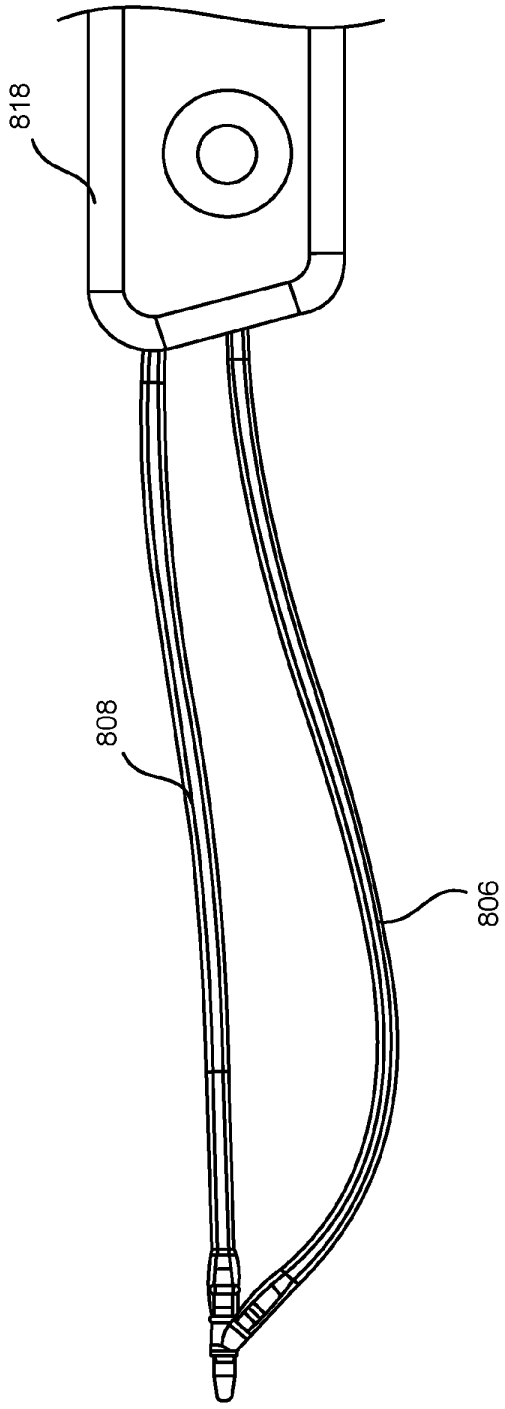


FIG. 8E

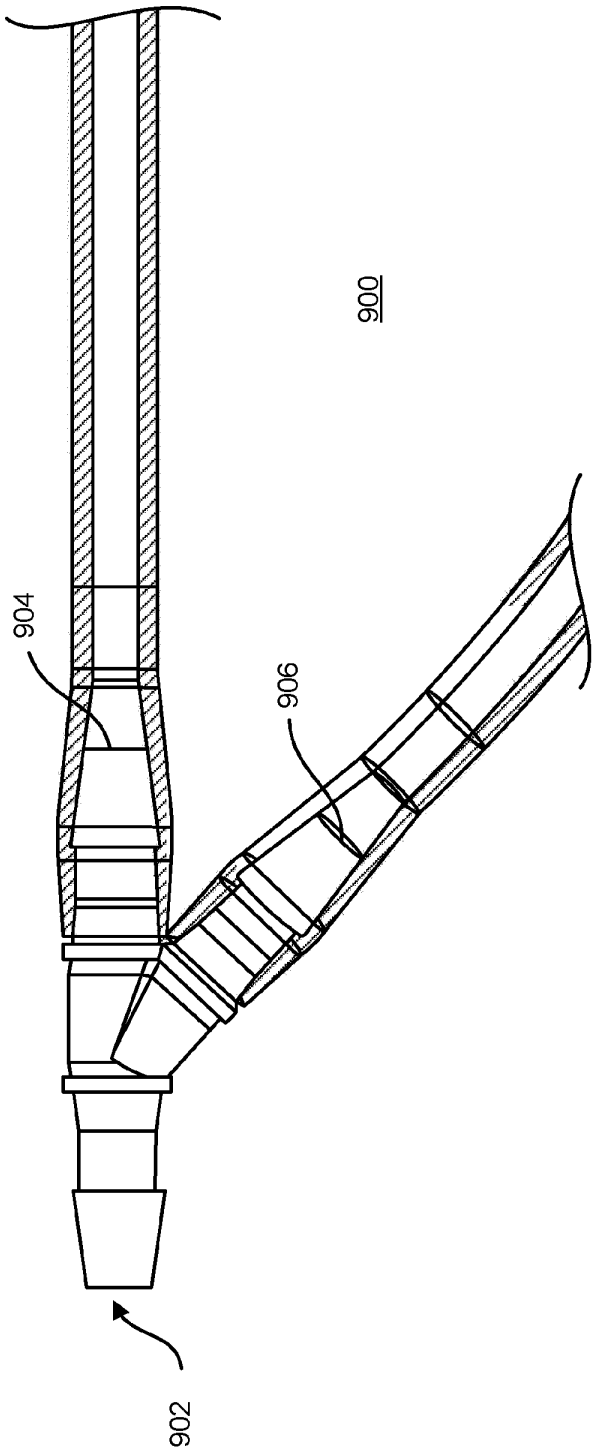


FIG. 9

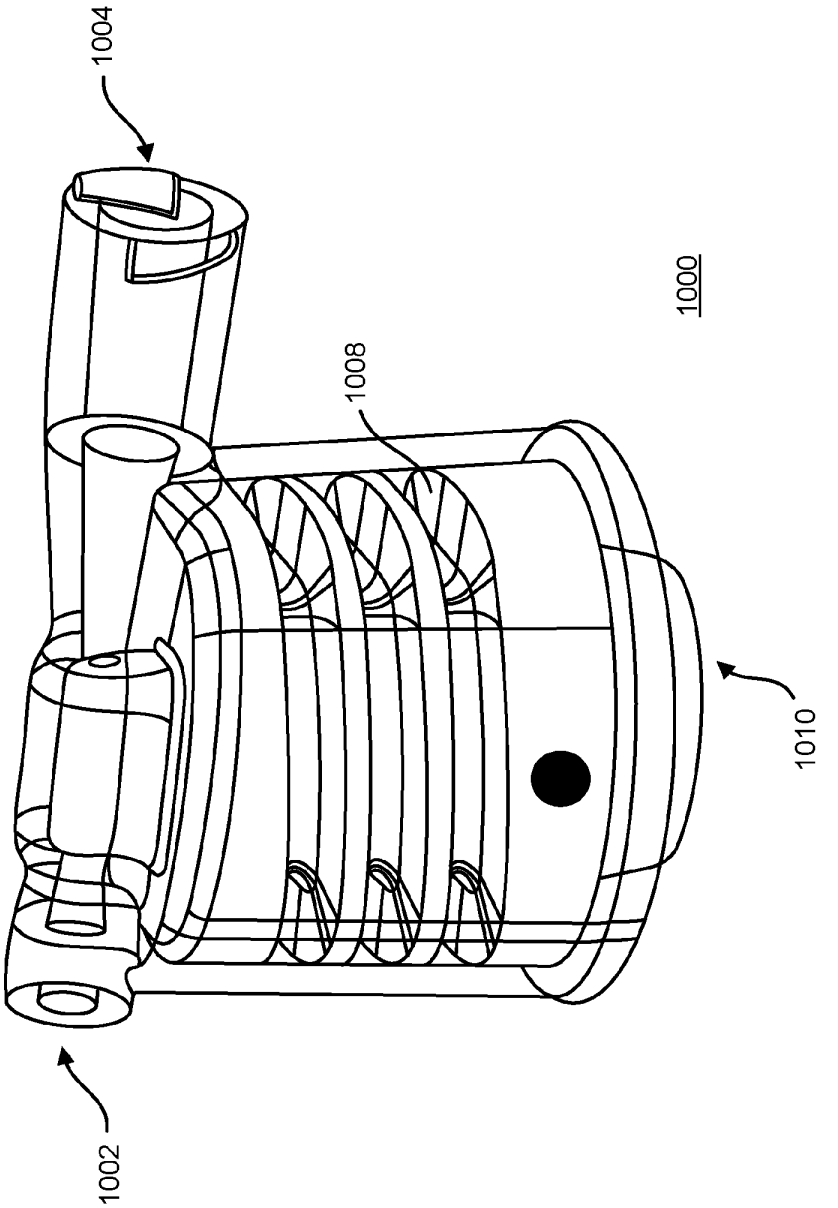


FIG. 10A

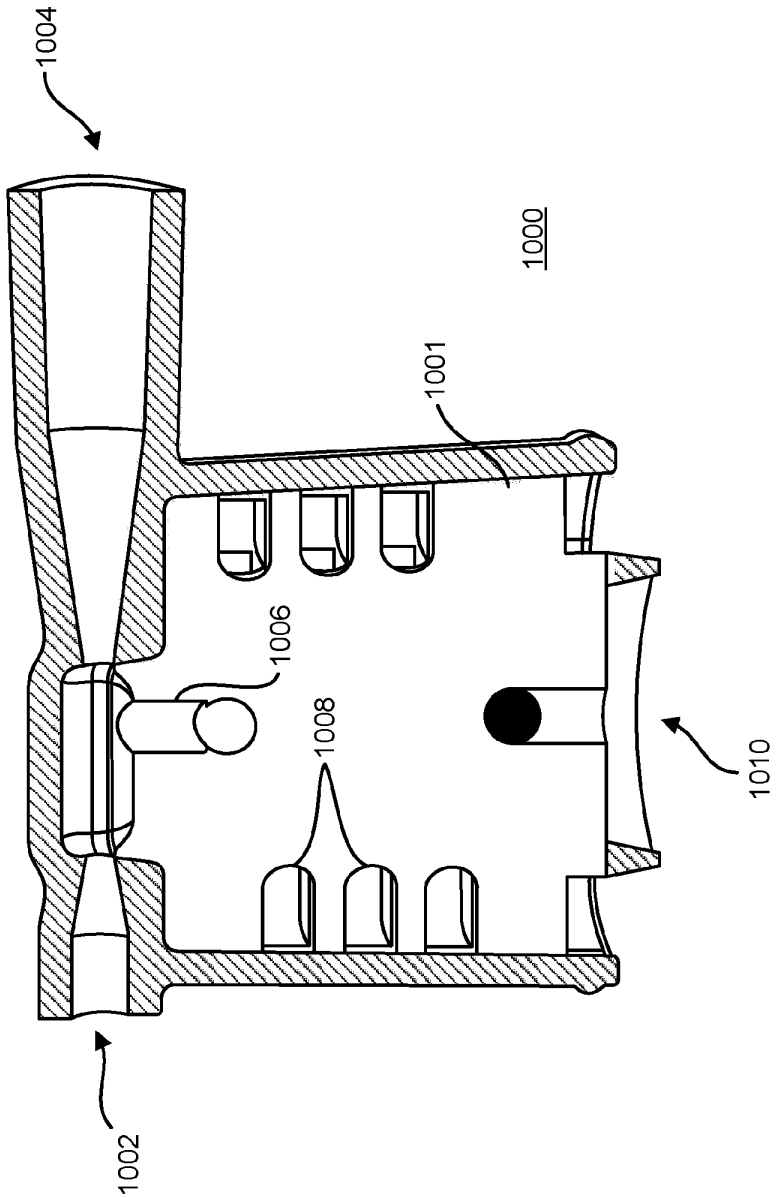


FIG. 10B

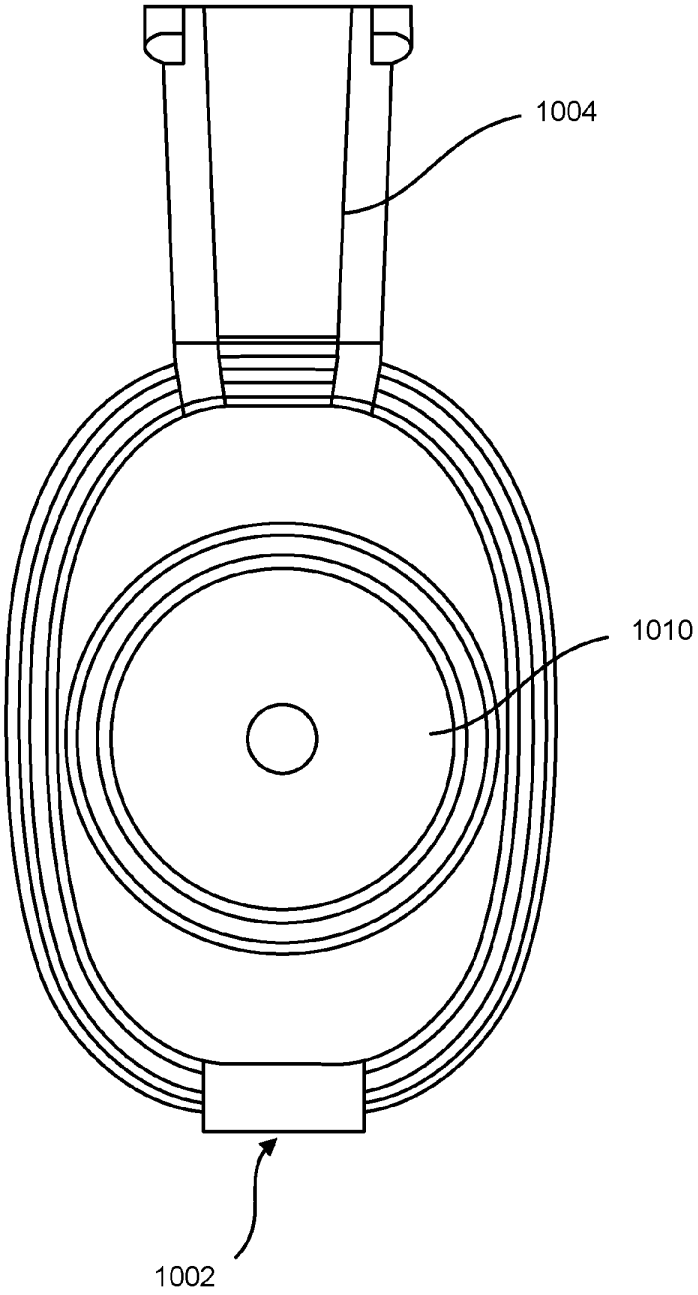


FIG. 10C

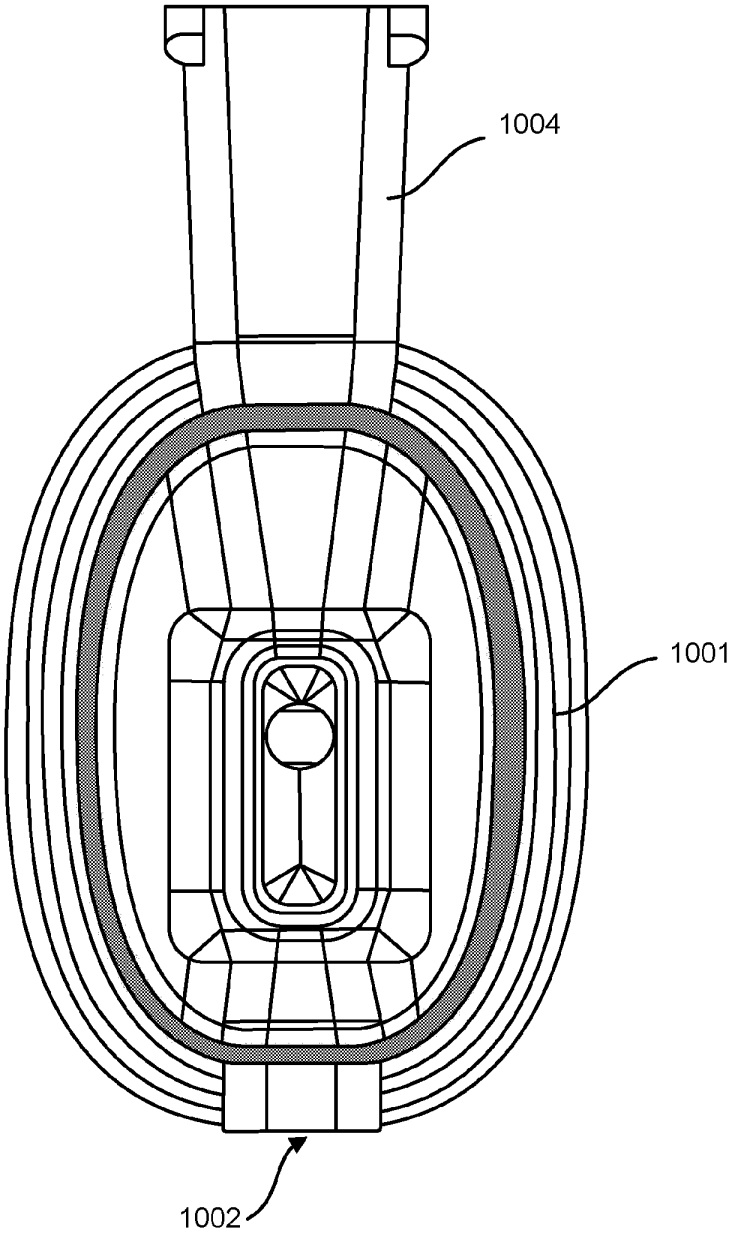


FIG. 10D

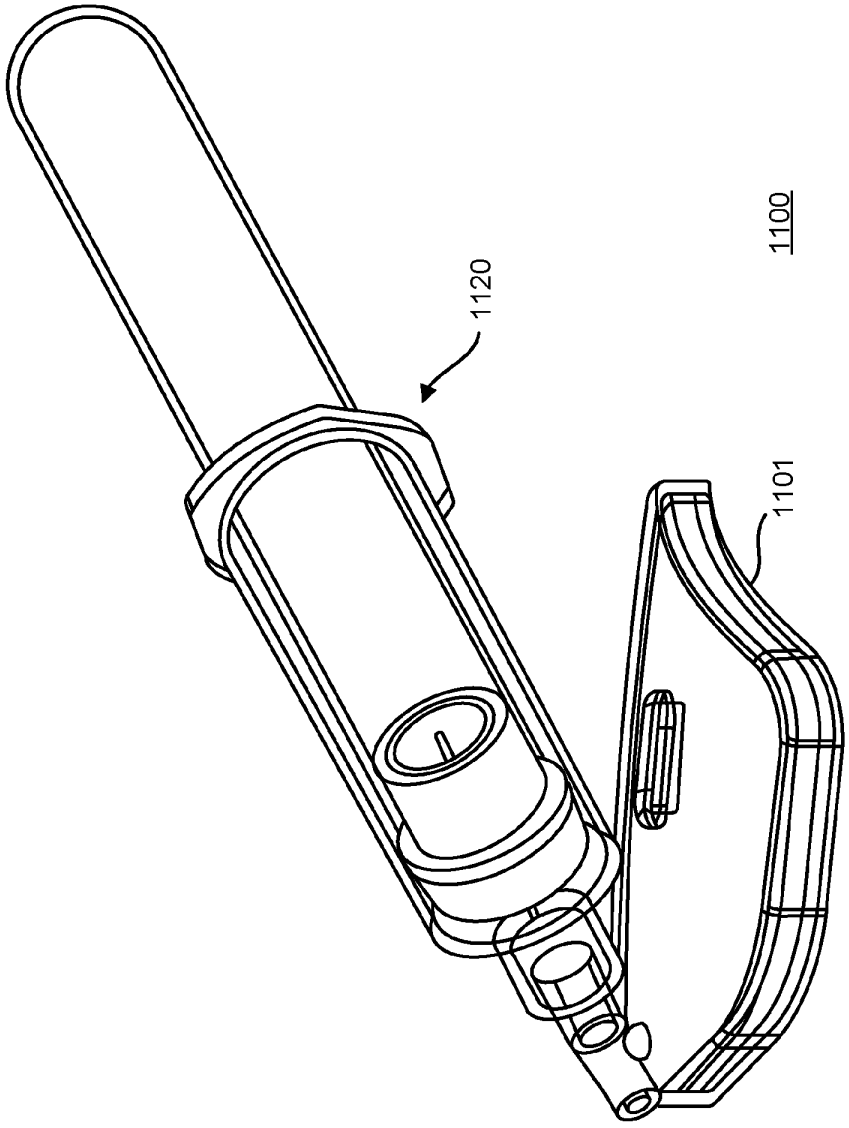


FIG. 11A

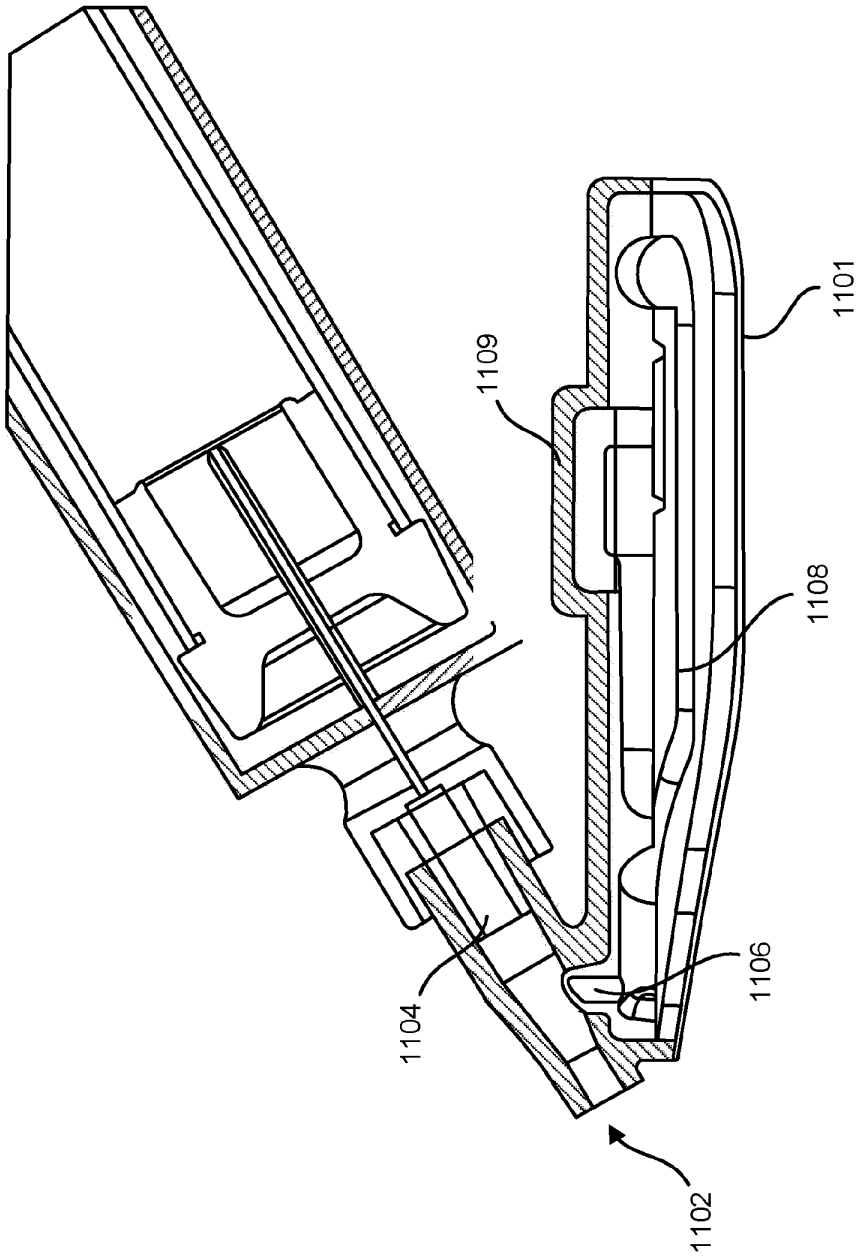


FIG. 11B

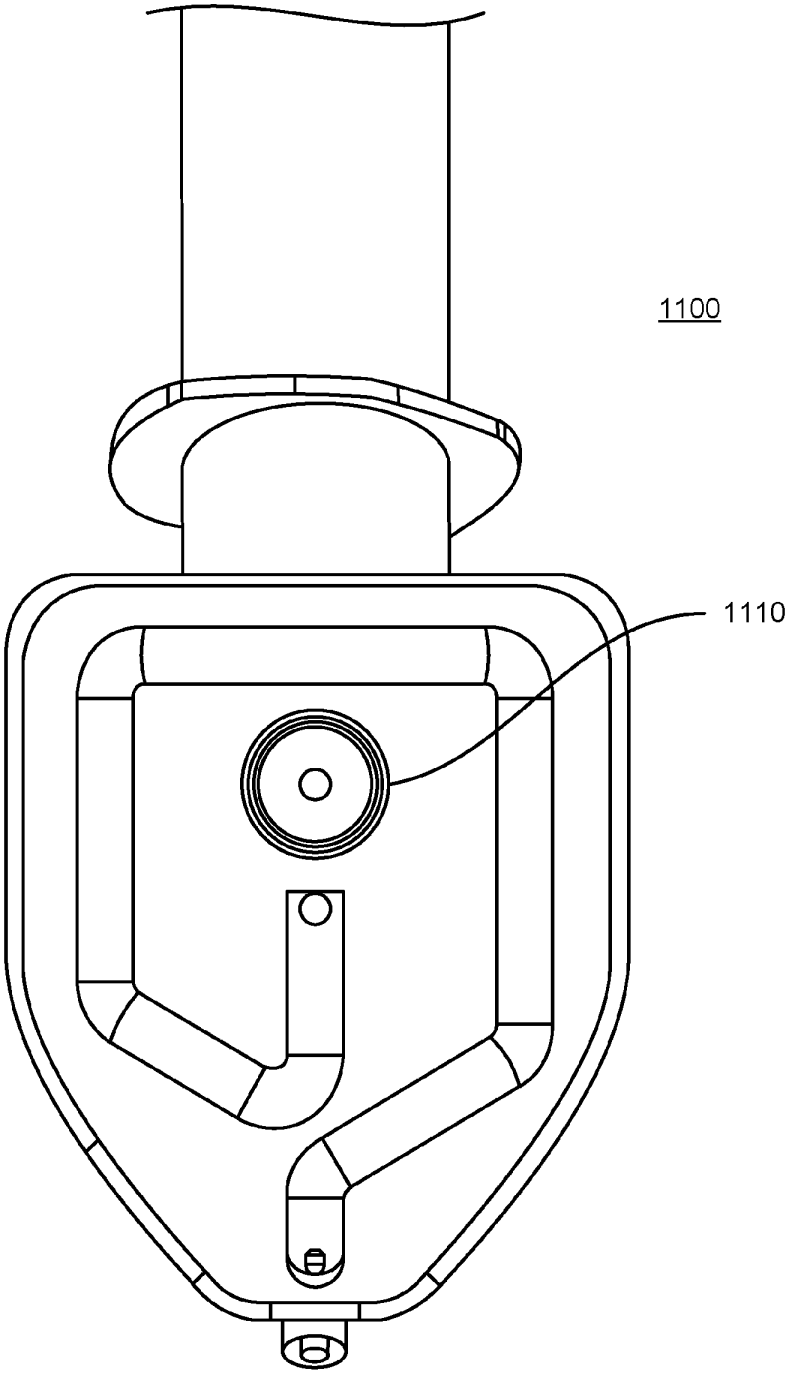


FIG. 11C

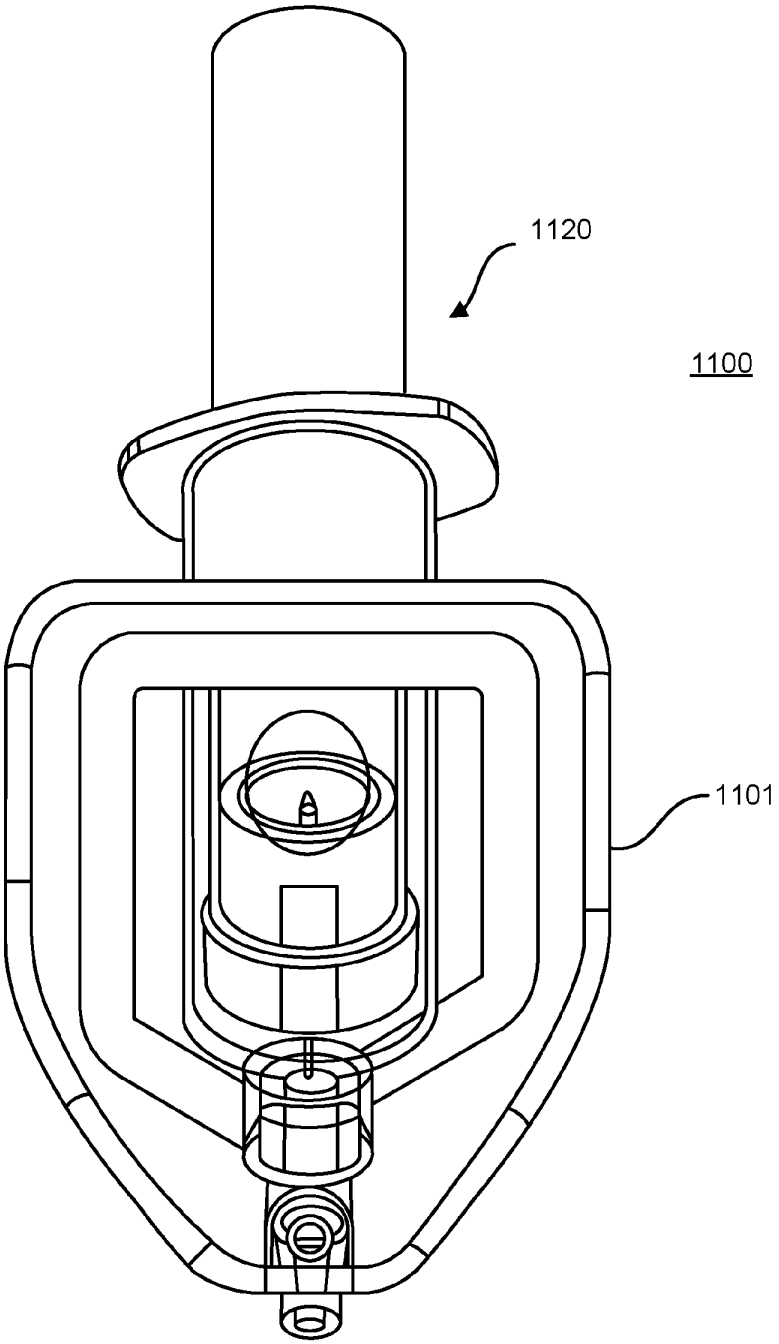


FIG. 11D

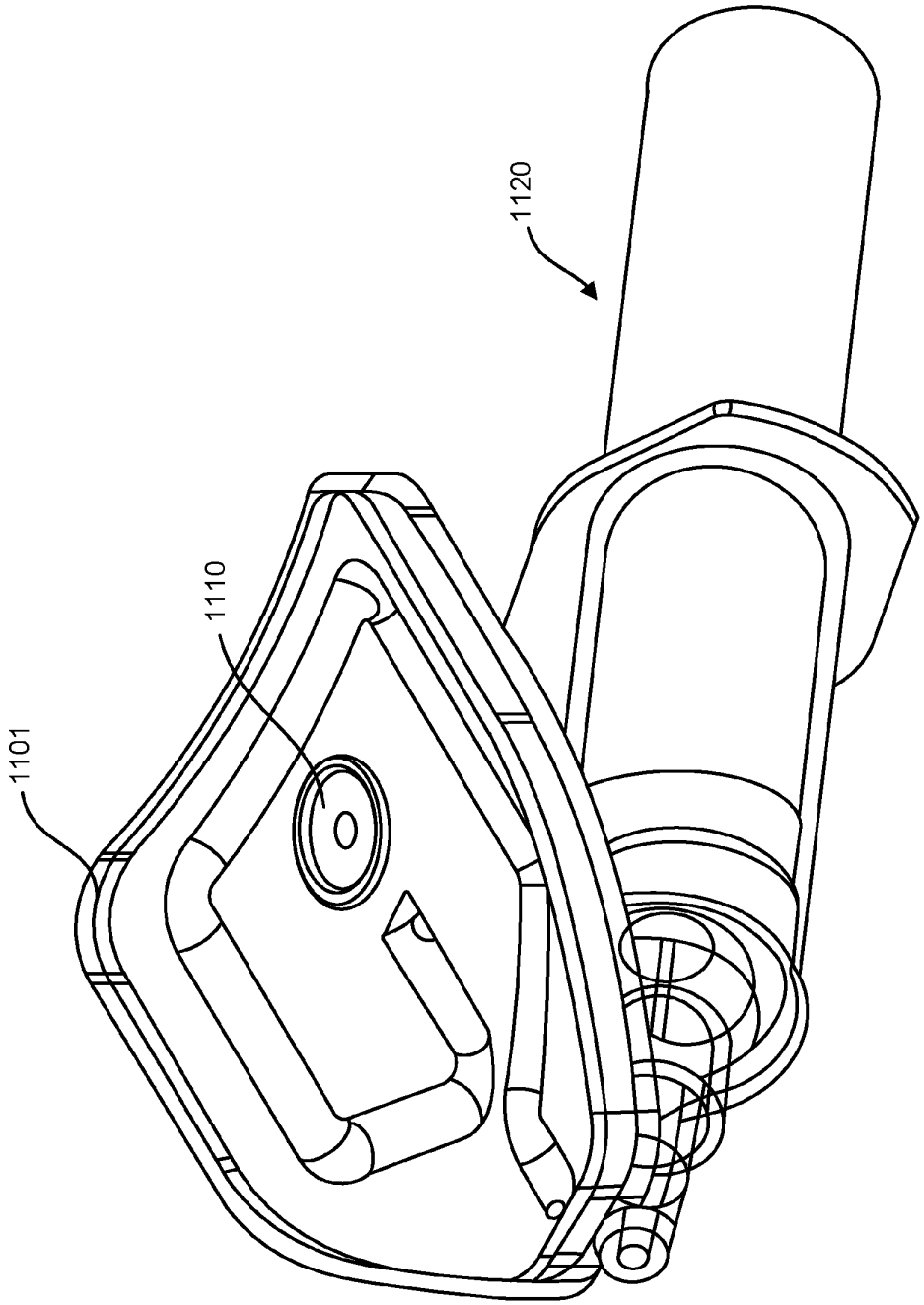


FIG. 11E

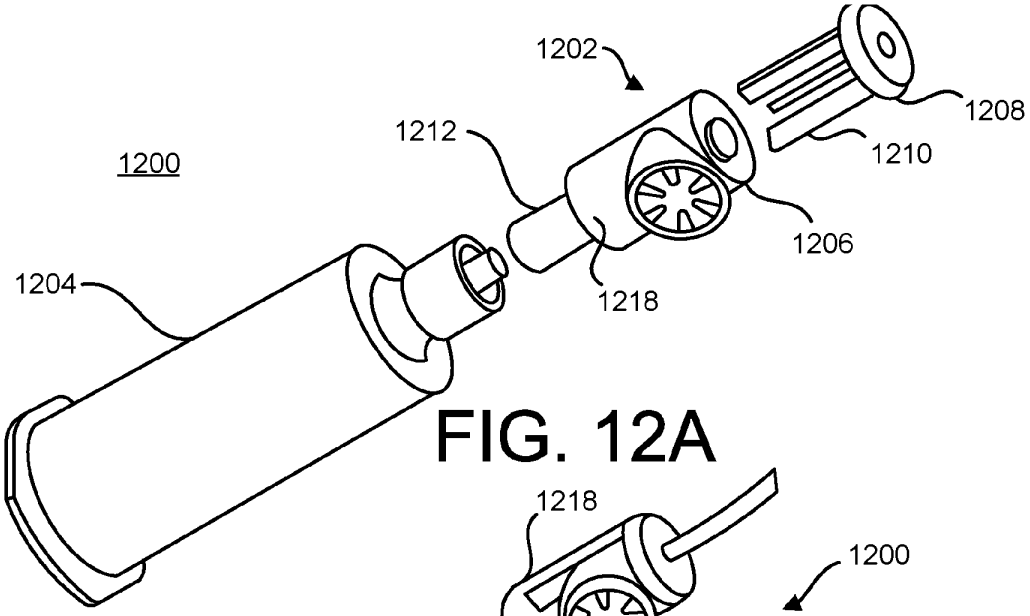


FIG. 12A

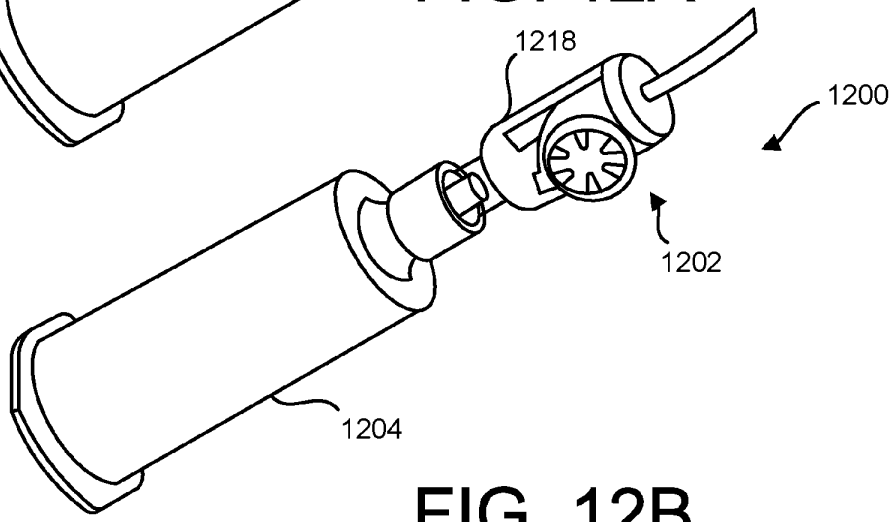


FIG. 12B

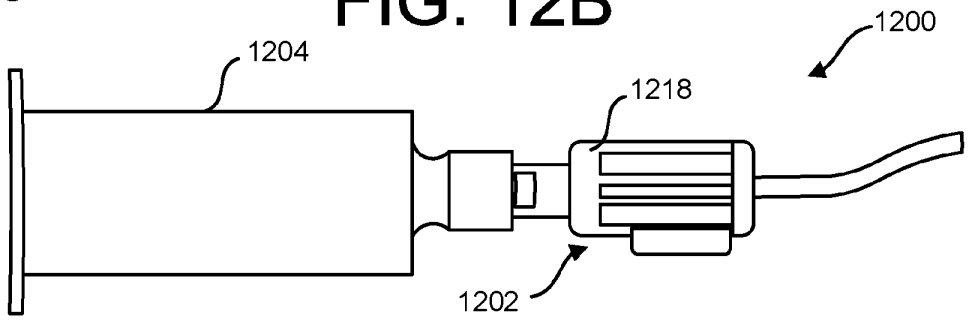


FIG. 12C

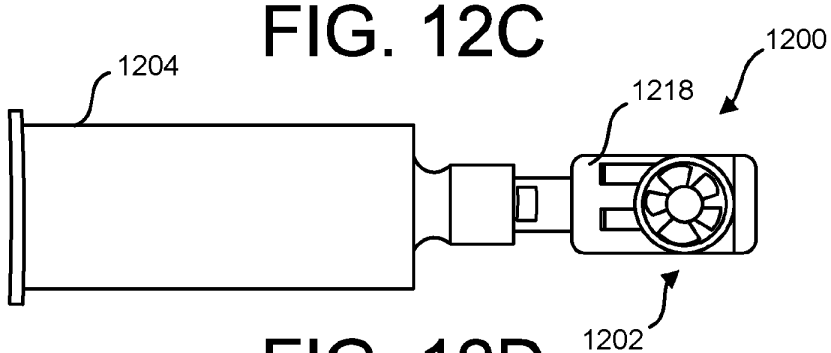


FIG. 12D

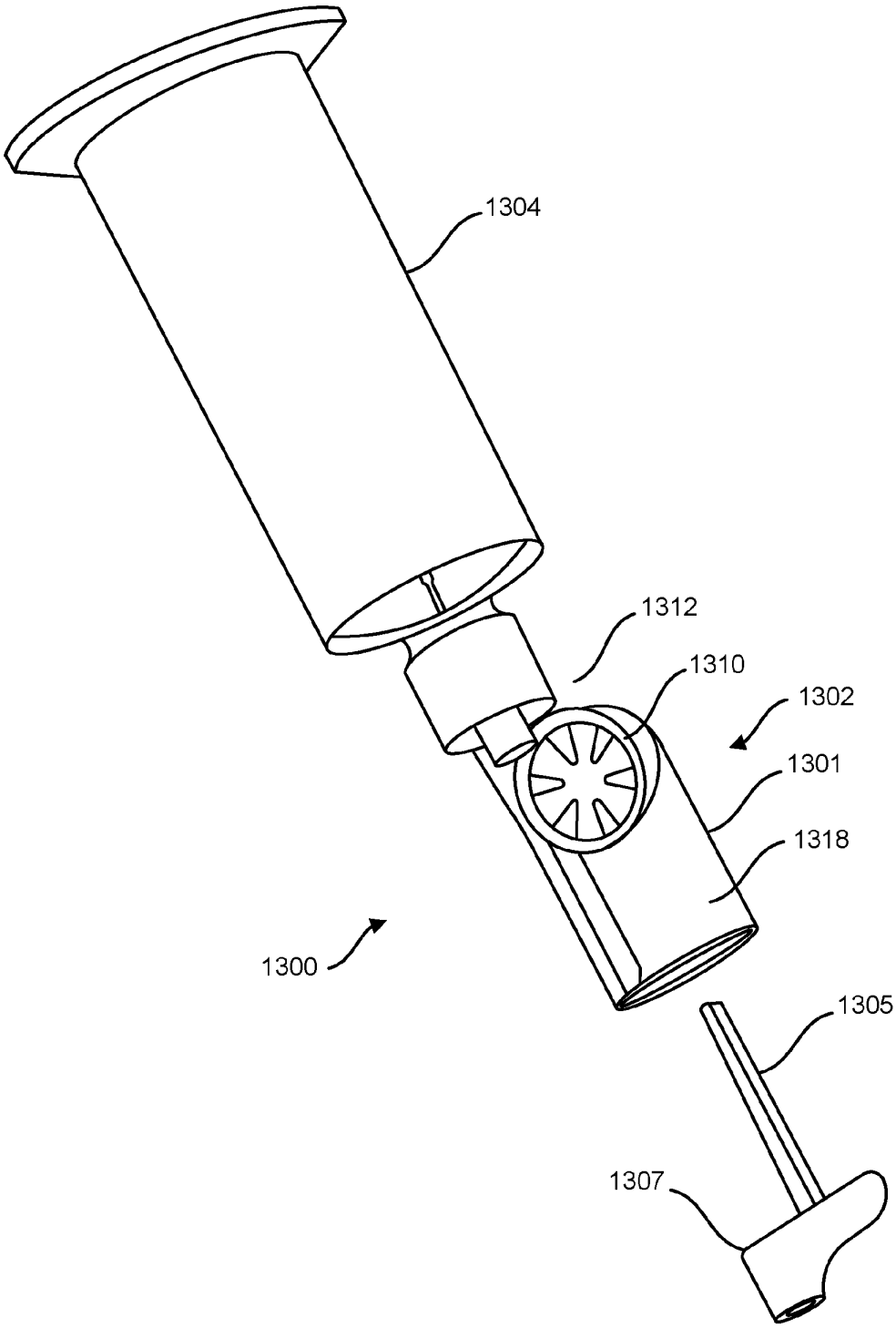


FIG. 13A

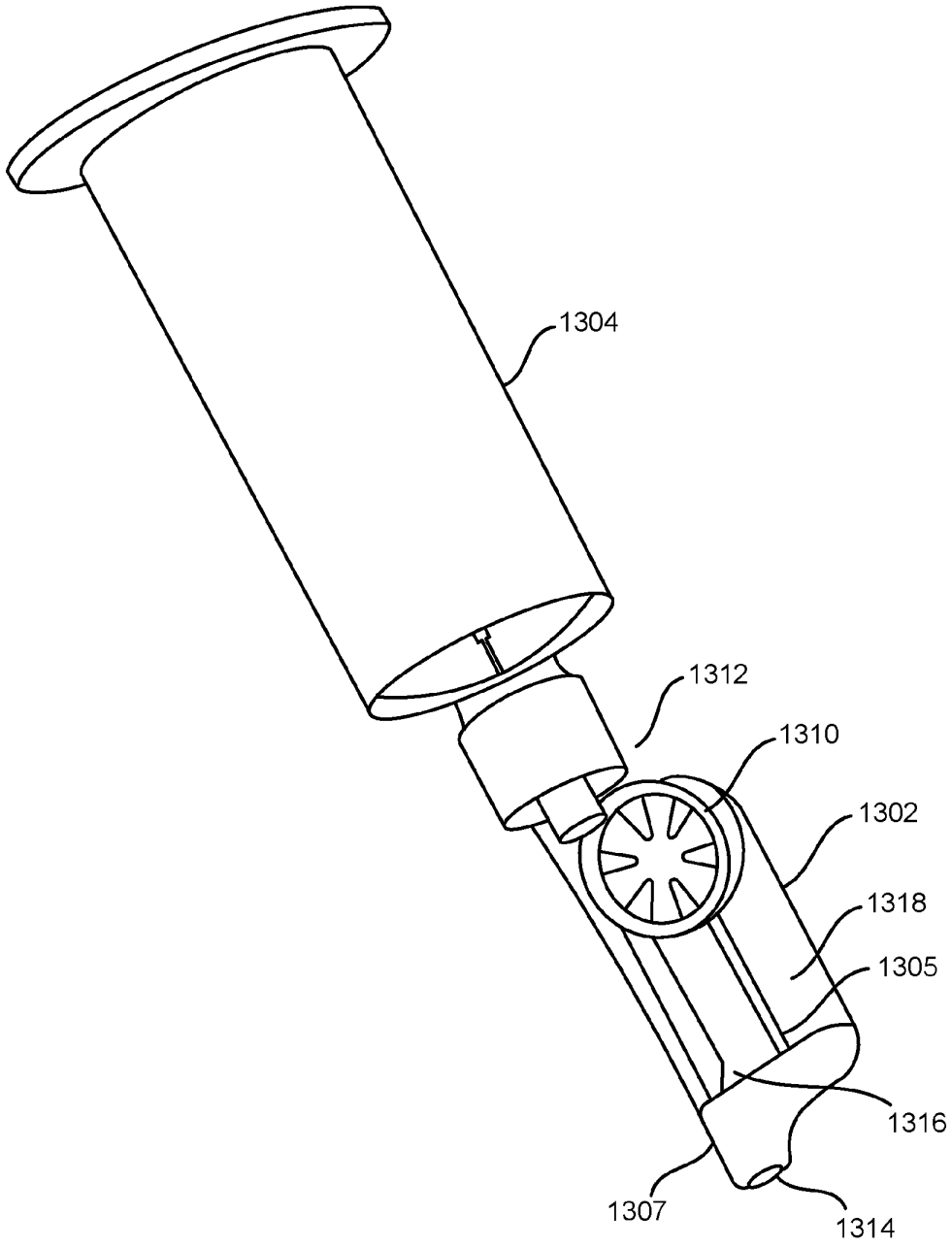


FIG. 13B

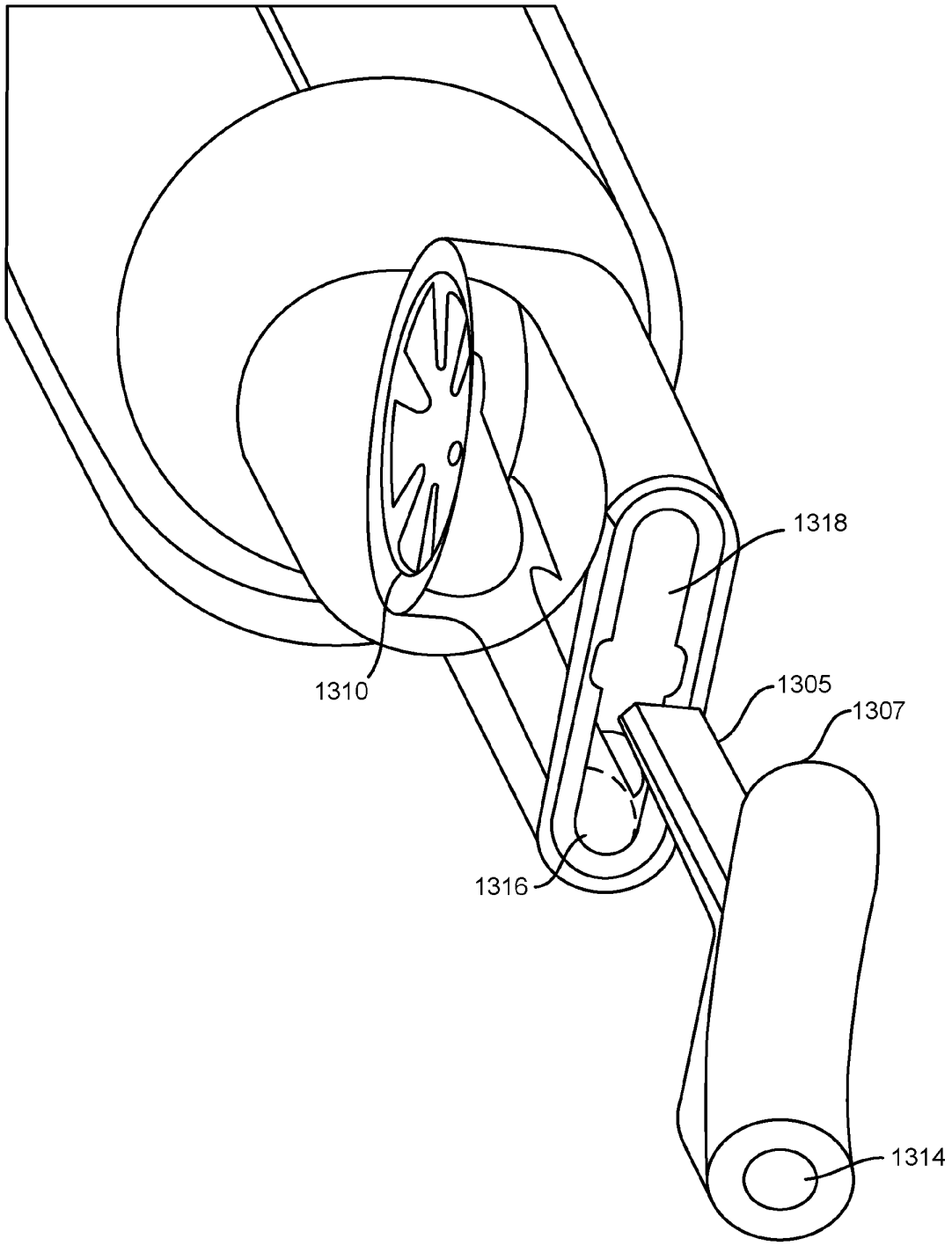


FIG. 13C

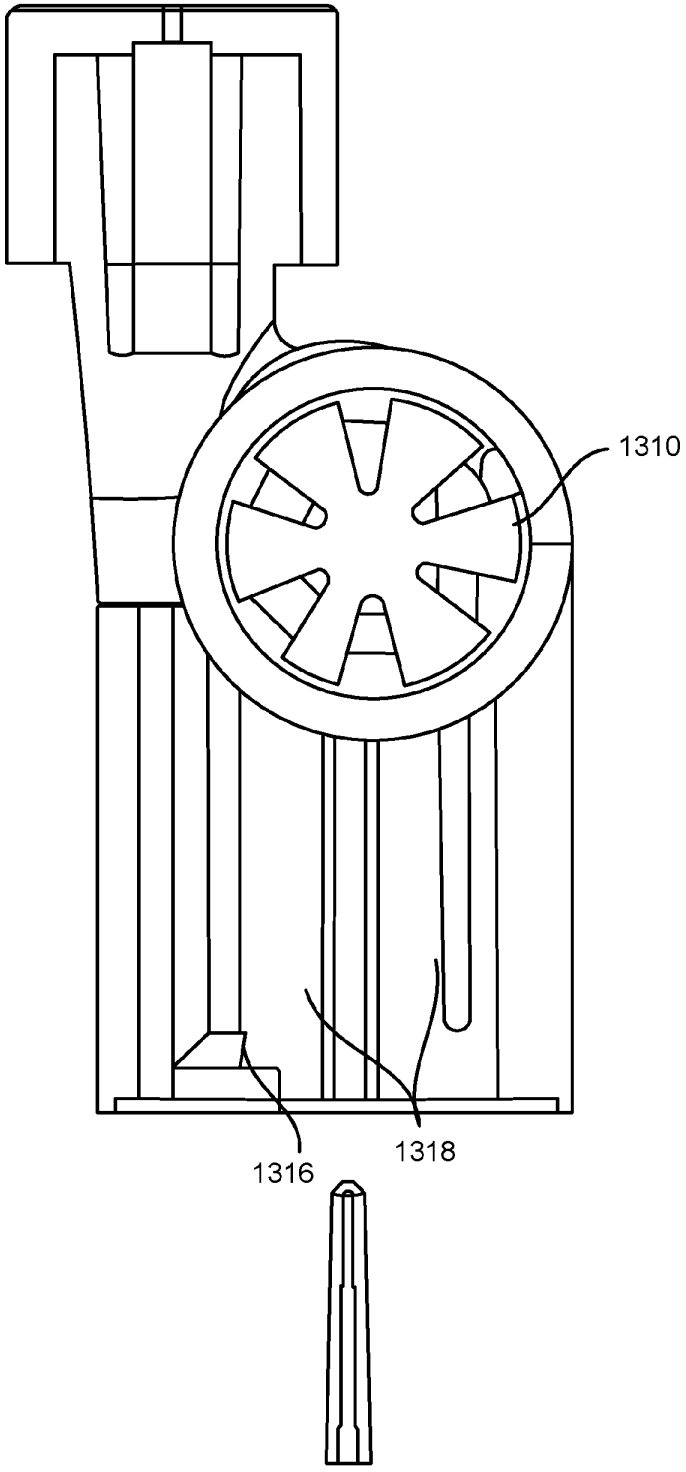


FIG. 13D

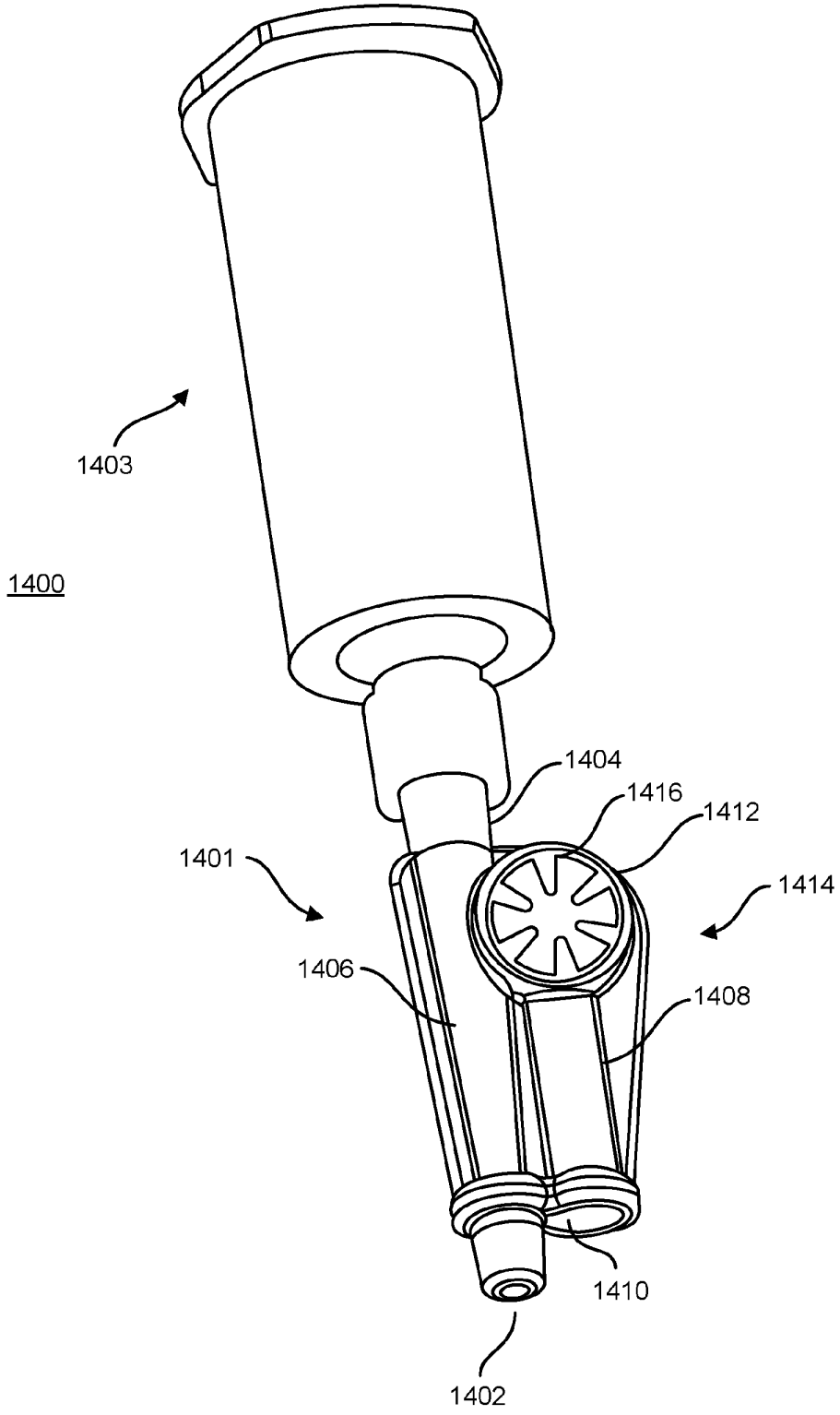


FIG. 14A

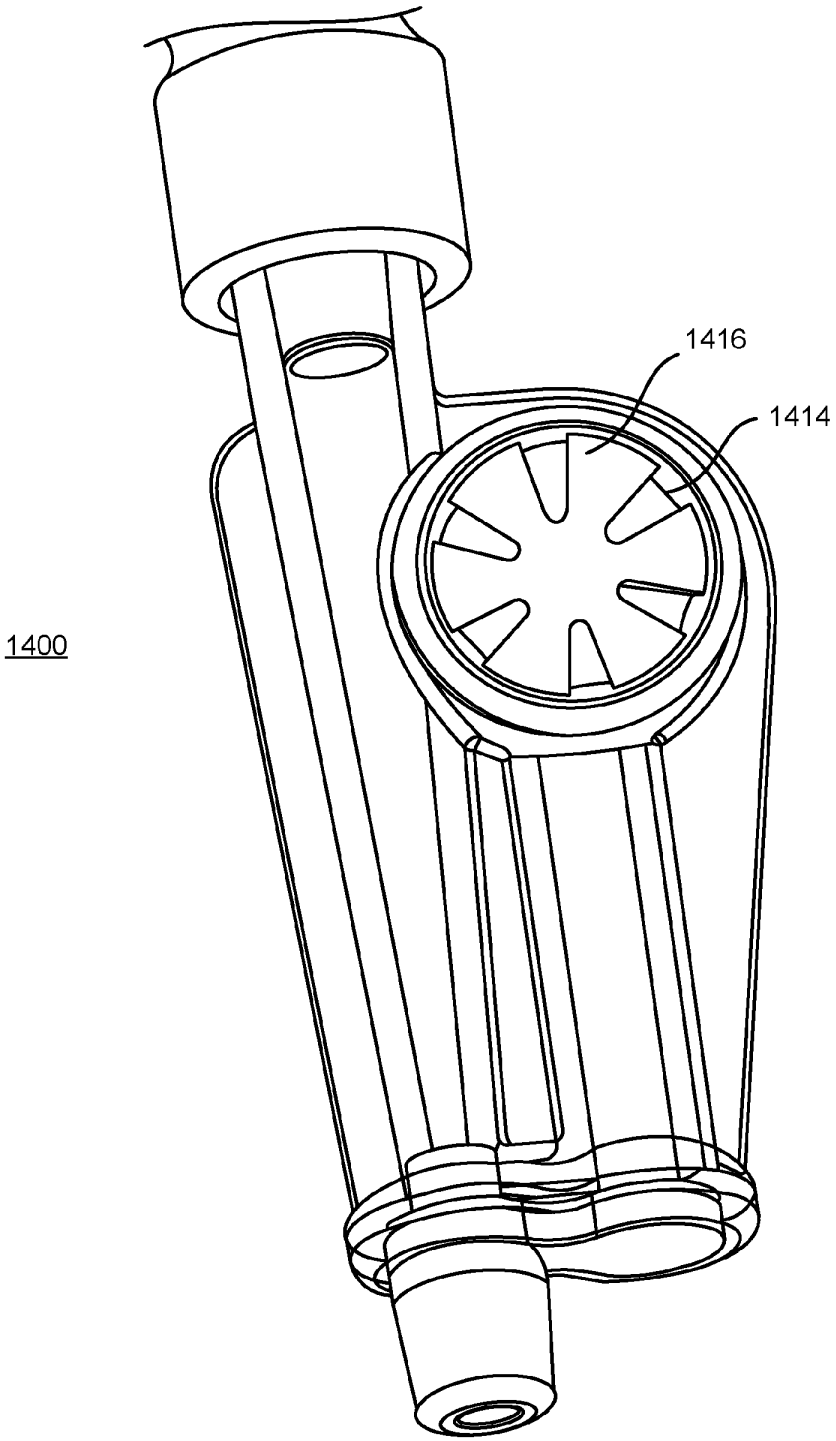


FIG. 14B

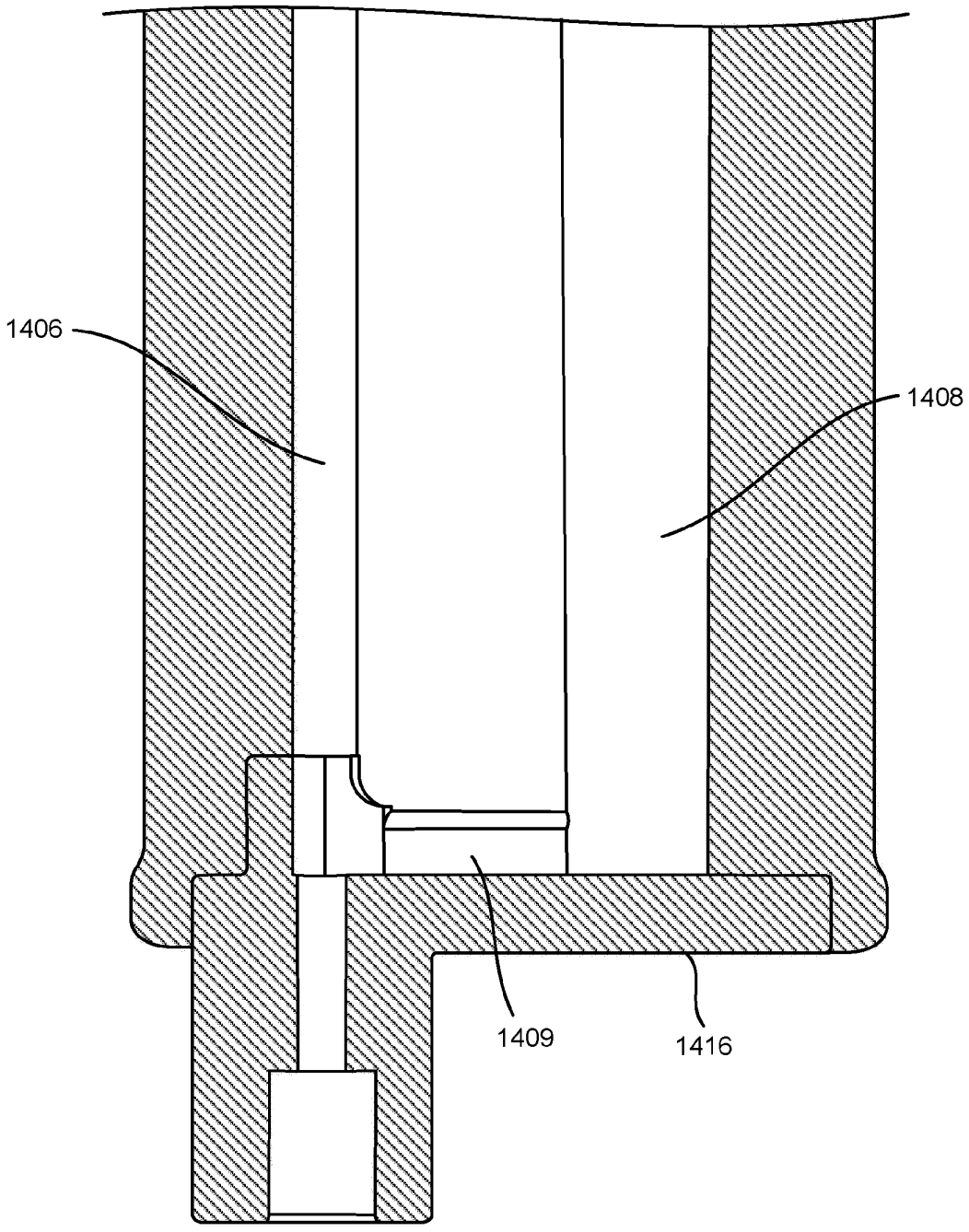


FIG. 14C

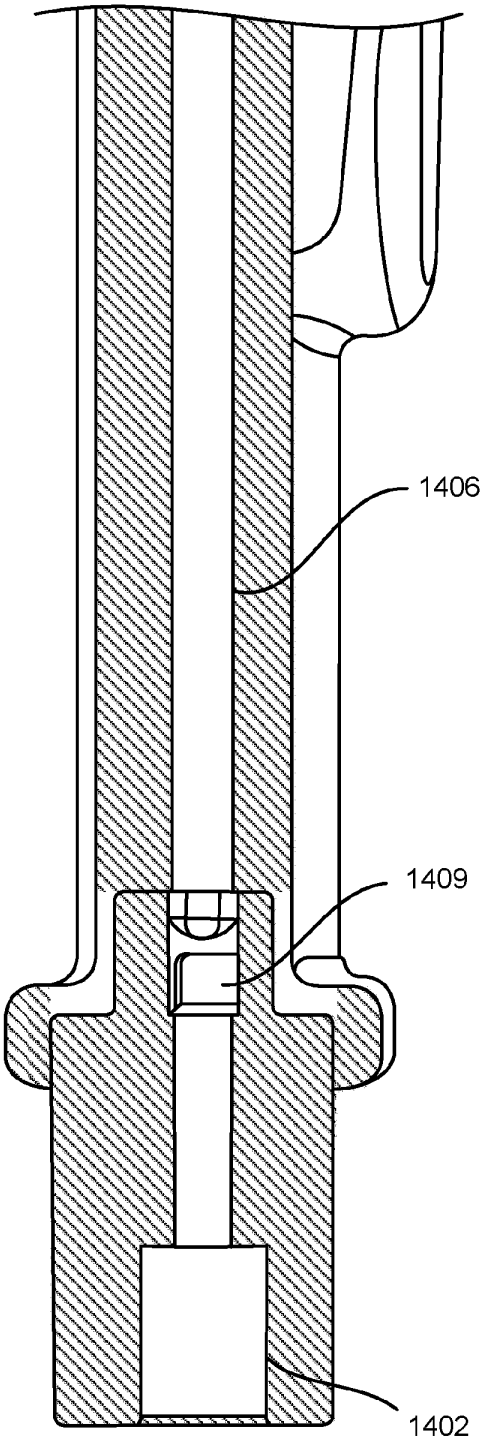


FIG. 14D

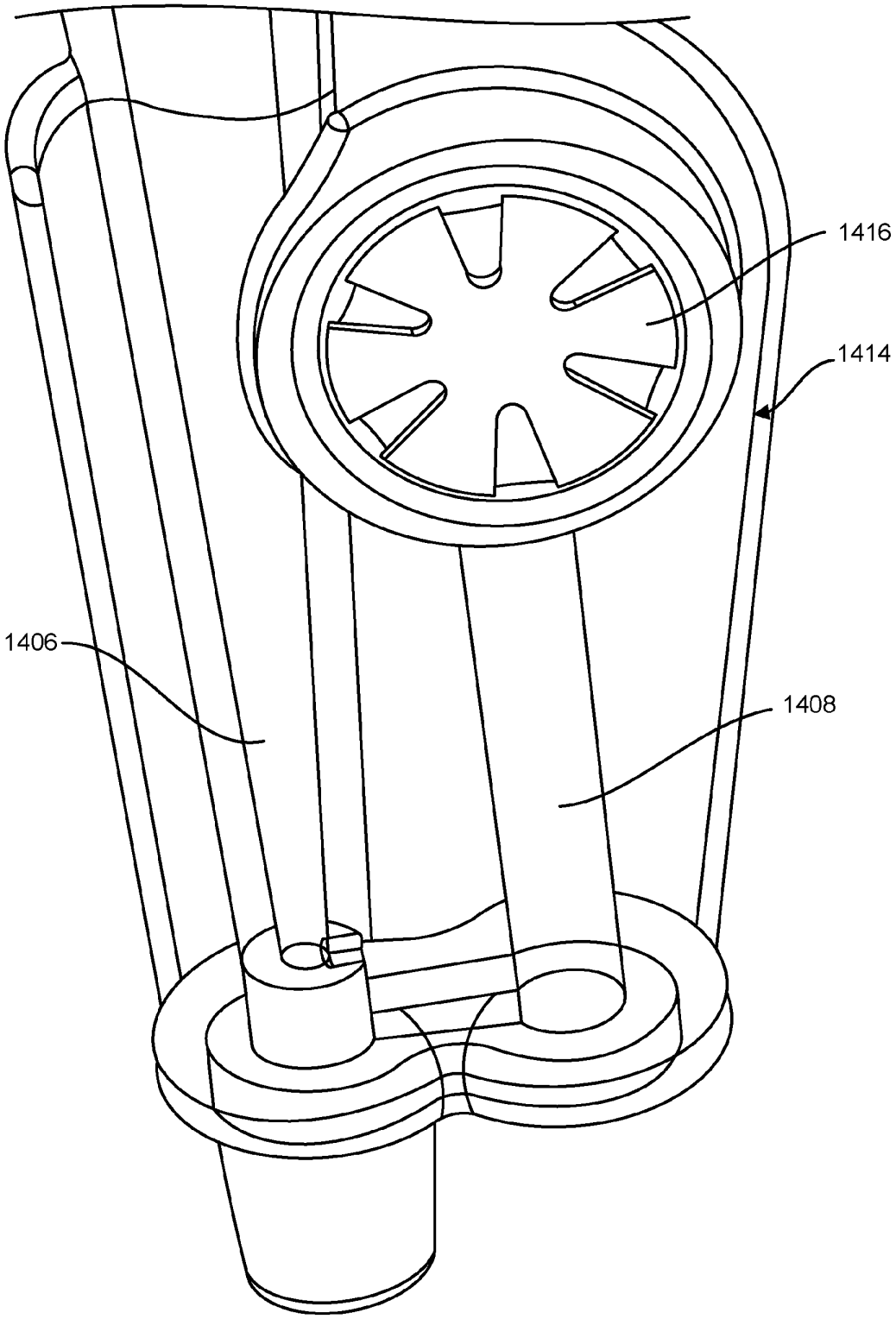


FIG. 14E

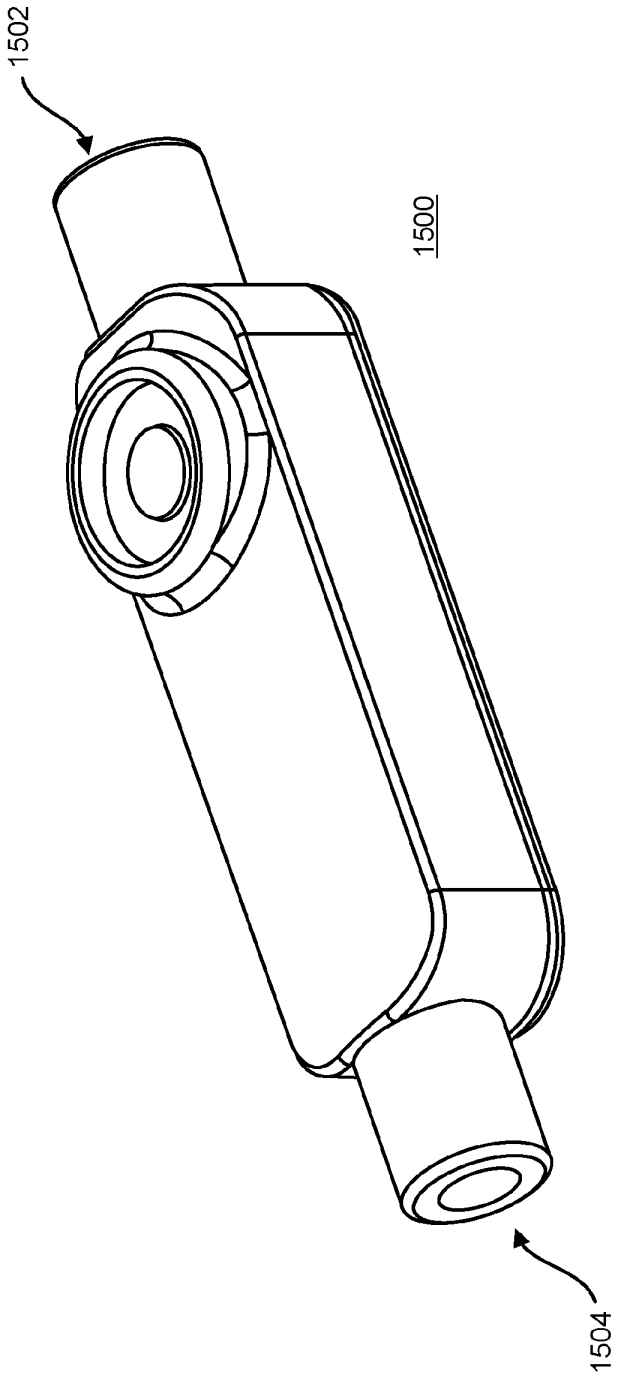


FIG. 15A

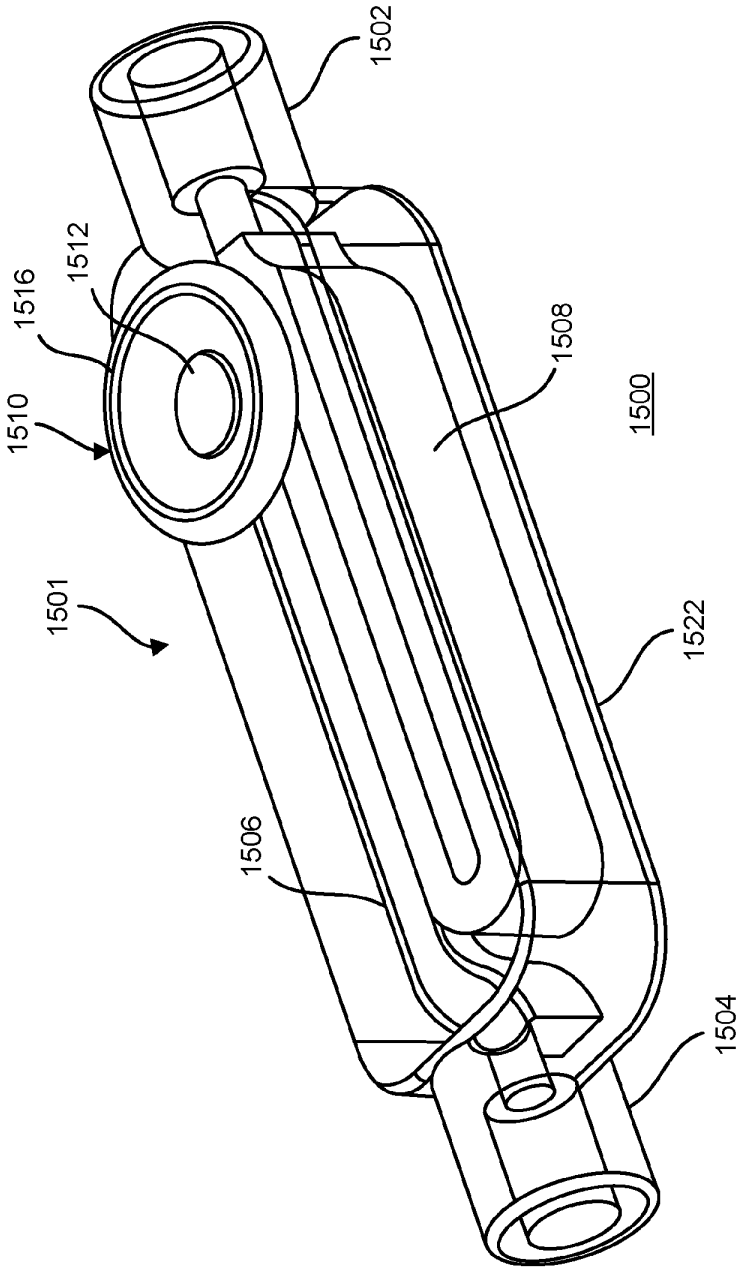


FIG. 15B

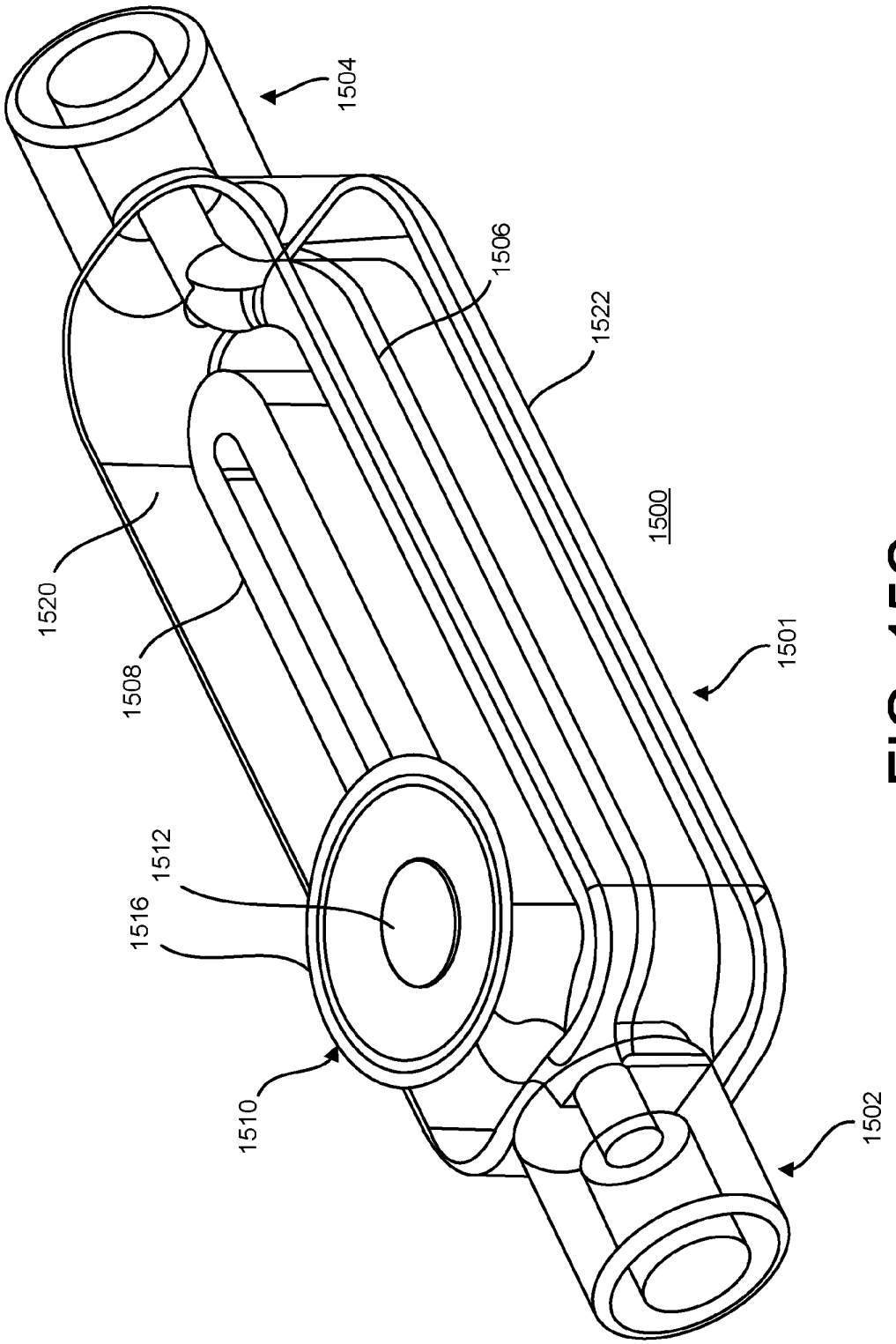


FIG. 15C

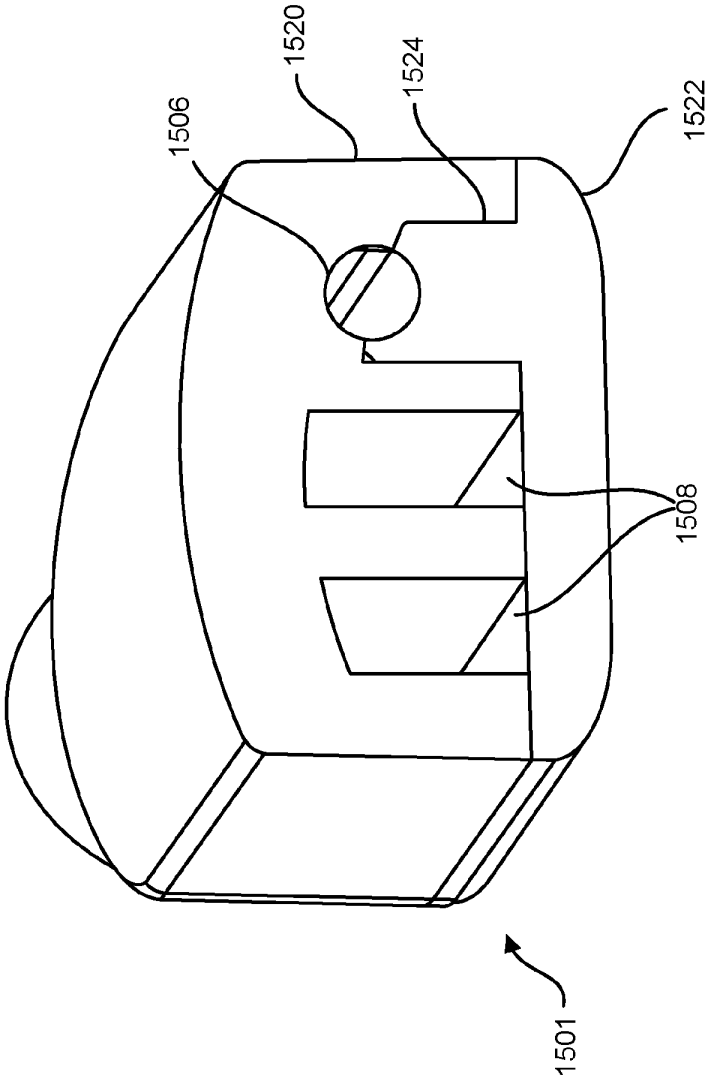


FIG. 15D

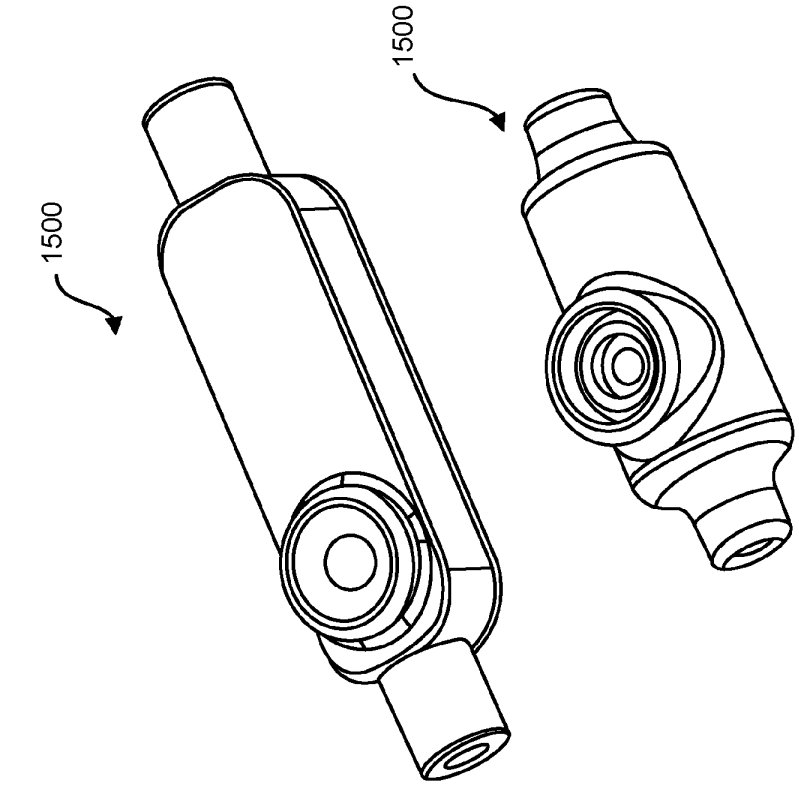


FIG. 15F

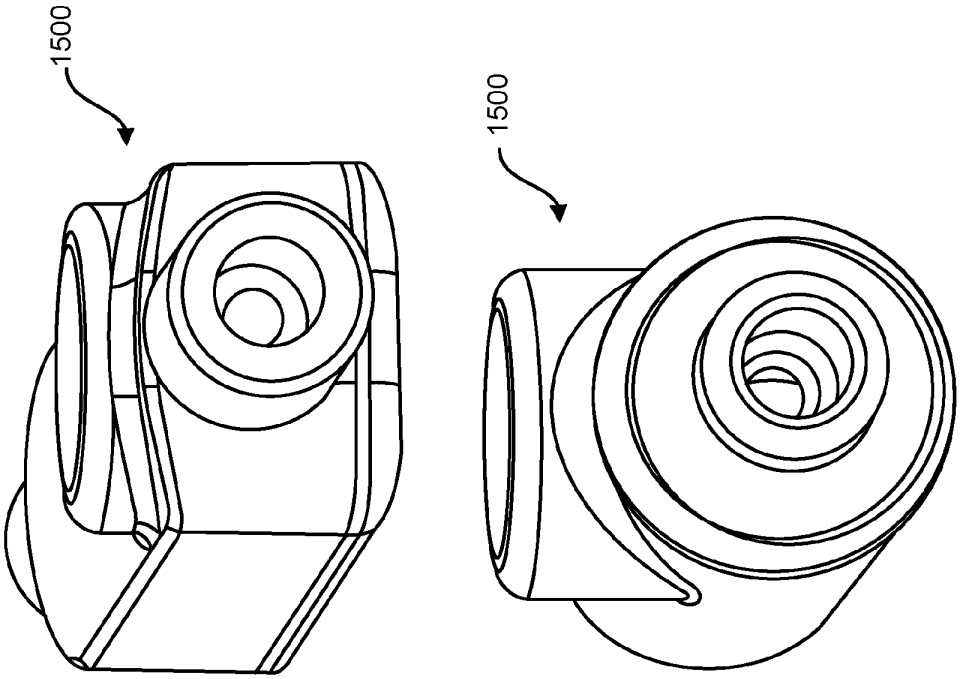


FIG. 15E

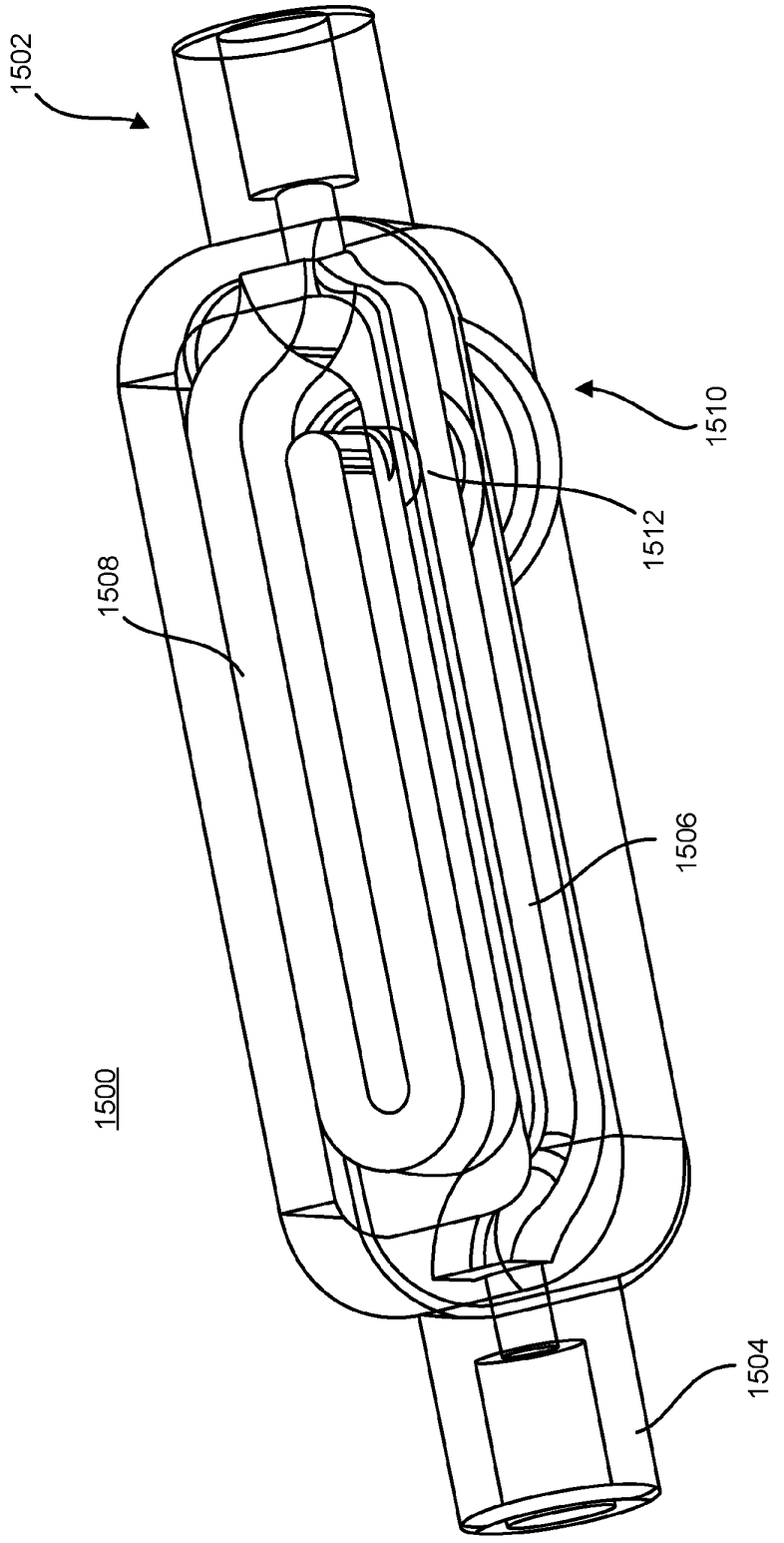


FIG. 15G

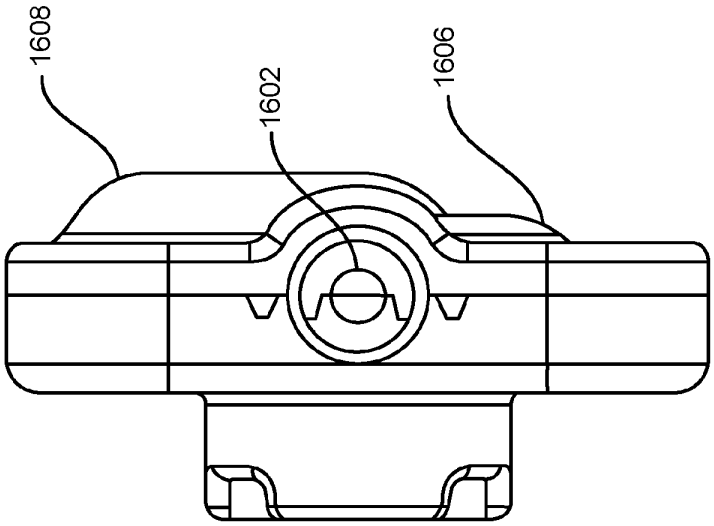


FIG. 16C

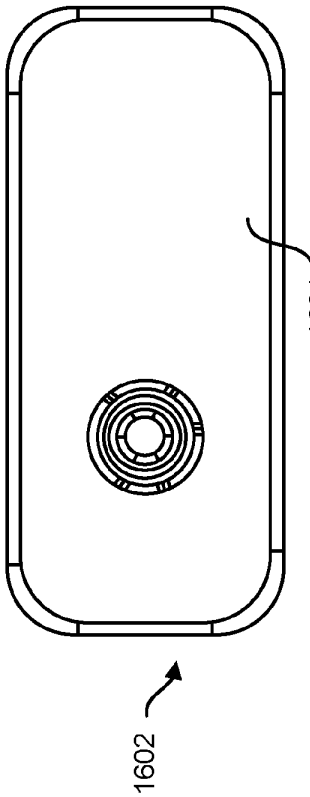


FIG. 16A

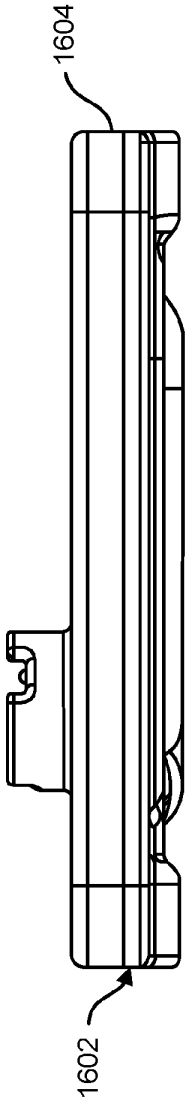


FIG. 16B

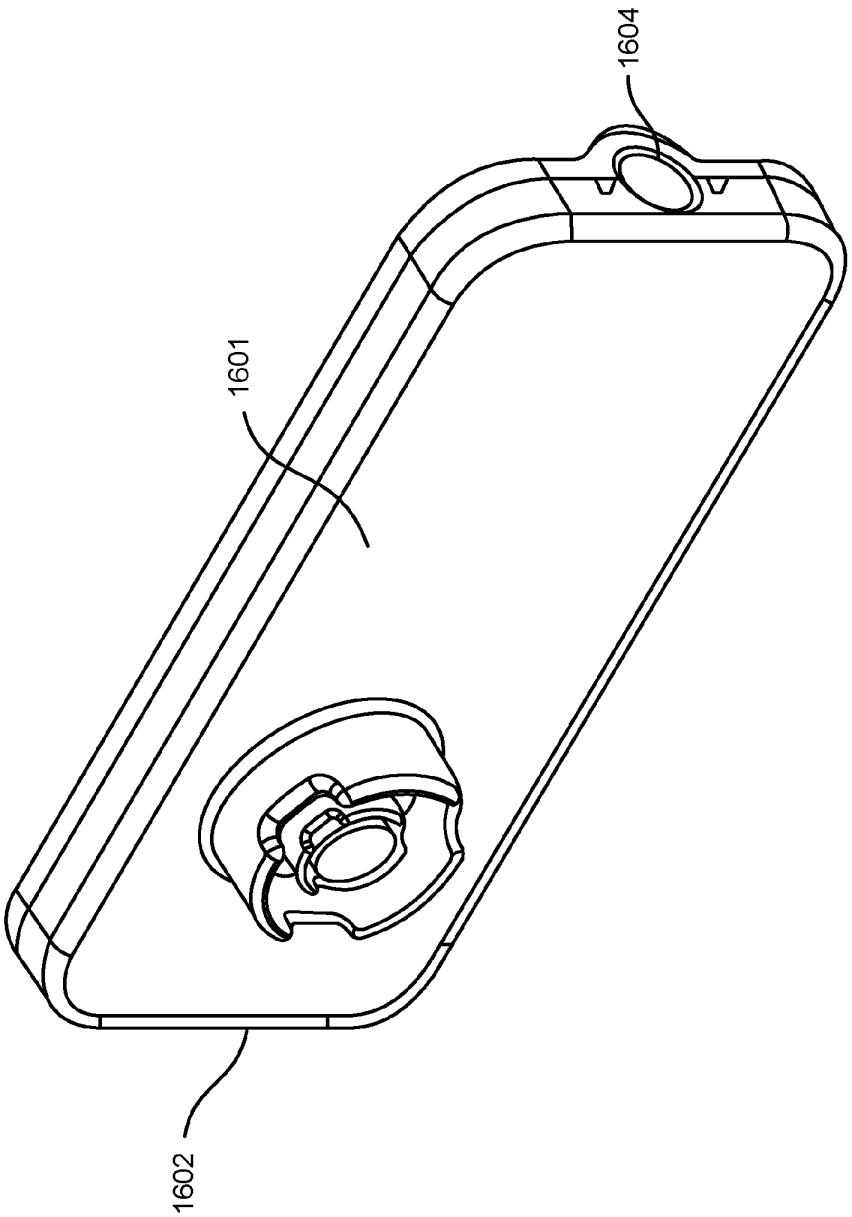


FIG. 16D

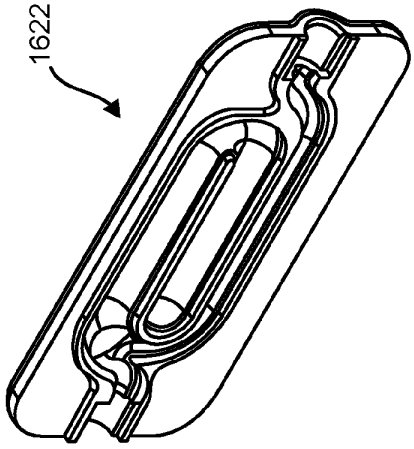


FIG. 17B



FIG. 17E

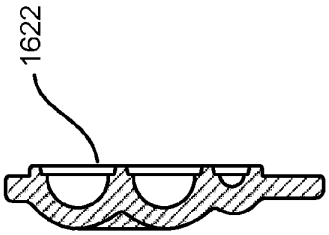


FIG. 17D

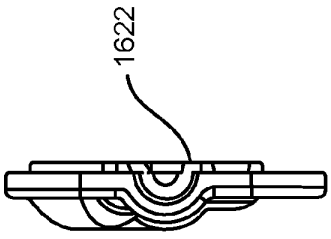


FIG. 17C

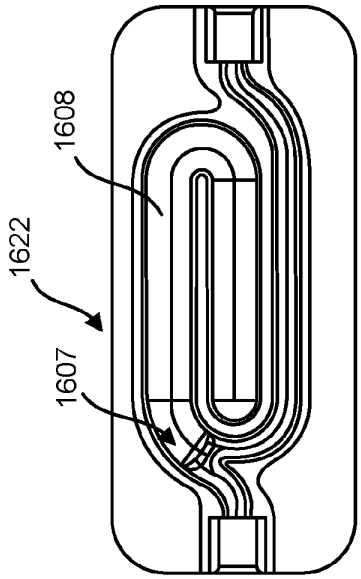


FIG. 17A

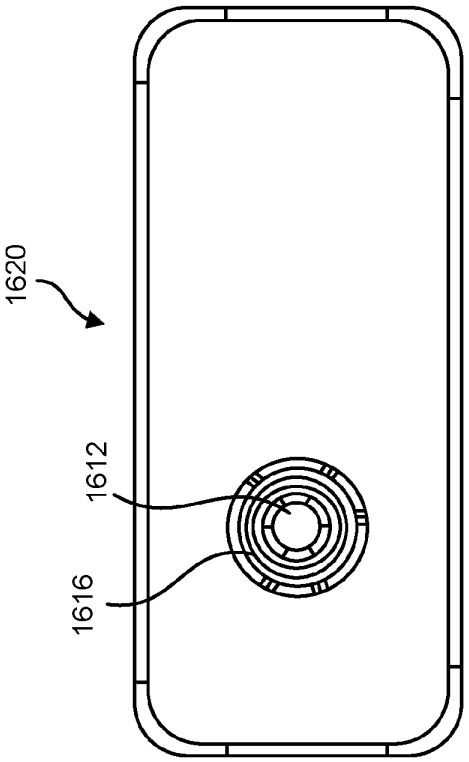


FIG. 18A

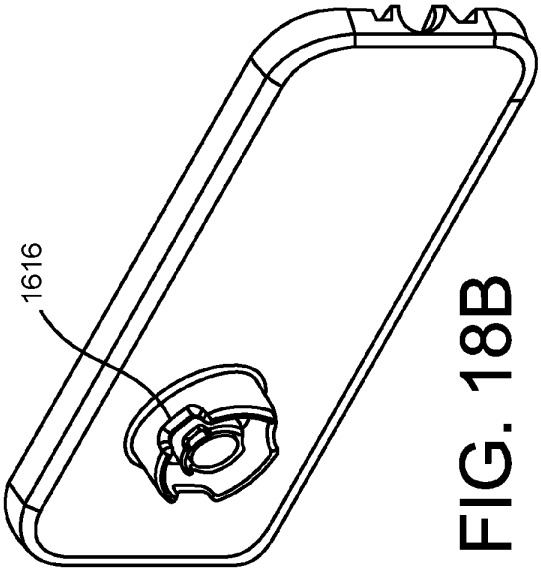


FIG. 18B

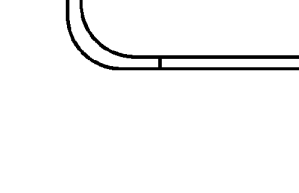


FIG. 18C

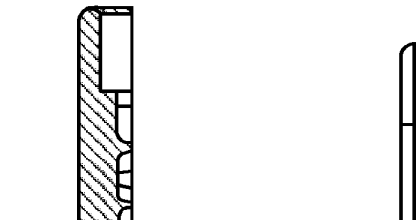


FIG. 18F

FIG. 18D

FIG. 18E

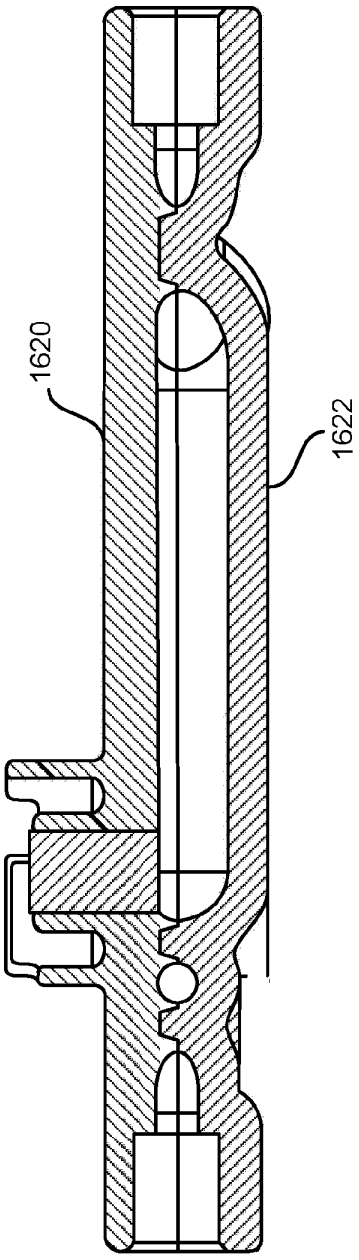


FIG. 19A

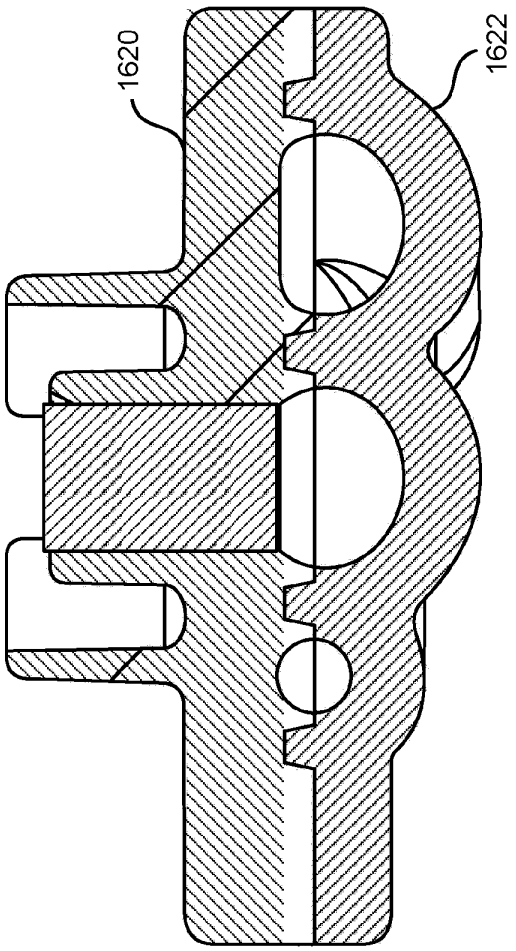


FIG. 19B

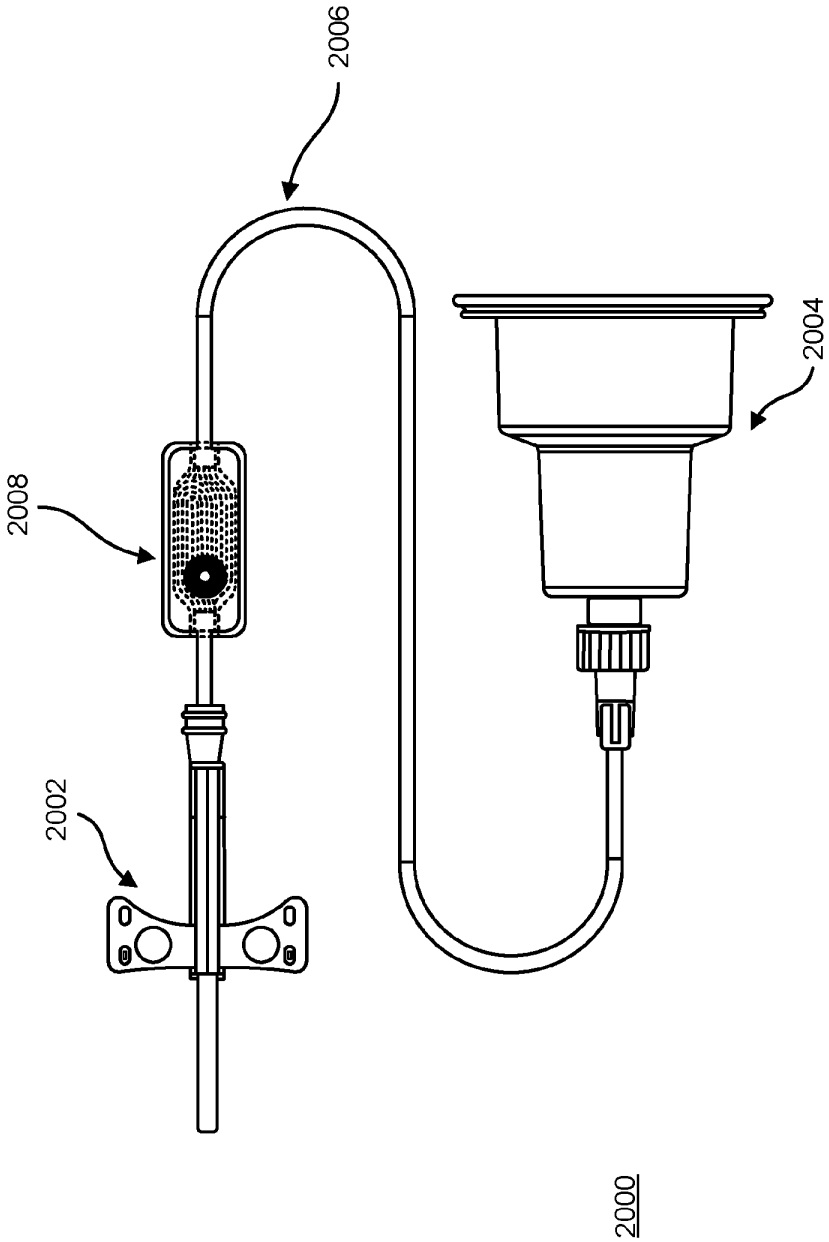


FIG. 20

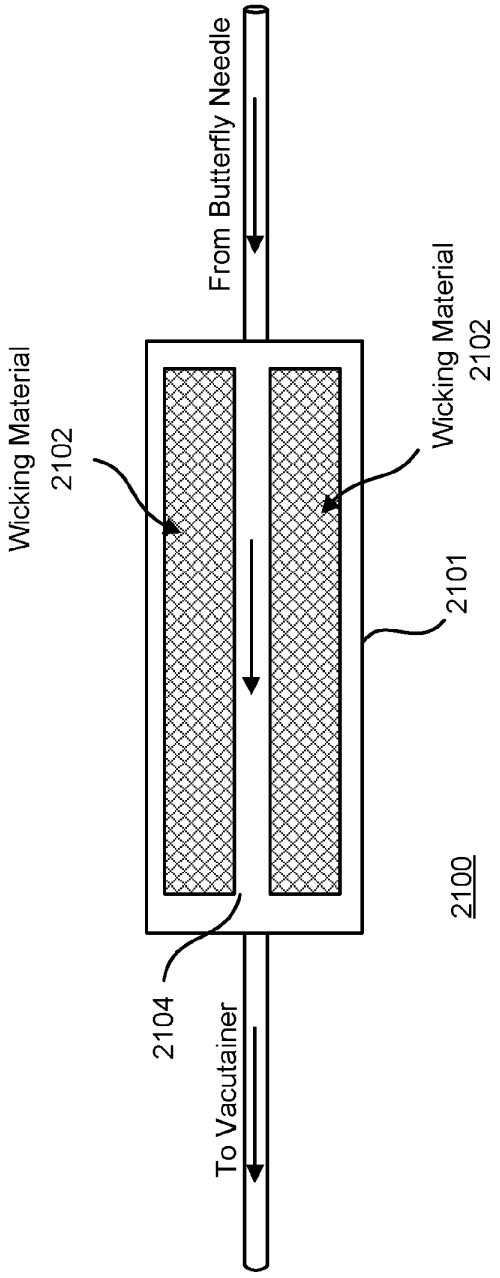

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

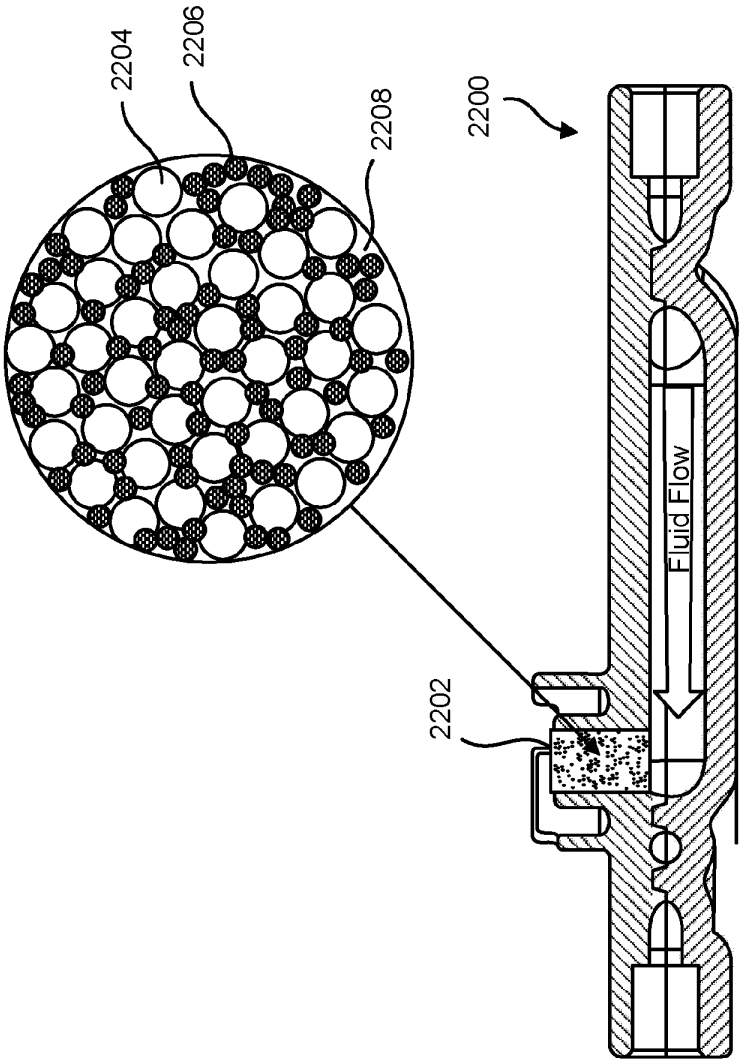


FIG. 22A

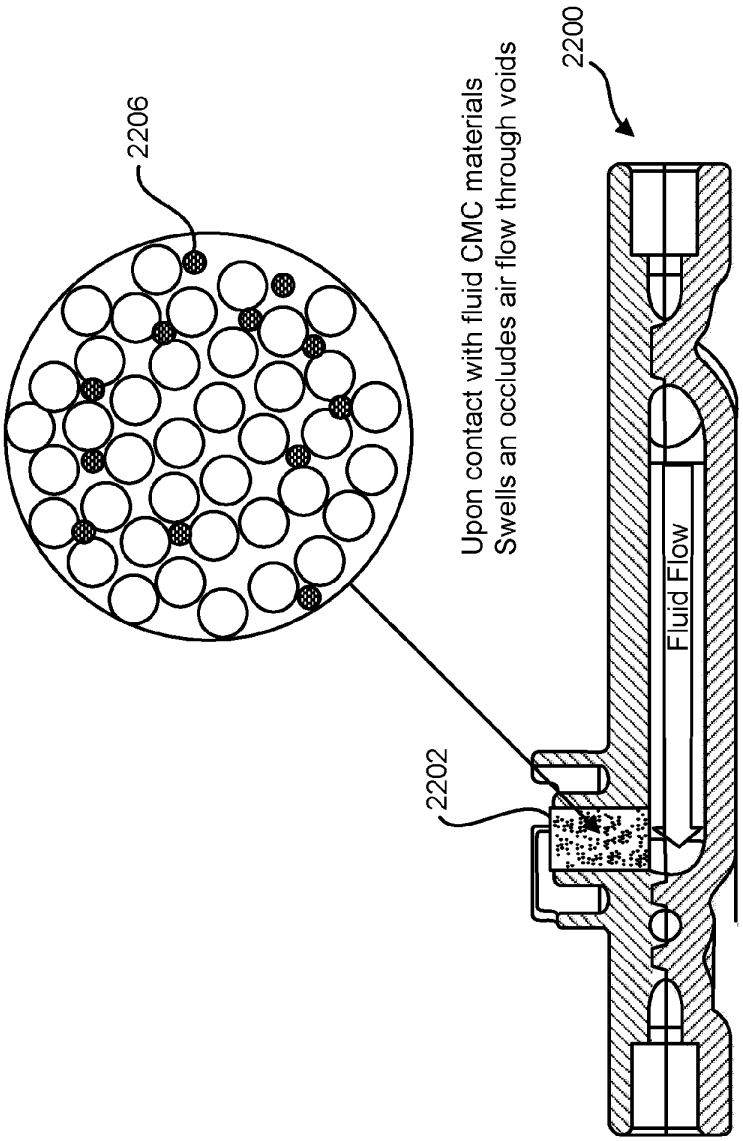

2206
2200
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
Fluid Flow
2202

FIG. 22B

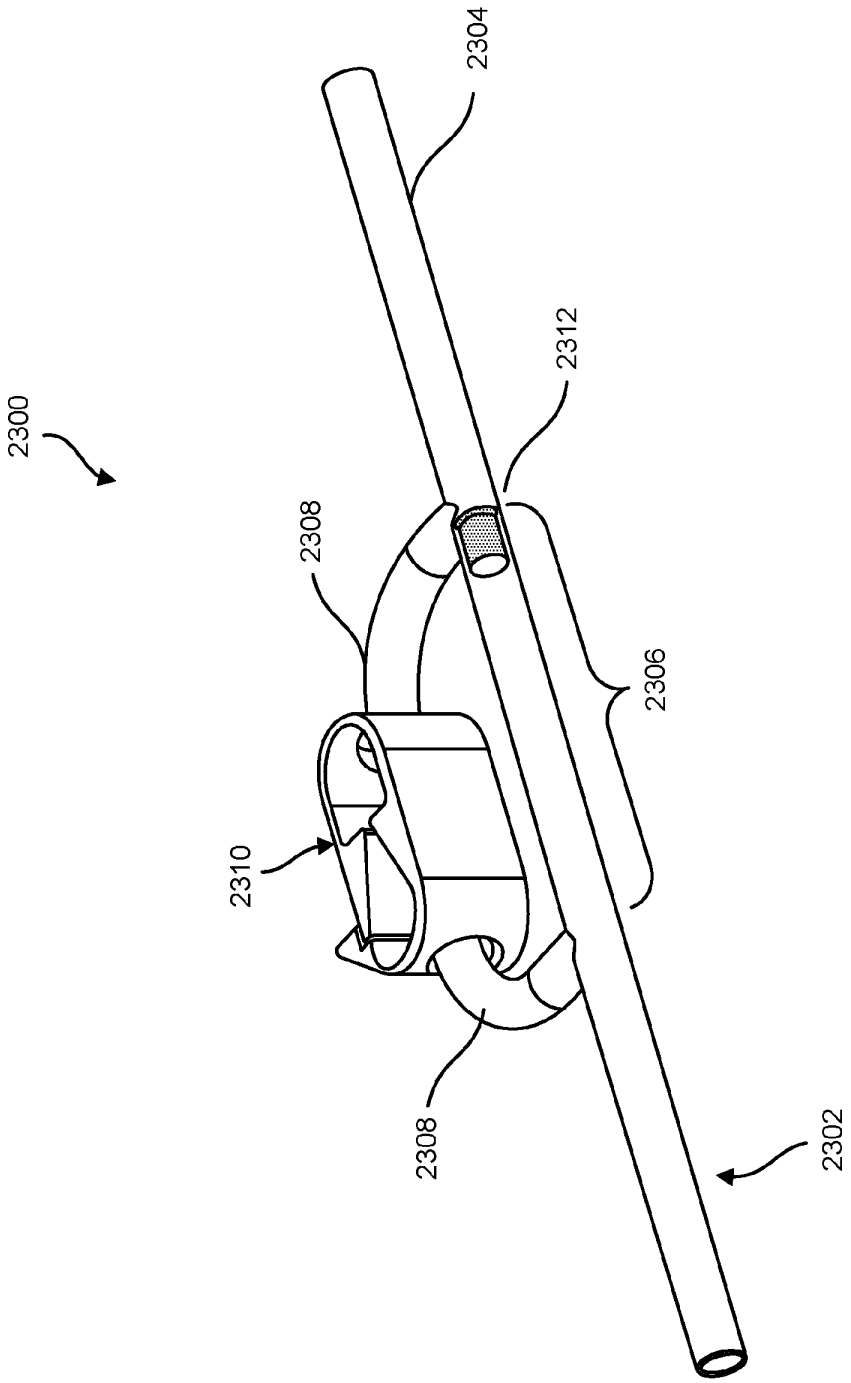


FIG. 23A

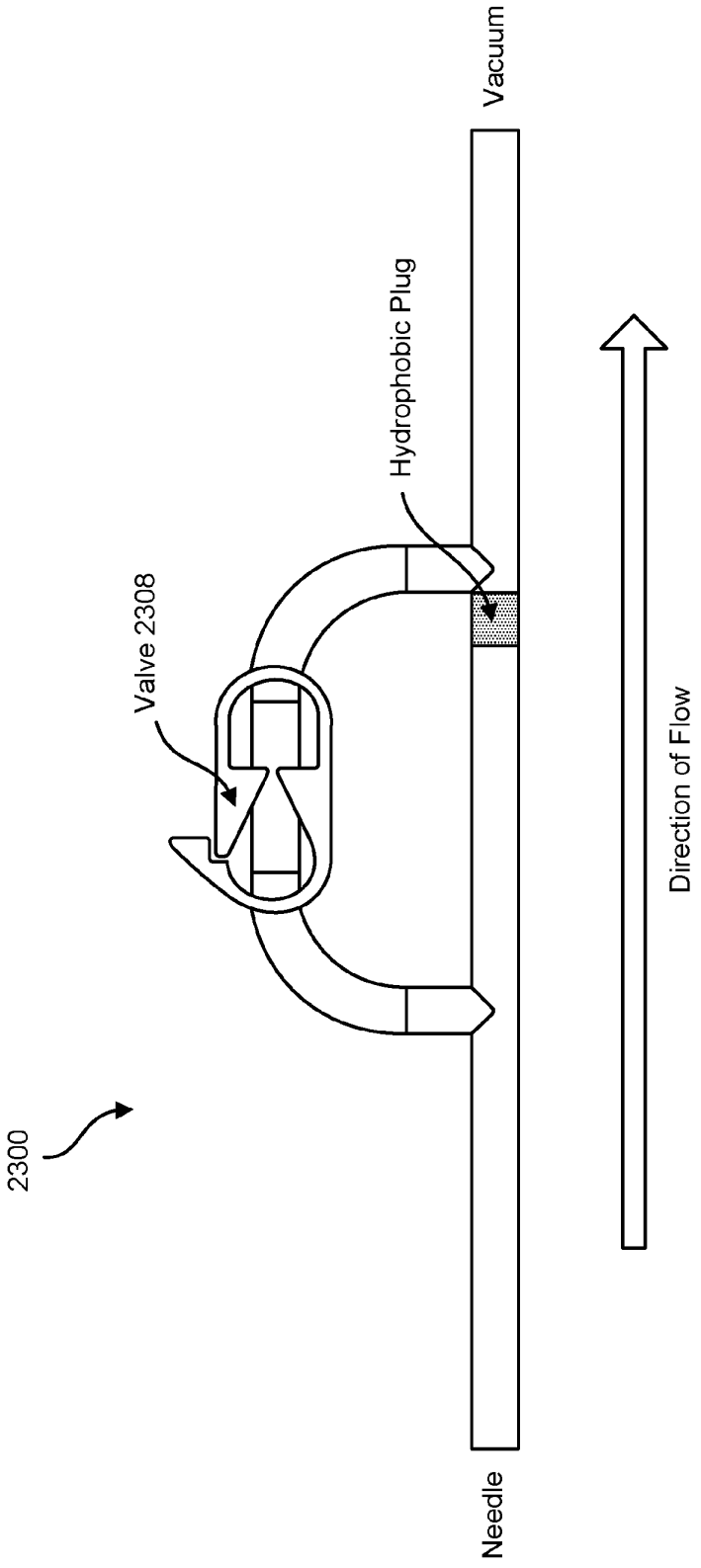

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

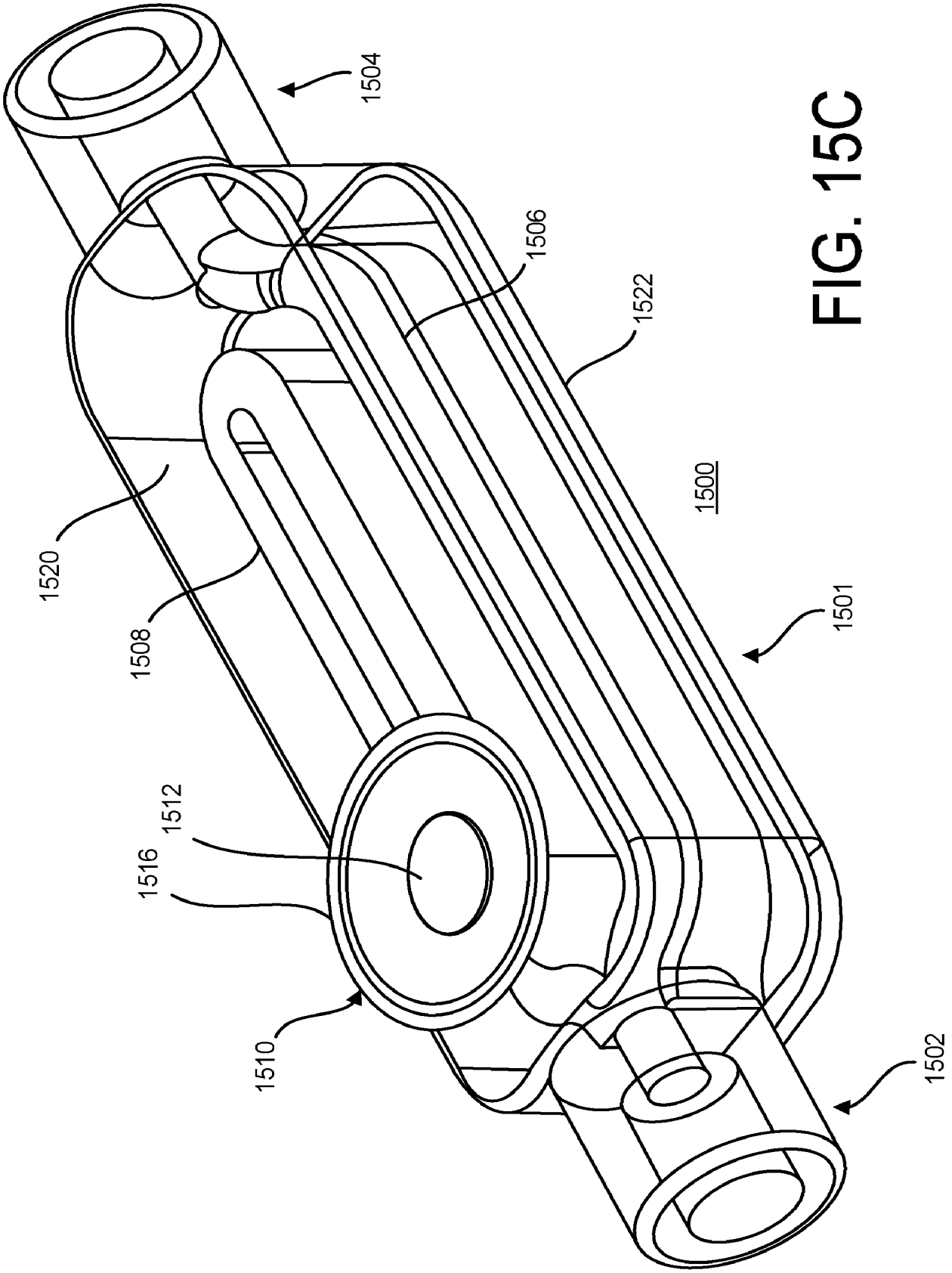


FIG. 15C

Espacenet

Bibliographic data: WO9605875 (A1) — 1996-02-29

CLOSED SYSTEM BLOOD SAMPLING DEVICE

Inventor(s): DESECKI VINCENT C; BROWNE GLENNIE ± (DESECKI, VINCENT, C, ; BROWNE, GLENNIE)

Applicant(s): BAXTER INT [US] ± (BAXTER INTERNATIONAL INC)

Classification: **- international:** ***A61B5/15;*** (IPC1-7): A61M5/00
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150259 (EP, US); A61B5/150992 (EP, US); A61B5/155 (EP, US)**

Application number: WO1995US10702 19950822 Global Dossier

Priority number(s): US19940296207 19940825

Also published as: ATE208640 (T1) AU3412795 (A) AU686450 (B2) CA2173331 (A1) DE69523887 (T2) more

Abstract of 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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International Bu

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(71) Applicant: BAXTER INTERNATIONAL INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).

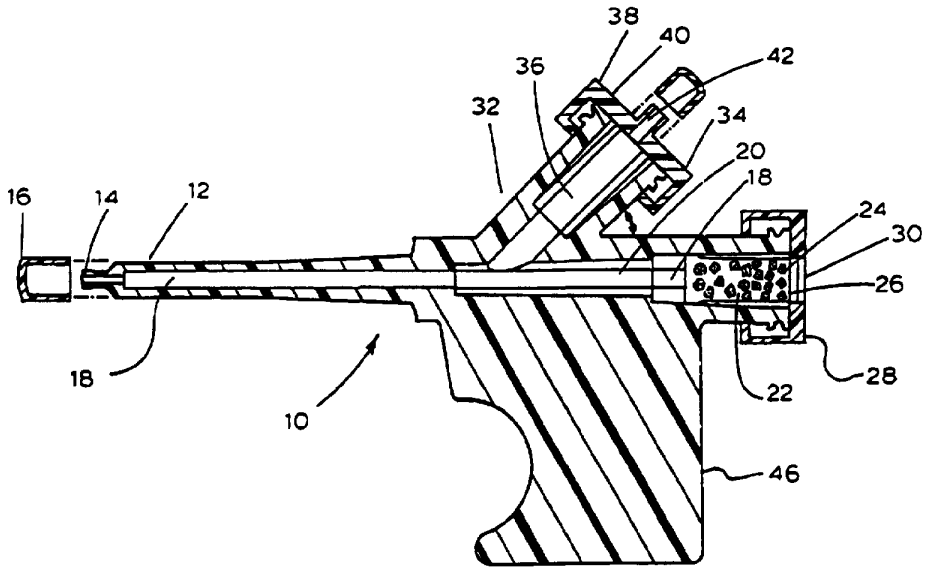
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(74) Agents: NICHOLS, Jeffrey, C. et al.; One Baxter Parkway, Deerfield, IL 60015 (US).

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(57) Abstract

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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GA	Gabon				

CLOSED SYSTEM BLOOD SAMPLING DEVICE

FIELD OF THE INVENTION

The invention relates to closed system blood sampling devices.

BACKGROUND OF THE INVENTION

Arterial blood gas sampling is a standard procedure often used to help assess respiratory function in the critically ill. In some cases, samples can be drawn as many as 20 times a day. For the typical neonatal patient weighing 1000 grams and having approximately 85 cc of total body fluid capacity, the volume of blood samples becomes a critical factor.

A technique called the 3 drop method is gaining substantial clinical acceptance in neonatal units across the country. This method calls for inserting a blunt hypodermic needle as far as possible into a standard sleeve stoppered T-Connector. Three drops of blood estimated to be approximately .06 cc are allowed to drip onto a gauge pad, thereby clearing the cannula of heparinized or non-circulating blood while providing a fresh arterial sample to the surface. 3 more drops are then collected in a micro container followed by cannula withdrawal. Blood cannula contents within the cannula lumen and the previously collected micro container sample are then aspirated into a tuberculin type syringe for transport to the blood lab for testing. A flush of the T-Connector to eliminate residual blood then ensues. This procedure provides the ability to withdraw a controlled blood volume; .06 cc as necessary

discard and .12 cc to perhaps .20 cc for actual blood gas testing.

Several opportunities for procedural improvement exist. One challenge is the open environment method of collection which could foster blood contamination and/or the spread of infectious diseases. Secondarily, the collection process in regard to volume accuracy is difficult to control and highly sensitive to variations in clinician technique, catheter positioning and arterial pressure. If a device can be designed for closed system collection which could also insure consistency of sample volume time after time, treatment of neonatal patients where blood volume levels are critical, accuracy improvements could be a major clinical benefit.

THE DRAWINGS

Fig. 1 is a horizontal cut away side view showing the closed system blood sampling device of the invention.

Fig. 2 is a vertical, partial schematic view showing the closed system blood sampling device connected to an injection site which, in turn, is fitted into a venipuncture device used to withdraw arterial blood.

In the drawings, like parts have like numbers.

THE INVENTION

The invention is a closed system blood sampling device comprising a bifurcated capillary tube which has a first branch having a cannula shaped end for withdrawing and conveying blood to a communicating blood collection zone. The blood

collection zone is for storing a quantity of withdrawn blood. It also feeds an initial fraction of withdrawn blood to a communicating blood disposal chamber which has an air permeable liquid sealed end.

The second branch of the bifurcated capillary tube 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.

In preferred embodiments the closed system blood sampling device the cannula shaped end is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and the blood disposal chamber contains a porous blood adsorbent. The second branch has an interior angle not greater than 90 degrees and preferably the interior angle is 60 degrees. It is also desirable that the cannula shaped end be tapered so that it snugly fits into the preferred injection sites more fully described hereafter.

Preferably, the closed system blood sampling device is removed from the injection site before the blood sample is withdrawn therefrom by means such as a tuberculum syringe or aspirated directly into a blood gas analyzer.

While the closed blood sampling device is particularly suited for obtaining neonatal blood samples it is readily adapted to obtain samples from a variety of patient types.

DETAILED DESCRIPTION OF THE INVENTION

In Fig. 1 the closed system blood sampling device is designated generally by the numeral 10. It is preferably constructed of a clear chemically inert non-toxic plastic such as polycarbonate. It comprises a blood withdrawal cannula shaped end 12. The cannula tip 14 is blunt and necked down to prevent injection site from blood flash back during arterial sampling. To maintain sterility the cannula tip is fitted with a removable cap 16 which is removed just before the blood sampling device is to be used.

Fig. 1 shows the cannula shaped end 12 to be tapered. This particular configuration was selected so that the cannula may engage and generally mate with a particular injection site, the details of which will be more fully described hereafter. The interior bore 18 of the cannula shaped end is dimensioned to allow withdrawn blood to move along the bore by means of capillary action driven by normally positive arterial blood pressure.

The interior capillary bore 18 connects with and continues into a larger outer diameter lumen 20. The continuous bore 18 of the cannula 12 and the lumen 20 comprise a blood collection zone. Bore 18 as it exits the lumen 20 empties into blood disposal chamber 22. In a preferred embodiment of the invention, blood disposal chamber 22 contains a blood retaining means such as adsorbing material 24 which may be rayon or cellulosic wadding. The open end 26 of the blood disposal

chamber 22 is closed with a cap 28 that has its top fitted with a liquid tight, air permeable hydrophobic membrane 30 which allows air to be evacuated from the blood sampling device 10 of the invention. A suitable membrane material is sheet polytetrafloroethylene having a thickness of about 0.8 microns.

Fitted to the lumen 20, and in fluid communication therewith, is the second branch or port 32. It is positioned so as to have an interior angle 34 not exceeding 90 degrees. The interior angle is preferably about 60 degrees. The bore 36 connects with and corresponds in dimension with bore 18. Port 32 terminates and is sealed by adapter cap 38 whose top 40 is fitted with a capillary luer 42. The capillary luer is protected from contamination by means of protective cap 44 which is removed just prior to blood being withdrawn from the closed blood sampling device. The port 32 and its bore 36 form a part of the blood collection zone previously described. For convenience of use, the closed blood sampling device is fitted with pistol grip handle 46.

The blood collection zone has a larger liquid capacity than the liquid capacity of the blood disposal chamber. If the closed blood sampling device described were to be used in neonatal blood sampling, the liquid capacity of the blood collection zone might be 0.12 cc and the liquid capacity of the blood disposal chamber 22 would be about 0.06 cc.

The use of the closed blood sampling device of the invention to withdraw and sample blood is illustrated in Fig. 2 which shows artery 48 in communication with a venipuncture

device 50 which was inserted through subcutaneous tissue 52. The neck 54 of the venipuncture device 50 is adapted to receive an injection site 56. While conventional injection sites may be used as such or adapted to be used in the practice of the invention, it is preferred that the injection site be of the type having a resilient resealable septum which is preferably pre-slit. An injection site of this type is available from Baxter Healthcare Corporation and is a Neonatal T-Connector Luer sold under the brand name, InterLink, a registered trademark of Baxter Healthcare Corporation.

Such pre-slit, resilient, resealable injection sites and their method of fabrication are described in U.S. 5,188,620 the disclosure of which is incorporated herein by reference. The pre-slit resilient resealable injection sites described in this patent are designed to receive blunt cannulas. Another injection site related to the injection sites detailed in U.S. 5,188,620 is described in U.S. 5,300,034. This patent also details numerous publications and references which describe the preferred injection sites used in the practice of this invention. This patent and the publications listed therein also are incorporated herein by reference.

The injection site 56 is fitted with T-connector 58 which, in turn, is fitted with microbore tubing which, through female luer 62, is connected to IV line 64. The distal end 64 of the injection site 56 is connected to the neck 54 of the venipuncture device 50. The proximal end 66 of the injection site 56 is fitted with a pre-slit resilient resealing septum 68 adapted to receive

the blood withdrawal cannula 12 which is dimensioned to fit snugly into the injection site. Inserted into the second branch or port 32 is a conventional syringe 70, such as a tuberculum blood draw syringe, or an arterial blood gas loss of resistance syringe.

The device's cannula 12 would be inserted through the septum 68 of the injection site 56 and positioned so that the tip 14 of the cannula 12 was fully inserted into the injection site adjacent to the venipuncture device. In doing so, the residual volume of the actual T-Housing would be eliminated as a measurable factor in blood draw volume. Arterial pressure would cause blood flow to enter and flow up the device via capillary action. As blood moved up the hydrophobic membrane 30 of the device, air would escape via the upstream hydrophobic membrane 30. Original blood first present in the catheter would be pushed beyond the luer bifurcation for retention in the device and eventual disposal. The device would be withdrawn from the T-Connector as soon as visual confirmation of the blood filled lumen was made. The vented removal cap 44 would be removed from the bifurcated luer 42 and replaced by the syringe 70 which would be aspirated to remove the arterial blood sample. Residual blood volume upstream of the bifurcation would remain in the device for subsequent disposal.

WE CLAIM:

1. A closed system blood sampling device comprising a bifurcated capillary tube comprising:

a. a first branch having a cannula shaped end for withdrawing and conveying blood to a communicating;

b. blood collection zone for storing a quantity of withdrawn blood and feeding an initial fraction of withdrawn blood to a communicating;

c. blood disposal chamber having an air permeable liquid sealed end; and,

d. a second branch connected to and in fluid communication with the blood collection zone which terminates in an opening adapted to receive a blood withdrawal device.

2. The closed system blood sampling device of Claim 1 where the cannula shaped end is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and the blood disposal chamber contains a porous blood adsorbent.

3. The closed system blood sampling device of Claim 1 where the second branch has an interior angle not greater than 90 degrees.

4. The closed system blood sampling device of Claim 3 where the second branch has an angle of about 60 degrees.

5. The closed system blood sampling device of Claim 2 where the cannula shaped end is tapered.

6. The closed system blood sampling device of Claim 2 where the blunt cannula shaped end is adapted to be received by a injection site which contains a resilient resealing means.

7. The closed system blood sampling device of Claim 6 where the injection site is a pre-slit injection site.

8. The closed system blood sampling device of Claim 2 where the blood collection zone has a volume greater than the volume of the blood disposal chamber.

9. A method of sampling blood from a patient having an artery fitted with a venipuncture device which is attached to an injection site containing the closed blood sampling device of Claim 1 which comprises the steps of:

a. withdrawing blood through the cannula shaped end of the closed blood sampling device thereby sequentially filling the blood disposal chamber and then the blood collection zone;

b. withdrawing through the opening in the second branch the blood contained in the blood collection zone for subsequent processing; and, then,

c. discarding the closed system blood sampling device

10. The method of Claim 9 where the cannula is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and contains a porous blood adsorbent.

11. The method of Claim 9 where the second branch has an interior angle not greater than 90 degrees.

12. The method Claim 11 where the second branch has an angle of about 60 degrees.

13. The method of Claim 10 where the cannula shaped end is tapered.

14. The method of Claim 10 where the blunt cannula shaped end is adapted to be received by a injection site which contains a resilient resealing means.

15. The method of Claim 14 where the injection site is a pre-slit injection site.

16. The method of Claim 10 where the blood collection zone has a volume greater than the volume of the blood disposal chamber.

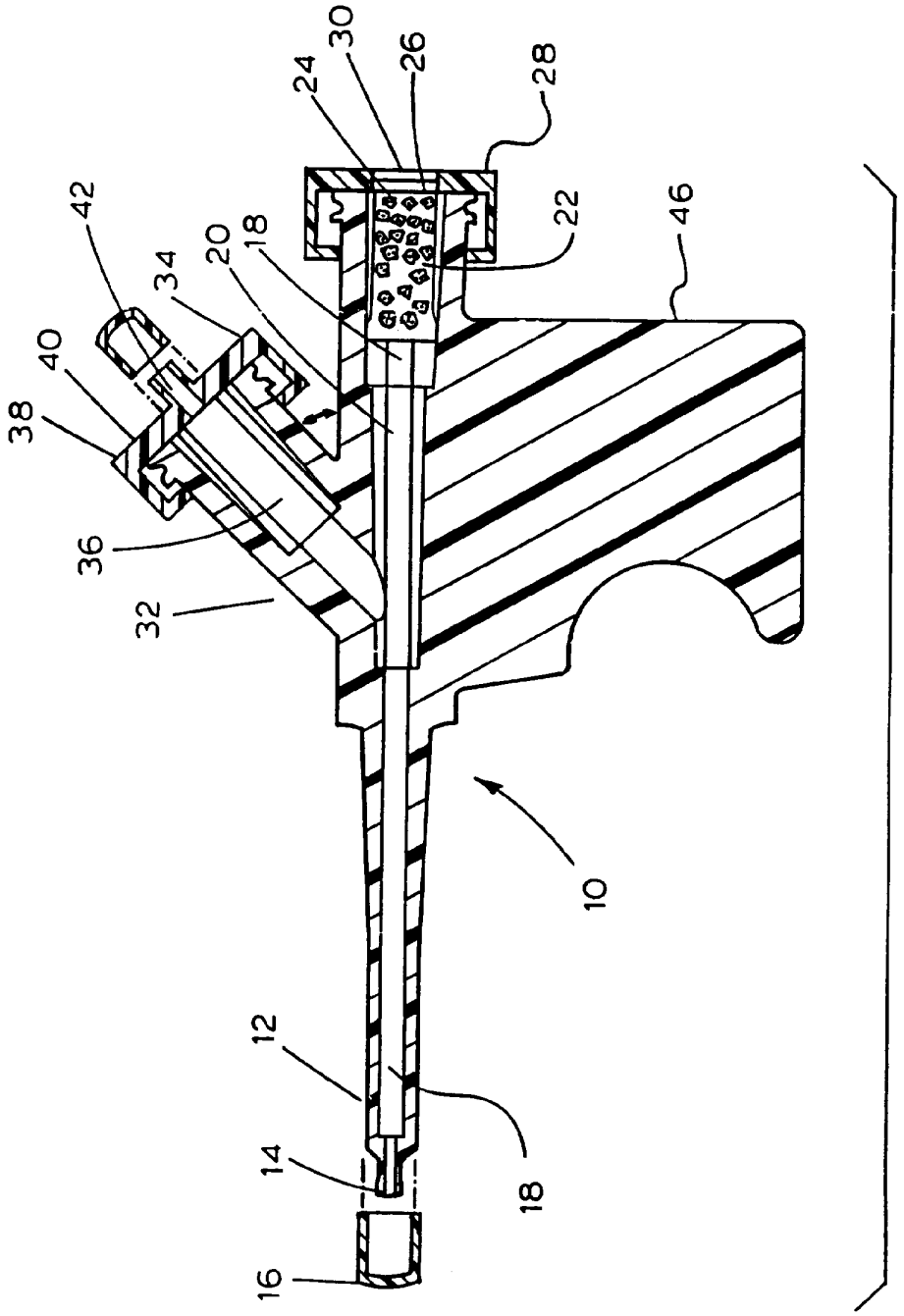


FIG. 1

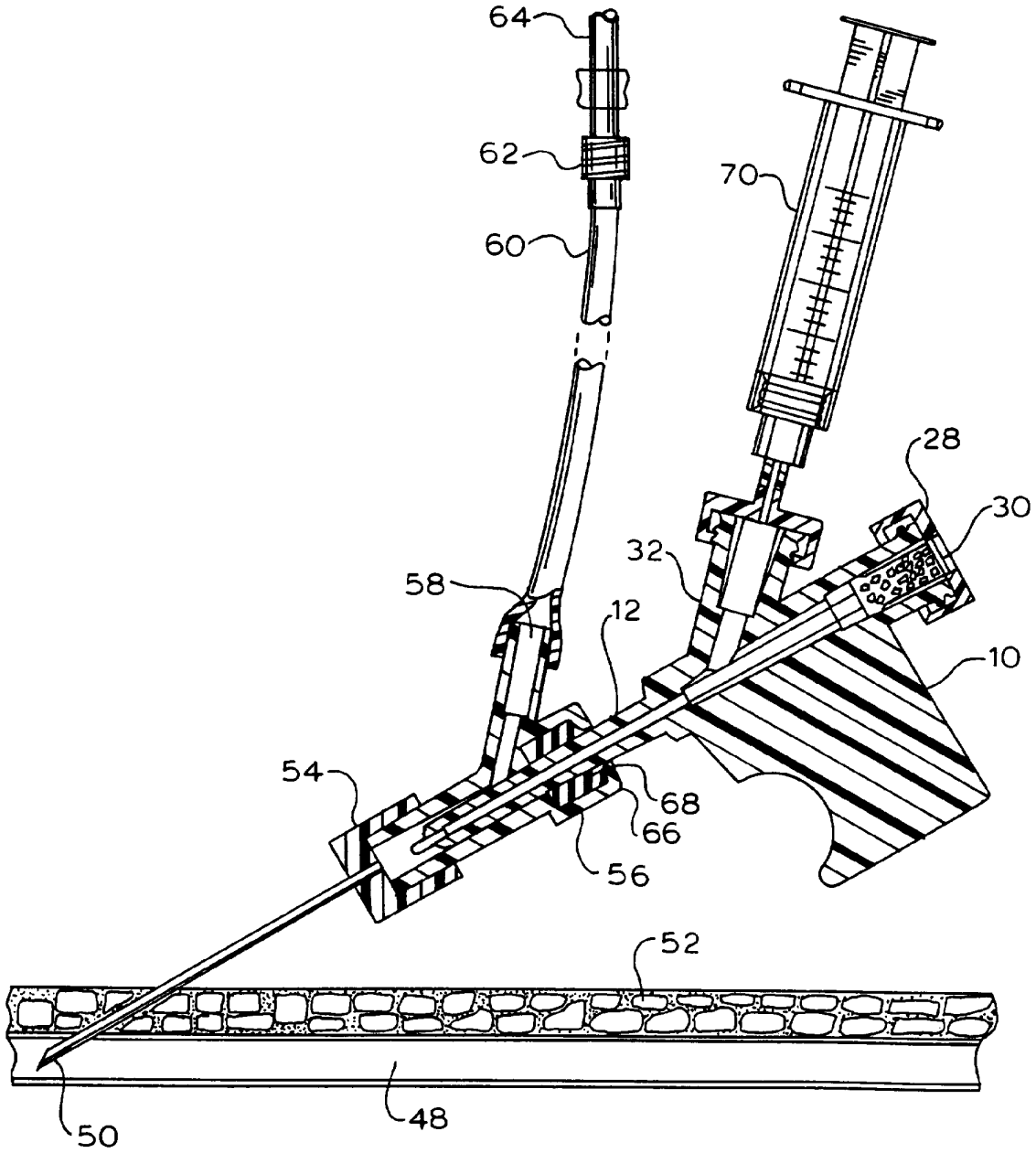


FIG. 2

SUBSTITUTE SHEET (RULE 26)

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
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Date of the actual completion of the international search 08 DECEMBER 1995	Date of mailing of the international search report 04 JAN 1996
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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.

Check for updates



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**

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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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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

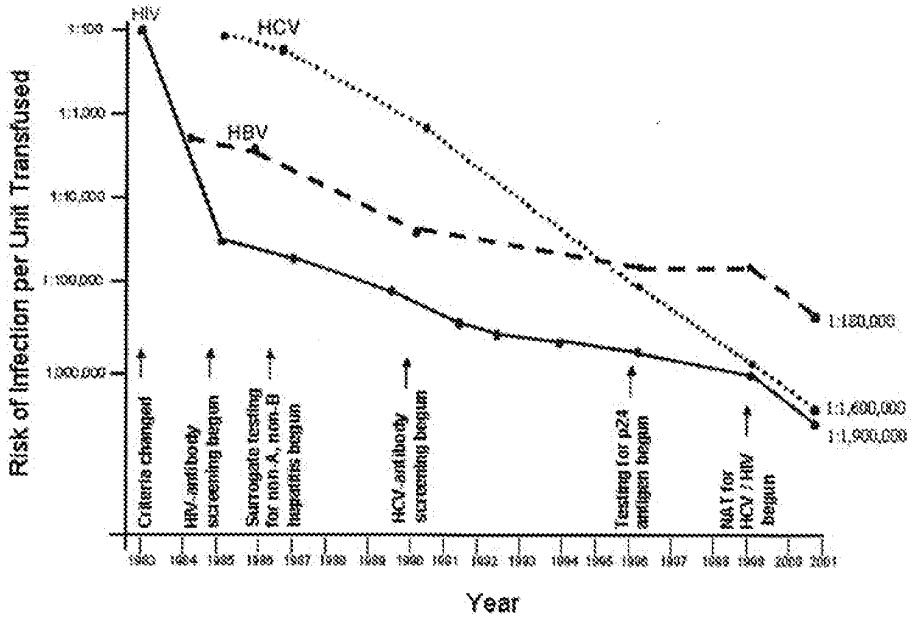


Figure 1. New test implementation and declining risk of viral infections from transfusion.[20]

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,

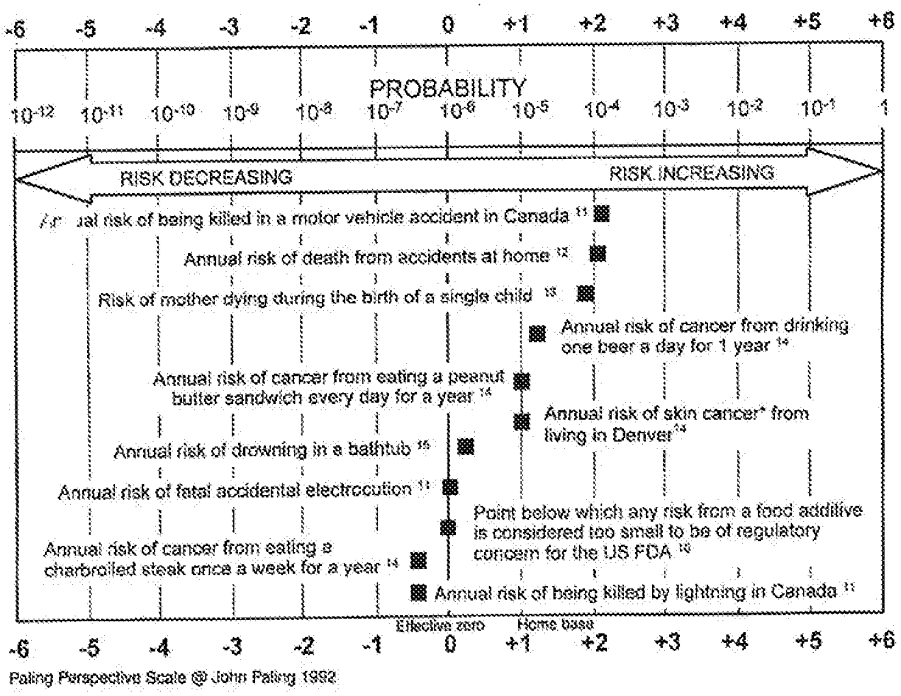


Figure 2. Risks with which the public is comfortable.

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]

Reprinted with permission from Lee DH, Paling JE, Blajchman MA. A new tool for communicating transfusion risk information. Transfusion. 1998;38:184-188.

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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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Updated Review of Blood Culture Contamination

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INTRODUCTION

The blood culture represents a critical tool for the health care professional as a means of detecting the dangerous presence of living organisms in the bloodstream. A positive blood culture can suggest a definitive diagnosis, enable the targeting of therapy against the specific organism(s) in question, and provide prognostic value (22). Like any test, however, false-positive results can limit the utility of this important tool. In blood cultures, false positives arise due to contamination, which occurs when organisms that are not actually present in a blood sample are grown in culture. Contaminated cultures have been recognized as a troublesome issue for decades and continue to be a source of frustration for clinical and laboratory personnel alike. Faced with a positive blood culture result, clinicians must determine whether the organism represents a clinically significant infection associated with great risk of morbidity and mortality or a false-positive result of no clinical consequence. Further complicating the issue in recent years is the increasing use of central venous catheters (CVC) and other indwelling vascular access devices (5, 90). Interpretation of culture results for patients with these devices in place is particularly challenging because while these individuals are at increased risk for bacteremia, such results may also indicate culture contamination or colonization of the line. The clinical uncertainty associated with the interpretation of ambiguous culture results is costly, as has been demonstrated in a number of studies of both adult and pediatric patients (13, 115, 125, 138).

Prevalence and Significance

While target rates for contamination have been set at 2 to 3% (30, 131), actual rates seem to vary widely between institutions, from as little as 0.6% to over 6% (13, 64, 67, 82, 89, 112, 113, 125, 131, 150). The College of American Pathologists (CAP) Q-Probes quality improvement study involved the prospective examination of 497,134 blood culture specimens from 640 U.S. health care institutions (113). While the median adult inpatient contamination rate was 2.5%, some organizations had a rate of less than 1.0%, while for other organizations, more than 5.0% of their blood cultures were contaminated. More recently, the CAP Q-Tracks study found an overall median contamination rate of 2.92% for data collected from 356 institutions from 1999 to 2003. There is also some evidence to suggest that in recent decades, these rates have been on the increase (150), although the Q-Tracks study found no increase over the 4-year time frame for their data. The suggested reasons for this increase include technological advances that allow the detection of smaller quantities of living microorganisms in the blood, the increased use of indwelling catheters for the

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TABLE 1. Addressing the challenge of blood culture contamination

Approach	Rationale
Detecting contaminants	Given that contamination can likely never be eliminated, having reliable factors to help identify true positives vs false positives is critical for patient management and population-based surveillance
Prevention	Reducing contamination rates will improve the specificity of the blood culture and result in a higher PPV, resulting in a significantly more useful test
Supporting optimal use of blood cultures	Reducing the use of blood cultures in patients with a very low likelihood of bacteremia will result in a higher PPV and reduced costs associated with contamination; pretest probability of bacteremia can be estimated using population-based studies of disease prevalence or clinical prediction rules

provision of therapy, and changes in phlebotomy practices to minimize the risk of needlestick injuries (151).

The financial impact of blood culture contamination has been described in a number of studies (13, 35, 125, 145). Bates et al. found that contaminant results, compared with true-negative results, were independently associated with increased subsequent laboratory charges (20% increase) and intravenous antibiotic charges (39% increase) (13). In a subsequent prospective study focused on blood culture contamination caused by coagulase-negative staphylococci, Souvenir et al. reported that almost half of the patients with a false-positive result were treated with antibiotics, often with vancomycin (125). According to their estimates, the additional costs associated with this unnecessary treatment were approximately $1,000 per patient. Other investigators focused on the consequences of contaminated cultures in pediatric populations (115, 138). Segal and Chamberlain estimated that the additional charges associated with contaminated cultures in 85 children aged 3 to 36 months who were evaluated in an emergency department and believed to be at risk for occult bacteremia totaled $78,904, the majority of which was due to subsequent hospital admission (115). In a retrospective study of 9,959 blood cultures performed in children aged 1 month to 18 years, Thuler et al. found that 26% of children with false-positive cultures who were initially evaluated as outpatients were subsequently admitted to the hospital on the basis of initial culture results (138). Measured in costs or charges, there is compelling evidence that the financial impact of blood culture contamination is significant.

Given these excessive costs, how can we address the problem of contaminated blood cultures? There has been significant effort in recent years to attempt to identify ways of preventing contamination in the first place. In addition, investigators have studied factors that help distinguish true positives from false positives. Since a major consequence of contaminated cultures is a lower positive predictive value (PPV) for the blood culture test, and the pretest probability of bacteremia is a key determinant of PPV (6), there have been increasing endeavors to discourage the utilization of blood cultures in patients at very low risk for this disease. For example, clinical bacteremia prediction rules have been developed and studied to help guide clinical decision-making in the use and interpretation of blood cultures and the initiation of empirical antibiotic therapy. In addition, population-based studies of bacteremia prevalence for specific patient groups have been performed in the past decade. Such information, while not completely individualized to a given patient, provides a rough estimate of pretest probability for bacteremia. In summary, the challenge of blood culture contamination can be addressed by at least three different avenues of approach, as summarized in Table 1.

In the last decade, significant progress has been made in each of these three broad areas. New evidence for measures to reduce contamination rates is emerging, and we are becoming better able to ascertain bacteremia risk at both the individual and patient population levels. In addition, much has been learned about how to accurately distinguish between true bacteremia and contamination. In this review, we provide an updated analysis of this important, complex topic with special attention paid to each of these areas. We also highlight specific challenges associated with blood culture contamination in the pediatric population, although an in-depth analysis is beyond the scope of our review.

DETECTION OF CONTAMINATED BLOOD CULTURES

Despite its limitations, the blood culture remains the "gold standard" for the detection of bacteremia. An accurate interpretation of culture results is critical not only from the perspective of individual patient care but also from the standpoint of hospital epidemiology and public health. The tracking and reporting of nosocomial infections and monitoring of bloodstream infection rates are both essential infection control activities that depend heavily on the accurate differentiation of contamination from true bacteremia. Reliably making this determination continues to be very challenging for clinicians, epidemiologists, and microbiologists. In recent decades, multiple approaches have been studied, advocated, and utilized for this purpose. Clues that may help to differentiate contamination from bacteremia include identity of the organism, number of positive culture sets, number of positive bottles within a set, time to growth, quantity of growth, clinical and laboratory data, source of culture, and automated classification using information technology.

Identity of Organism

Often, the identity of the microbe that grows from a blood culture is a very helpful clue that the results may or may not represent contamination. The CAP Q-Probes study described above found that the most important indicator when interpreting blood culture results was the identity of the organism, which was cited as very important to 79% of laboratories (113). Bates et al. found that the identity of the organism was the most important predictor in a predictive model for differenti-

TABLE 2. False-positive rates for organisms that frequently represent contamination

Organism(s)	Source			
	1,585 blood culture-positive episodes from 3 U.S. hospitals[a]		497,134 blood cultures from 640 U.S. institutions[b]	
	% of all positive cultures (n = 1,585)	Contamination rate (%)	% of all positive cultures	Contamination rate (%)
Coagulase-negative staphylococci	44.3	82	Not reported	62–63
Corynebacterium spp. (other than *C. jeikieum*)	33.4	96	Not reported	68–78
Bacillus spp.	0.8	91.7	Not reported	68–70 (other than *B. anthracis*)
Propionibacterium acnes	3.0	100	Not reported	84–85
Viridans group streptococci	4.5	49.3	Not reported	32–33
Clostridium perfringens	0.8	76.9	Not reported	Not reported

[a] Data are from reference 155.
[b] Data are from reference 113.

ating contaminated blood culture results from results indicating bacteremia (14).

Weinstein et al.'s study of 843 episodes of positive blood cultures in adult inpatients from three hospitals around the country suggested that certain organisms should almost always be thought to represent true bacteremia or fungemia when isolated from a blood culture (155). These organisms included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and other *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Candida albicans*. Furthermore, Weinstein's personal observation is that the following organisms almost always represent a true infection when isolated from a blood culture: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, members of the *Bacteroides fragilis* group, all *Candida* species, and *Cryptococcus neoformans* (151).

Along the same vein, certain organisms have been found to represent contamination in a significant proportion of cases. These organisms include coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species other than *Bacillus anthracis*, *Propionibacterium acnes*, *Micrococcus* species, viridans group streptococci, enterococci, and *Clostridium perfringens* (151, 155). However, it is crucial to recognize that each of these organisms can also represent true bacteremias with devastating consequences, particularly if untreated due to misinterpretation as contaminants. Of these organisms, the ones that are thought to represent true bacteremia only rarely are *Corynebacterium* species, *Bacillus* species other than *B. anthracis*, and *Propionibacterium acnes* (151, 155). In addition to the work of Weinstein et al., the CAP Q-Probes study provided valuable information on contamination rates for organisms that frequently represent contamination (Table 2).

Despite the high likelihood that certain organisms usually represent contaminants when isolated from blood cultures, determining the likelihood of true bacteremia can be challenging for clinicians. Coagulase-negative staphylococci represent an important, all-too-frequent case in point. In the past, coagulase-negative staphylococci were usually believed to represent contamination when isolated from blood cultures. In fact, coagulase-negative staphylococci are the most common blood culture contaminants, typically representing 70% to 80% of all contaminated blood cultures (25, 92, 105, 113, 125).

Recently, however, studies have shown that these organisms are an increasing source of true bacteremia in patients with prosthetic devices and central venous catheters (30, 53, 105, 139, 155), although the majority of isolates of coagulase-negative staphylococci from blood cultures continue to be contaminants. Weinstein et al. found that even though only 12.4% of coagulase-negative staphylococcal isolates were clinically significant, they ranked as the third most common cause of bacteremia because of their high prevalence (155). In another study, among 81 episodes of coagulase-negative staphylococcal blood culture results, the incidence of clinically significant bacteremia was 20 (24.7%) episodes, that of indeterminate bacteremia was 10 (12.3%) episodes, and that of contamination was 59 (72.8%) episodes (125). Other studies found rates of true bacteremias ranging from 10% to 26.4% when coagulase-negative staphylococci are isolated from blood cultures (51, 125).

Similarly, other organisms can be difficult to interpret when isolated from blood cultures. One study found that enterococci were pathogens 70% of the time, whereas viridans group streptococci were pathogens 38% of the time (155). Furthermore, that same study found that *Clostridium perfringens* was a contaminant 77% of the time, whereas other *Clostridium* species were true pathogens 80% of the time. Given these data, clinicians attempting to differentiate true infections from simply contaminated blood cultures cannot rely solely on the identity of the organism.

Often, bloodstream infections involve only a single organism, prompting clinicians to sometimes conclude that a blood culture bottle that grows multiple organisms is contaminated. However, studies have found that 6% to 21% of all true bacteremias are polymicrobial, usually in patients in high-risk groups (121). Furthermore, multiple coagulase-negative species have been found to cause polyclonal coagulase-negative staphylococcal infections (42, 142, 143). Therefore, one cannot conclude that the mere presence of multiple organisms in a blood culture bottle always indicates contamination.

Number of Positive Blood Culture Sets

One proven methodology that can help differentiate blood culture contamination from true infection is the number of blood culture sets that grow organisms. The proportion of positive sets as a function of the total number of sets obtained can be a particularly useful tool (16, 69, 154, 155). If only one

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set of at least two sets grows an organism known to often cause contamination, this often represents a contaminant. For true bacteremias, multiple blood culture sets will usually grow the same organism (53, 139, 155). In fact, this indicator is one of the most frequently used tools to help differentiate contamination from bacteremia as indicated in the CAP Q-Probes study, which revealed that 77% of laboratories cited the proportion of positive blood cultures in a series of cultures as very important for interpreting blood culture results (113). In their examination of 11,167 episodes in which coagulase-negative staphylococci were isolated from blood cultures, 27.8% were interpreted as contaminants if at least two sets were positive compared to 75.2% if only one of at least two sets were positive. In 2,440 cases, only a single blood culture was available; in these cases, 66.9% of the isolates were determined to be contaminants.

When multiple cultures are obtained and return positive, the positive predictive value for true bacteremia has been shown to improve (51). In one modeling study of patients with a central vascular line and a positive culture for coagulase-negative staphylococci, the positive predictive value was 55% when one of one culture was positive, 20% when one of two cultures was positive, and only 5% when one of three cultures was positive (139). In the face of such data, it has become increasingly clear that maximizing the diagnostic utility of blood cultures requires at least two sets be performed.

Because coagulase-negative staphylococci represent contaminants more often than true infections when isolated from blood culture bottles, even when two sets are positive for this organism, it can be difficult to determine whether both sets are contaminated as opposed to representing a true infection. Souvenir et al. found that only a single set of blood cultures was positive for 35% of samples from patients with coagulase-negative staphylococcal bacteremia, whereas two or more sets were positive for 12% of the patients in the contamination category (125).

Evidence based on molecular studies also highlights the fact that multiple positive culture results may be helpful but imperfect in discerning contamination. An approach using pulsed-field gel electrophoresis (PFGE) was explored in 14 febrile neutropenic patients who had matched peripheral and catheter-drawn cultures that both grew *Staphylococcus epidermidis* (86). Of these 14 patients, 10 had identical or closely related strains, and the remaining 4 were thought to represent either mixed infection or contamination. Another study of 42 patients with at least two positive cultures for coagulase-negative staphylococci drawn within a 14-day interval found that PFGE plus arbitrary primed PCR detected the same strain in 19 (45%) cultures, suggesting that the 23 (55%) cultures that grew different strains were either contamination events or infections involving multiple strains of coagulase-negative staphylococci (117). In that study, patients with three or more positive blood cultures were significantly more likely to have same-strain bacteremia than those with only two positive cultures (11 [73%] of 15 versus 8 [30%] of 27; $P = 0.006$). A similar study that used clinical criteria to differentiate true bacteremia from contamination in 22 patients who had at least two positive cultures for coagulase-negative staphylococci found that only 1 of 41 blood cultures in bacteremic patients had an unrelated strain by PFGE, compared to 6 of 16 in contaminated samples (121). Their statistically significant findings provide further evidence that genotypic variation is more common in contaminated samples, and recurring identical strains of coagulase-negative staphylococcal are more likely to represent bacteremia.

Because molecular testing of culture isolates is not realistic in clinical practice, many clinicians use the antimicrobial susceptibility patterns to indicate whether the isolates represent identical strains (51, 58). In the aforementioned study, of the 14 patients who grew *S. epidermidis* from matching sets, 13 had identical susceptibility patterns, whereas 10 had identical or closely related PFGE patterns (as defined by $\leq$3 band differences), thereby indicating that three of the four patients who did not match on the basis of PFGE would have been misclassified as identical isolates if only antimicrobial susceptibility patterns had been used (86). Another study of paired blood culture isolates of identical species with identical MICs found that 9 to 18% of the isolates were actually distinctly different strains (121). Khatib et al. found that the antibiograms of all 21 episodes of true bacteremia (as indicated by molecularly identical coagulase-negative staphylococcal strains in multiple sets) were identical and that 7 (15.9%) of 44 unrelated pairs of coagulase-negative staphylococci had identical antibiograms (57). In that study, identical antibiograms, determined by using the individual MICs of 10 antibiotics, were highly predictive of strain relatedness, with a sensitivity of 100% and a specificity of 83.7%, and a fourfold difference in a single MIC was always predictive of strain variation even if the difference did not change the susceptibility category for the strain. Moreover, the specificity of the antibiogram was lower when nonquantitative methods were used, and the level of specificity correlated with the number of antibiotics compared.

Clearly, speciating any coagulase-negative staphylococci that grow from multiple blood cultures can help determine the likelihood of contamination, because if the species from one set differs from the species from the other set, the culture results indicate either mixed infection or contamination (153). However, speciation of coagulase-negative staphylococci is not always automatically performed by clinical microbiology laboratories. Indeed, one study found that only 20 (59%) of 34 hospitals surveyed routinely identified coagulase-negative staphylococci to the species level (105).

For these reasons, it has been recommended that multiple sets of blood cultures be obtained to work up potential bloodstream infections. The presence of only one positive set among at least two sets drawn at the same time may be indicative of culture contamination. Additionally, the presence of one positive set over several cultures drawn over a period of time may also indicate contamination, although it may conversely indicate transient bacteremia. In order to differentiate transient bacteremia from contamination, it has been recommended that at least two sets of cultures be obtained at the same time (6, 30, 53, 71, 102, 107, 118, 152).

However, obtaining at least two sets is not always done (93, 105, 111). In a study of 333 small public and private hospitals (median occupancy of 57), the median rate of obtaining only a solitary blood culture was 12.7%, and the rates for the 10th and 90th percentiles were 42.5% and 3.4%, respectively (93). The same study found that solitary blood culture rates were lower for institutions with phlebotomists, with institutional policies

that required at least two sets, with notification of ordering clinicians when only one set was ordered, and with quality control programs aimed at monitoring solitary blood cultures. In two broader Q-Probes studies described by Schifman et al., significant variation in the utilization of solitary blood cultures was also found. In 289,572 blood culture sets from 909 hospitals, those authors found median proportions of solitary blood cultures of 10.1% and 12.1% among adult inpatients, 25.4% and 33.3% among adult outpatients, and 89.0% and 100% among pediatric/infant patients in the two studies, respectively (111).

Number of Positive Blood Culture Bottles within a Blood Culture Set

Another method that has been used by health care workers to differentiate contaminated blood cultures from cultures that represent bacteremia is the number of blood culture bottles that exhibit growth within a given blood culture set. Theoretically, if only one bottle exhibits growth within a given set, the likelihood of contamination is greater. However, there is at least one study that suggested that these criteria should not be used for this purpose (84). In their study, Mirrett et al. found that the number of bottles positive for coagulase-negative staphylococci within blood culture sets comprising two, three, or four bottles was not correlated with the likelihood of infection using clinical parameters (84). Among 486 sets that were comprised of two bottles, the positive predictive value for sepsis was 18% when one bottle was positive versus 37% when both bottles were positive. Among 235 sets comprised of three bottles, the positive predictive value for sepsis was 28, 52, and 30% when one, two, and three bottles, respectively, were positive. For 303 sets comprised of four bottles, the positive predictive value was 27, 28, 19, and 27% when one, two, three, and four bottles, respectively, were positive. Those authors concluded that the number of positive bottles in a given set did not reliably predict clinically significant infection. Another study found that increasing numbers of positive bottles did predict the likelihood of true bacteremia as defined by clinical parameters: of 129 patients with coagulase-negative staphylococci isolated from a single venipuncture using sets comprised of four bottles, the positive predictive value for true infection was 2% when one bottle was positive, 9% when two bottles were positive, 13% when three bottles were positive, and 27% when all four bottles were positive (94).

Usually, a set of blood cultures involves one aerobic bottle and one anaerobic bottle in an attempt to optimize the isolation of both aerobic and anaerobic organisms. It makes sense intuitively that if growth of a given organism is more likely in aerobic conditions than anaerobic conditions, the number of positive culture bottles within a set that consists of one aerobic and one anaerobic bottle should not be used to differentiate contaminated from clinically significant cultures. Not surprisingly, recent studies have found that the presence of growth for a given organism varies between the aerobic and anaerobic bottles. One study of 644 positive blood culture sets found that 413 (59.8%) were recovered from both bottles, 206 (29.8%) were recovered only from the aerobic bottle, and 72 (10.4%) were recovered only from the anaerobic bottle (108). In that study, the aerobic bottle was significantly superior to the anaerobic bottle for both recovery and detection time for overall organisms, and there was no significant difference in detection time for facultative anaerobic bacteria between the two bottles. Another study of coagulase-negative staphylococcal isolates found that the majority (59.7%) of isolates grew in the aerobic bottle only, whereas 27.7% grew in both bottles and 12.6% grew only in the anaerobic bottle (57). Other studies have shown the same lower yields for anaerobic blood cultures (87).

Time to Growth (Time to Positivity)

Another factor in determining contamination that has been explored by several investigators is the amount of time required for the organism to grow in the culture medium. Conceptually, it is thought that perhaps the blood from a bacteremic patient will have a much higher inoculum of bacteria than a contaminated culture. Theoretically, it follows that a larger inoculum will grow faster than a smaller inoculum, a theory that seems to have been verified in prior studies of catheter-related bloodstream infections (28, 41, 48, 53, 104). In support of this theory, several studies have shown that cultures that become positive more than 3 to 5 days after incubation have been more likely to represent contaminants (37, 49, 50, 53, 62, 75, 103, 108). Because it can be difficult to obtain more than one set of cultures in the pediatric population, Haimi-Cohen et al. used clinical parameters to differentiate true coagulase-negative infections from contaminants and found that a time to positivity of $\leq$15 h had a positive predictive value of 84% for true infection in children (48).

Bates et al. found that the time to growth was a useful variable in a multivariate algorithm for predicting true bacteremia from a positive culture result, although it did not perform as well as either the identification of the organism or the presence of multiple positive cultures (14). Other studies have not found time to growth to be a useful parameter. Souvenir et al.'s study, which differentiated coagulase-negative staphylococcus-contaminated cultures from bacteremias using clinical parameters, found no significant difference between the contaminant group and the true bacteremia in the time to detection of a positive culture (125). Khatib et al.'s molecular study of 47 episodes of multiple positive cultures for coagulase-negative staphylococci found that time to growth did not help differentiate cultures that grew identical strains (2.1 $\pm$ 1.4 days) from culture sets that differed by strain (1.9 $\pm$ 0.9 days) (57).

In the CAP Q-Probes study, the difference in time to detection for contaminant versus true-positive coagulase-negative staphylococci was statistically significant but, as those authors pointed out, probably not clinically significant due in part to a substantial overlap in growth time (113). Furthermore, as the technology of continuous monitoring of blood cultures to detect growth advances, the time to growth and sensitivity for detecting growth can be expected to change, making the use of this technology in this regard questionable (77, 83). Thus far, some experts recommend that this technological variable should not be relied upon to distinguish contaminants from pathogens in blood cultures (151).

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Quantity of Growth per Culture Bottle

Another method that has been used to determine the clinical significance of culture results is the quantity of growth in a given culture sample. This method has been used to differentiate sputum colonization from pneumonia, urine colonization from urinary tract infection, and catheter-related bloodstream infection from non-catheter-related bloodstream infection (2, 53, 106, 127, 128). However, limited data exist to support use of this methodology for differentiating contaminated blood cultures from truly positive blood cultures in adults. St. Geme III et al. found that quantitative cultures in conjunction with specific clinical information may distinguish sepsis from contamination with coagulase-negative staphylococci in young infants but cautioned that low colony counts should not be dismissed as contamination in this high-risk population (129).

Clinical and Laboratory Clues

Others have recommended that the addition of clinical information is essential to appropriately classify positive blood culture results (14, 43, 48, 51, 69). Studies have found that clinicians often diagnose infection when rigid laboratory-based algorithms for differentiating contamination from bacteremia would not have diagnosed infection. The CAP Q-Probes study noted that the median contamination rate differed depending upon whether a clinical assessment was used to make the determination (2.1%) versus laboratory assessment (2.5%) (113). In that study, when coagulase-negative staphylococci were isolated from only one of at least two sets, 84.3% of the cases were interpreted as contaminants by using laboratory methods compared to 73.9% by using laboratory and clinical evaluation.

Many clinicians use fever and other signs of sepsis syndrome to help with the interpretation of positive blood cultures. Weinstein et al. found that hypothermia (temperature of <36°C) or marked fever (temperature of >40°C), leukocyte counts of <4,000 leukocytes/μl or >20,000 leukocytes/μl, and hypotension predicted true infection as opposed to contamination (155). However, another study found that fever at the onset of a blood culture positive for *Staphylococcus epidermidis* did not help differentiate true bacteremia from contamination in leukemic patients (68). Other studies have found similar results in which sepsis-like syndromes, including fever, did not help differentiate episodes thought to be contaminants from true bacteremias (118).

Clinical criteria combined with laboratory data have been used in several studies to differentiate contaminated cultures from clinically significant cultures (14, 30, 43, 51, 59, 125, 129, 155). Bates et al. developed a multivariate algorithm utilizing many predictors, one of which was a "clinical risk score," which consisted of fever, rigors, outcome, intravenous drug abuse, acute abdomen, and comorbidities as variables (14). This clinical risk score was found to be predictive of contamination, as was the organism type, days to culture positivity, and the presence of multiple positive cultures. Khatib et al.'s molecular analysis of 47 episodes of coagulase-negative staphylococcus-positive cultures found that strain relatedness was more frequent in patients who had a fever (15 [71.4%] of 21), an identifiable source (7 [77.8%] of 9), or a bacteremia that met the definition of nosocomial acquisition (18 [50%] of 36) (57). The presence of an identifiable source, specifically, a central venous catheter, was found to be predictive of true bacteremia in another study as well (68).

National Nosocomial Infection Surveillance (NNIS) parameters and surveillance criteria often utilize the treating clinician's diagnosis of bloodstream infection to differentiate true bacteremia from contamination for common contaminants (43). However, one study that correlated cultures that grew the same strain of coagulase-negative staphylococci with the clinician's suspicion/treatment found that the classification of coagulase-negative staphylococcal bacteremias as the same strain correlated poorly with the clinical assessment utilizing the clinician's diagnosis (117). Furthermore, in another study, even though treating clinicians and reviewers who performed retrospective analyses agreed on 100% of coagulase-negative staphylococcal bacteremias and 95% of contaminations, one-half of patients with contaminated blood cultures were still treated with antibiotics, leading to vancomycin misuse in 34% of patients (125). Of course, this may be related to a lower threshold for interpreting an uncertain result as an infection until proven otherwise in the presence of a gravely ill patient rather than true disagreements about what represents contamination.

Other surrogate markers for infection have been studied as well, including the use of C-reactive protein measurements. In neonates, a single C-reactive protein obtained at least 12 h after the onset of symptoms has been found to be helpful to diagnose clinical sepsis (18, 98, 110). In another study of leukemic patients, the level of a single C-reactive protein did not help differentiate between contamination and bacteremia, but the median increase in C-reactive protein over 24 h from the first positive blood culture did help (68). Given these data, some neonatal intensive care unit (NICU) clinicians are beginning to utilize C-reactive protein for this purpose: a survey of 35 NICUs found that C-reactive proteins were routinely obtained at 23% of NICUs and by 30% of NICU clinicians (105).

Source of Cultures (Catheter Drawn versus Percutaneous)

When blood cultures drawn from a vascular catheter are positive, the results could indicate one of three possibilities: true bacteremia, catheter colonization, or culture contamination. Catheter colonization is not contamination, nor is it infection—it occurs when microorganisms grow on the surface of a catheter such that the colonizing organisms would be expected to grow in blood samples obtained from the catheter (in contrast to culture contamination). Catheter colonization may or may not progress to cause symptoms of infection or true bacteremia. Studies have shown that 15 to 25% of short-term central venous catheters are colonized, usually by coagulase-negative staphylococci, and most patients have no evidence of infection (46, 133). Therefore, cultures drawn from central lines could be expected to be positive due to colonization in a substantial number of patients.

Because of the uncertainties surrounding blood cultures obtained from vascular catheters, the clinical utility of these cultures has been evaluated. In one study that used blinded assessments by infectious disease experts to determine the presence of true bacteremia, catheter-drawn cultures had a

sensitivity of 89%, compared to 78% for peripheral cultures, with a positive predictive value of 63% for catheter-drawn cultures versus 73% for percutaneous cultures (34). The results of that study were similar to those of other studies, leading many to suggest that if cultures are obtained from a catheter, at least one set should be drawn percutaneously (13, 20, 38, 74, 76, 92). The advantage of drawing a percutaneous culture to aid the interpretation of catheter-drawn cultures was mathematically evaluated by Tokars in a modeling study of coagulase-negative staphylococcal bacteremia (139). Tokars found that when two of two cultures were positive, the positive predictive value would be 98% if both samples were obtained through the vein, 96% if one sample was obtained through a catheter and the other was obtained through a vein, and only 50% if both samples were obtained through a catheter (139). Other studies, however, have not found a significant difference between results of catheter-drawn and peripheral cultures (39, 125, 158). If it is in fact true that blood cultures obtained from vascular catheters are more likely to be contaminated than percutaneously obtained cultures, the reason may be that sterilizing catheters prior to accessing them is more difficult than sterilizing skin or that catheter colonization is confounding catheter-drawn culture results (151).

One instance in which multiple sets of cultures are often not obtained is in NICU infants for whom the removal of too much blood is of concern and difficulty obtaining peripheral cultures is a reality. Indeed, in a survey of 35 NICUs, 83% of clinicians drew only one blood culture when a catheter-drawn sample was unavailable (105). In that same study, if blood was able to be obtained from a catheter, 224 (80%) of 279 clinicians said that they would obtain at least two blood cultures, including at least one from a peripheral vein; 37 (13%) would obtain a single culture through the central venous catheter; and 18 (6%) would obtain a single blood culture from a peripheral vein. Because of these concerns in the NICU population, antimicrobials that are active against coagulase-negative staphylococci (usually vancomycin) are often overutilized in the NICU. When practice habits from 35 NICUs were evaluated, 47 to 85% of clinicians completed a full course of antimicrobials when a single blood culture was obtained and grew coagulase-negative staphylococci, whereas a significantly lower percentage (22 to 47%) completed a full course when one of two blood culture sets grew coagulase-negative staphylococci (105).

Role of Information Technology: Automated Classification of Positive Blood Cultures

In recent decades, health information technology has played an increasingly important role in the field of infectious disease. Infection control activities are extremely data intensive, and health care information technology offers tremendous potential for improvements in the efficiency of surveillance and reporting systems. Health care institutions are increasingly turning to data-warehousing technologies to support these activities (23, 47, 109, 157). With respect to the challenge of blood culture contamination, investigators have explored automated, computer-based approaches for the classification of culture results as likely contaminants or pathogens. Such an approach offers at least two potential benefits: assisting clinical interpretation and decision-making in the face of ambiguous culture results and providing objective, reproducible, cost-efficient approaches to surveillance of nosocomial infections and bloodstream infection rates. In addition, such methods are almost always significantly faster, as they do not rely on manual identification of positive blood cultures or subsequent labor-intensive review of potentially incomplete or unavailable clinical data.

From the standpoint of surveillance, differentiating contamination from true bacteremia is essential for the accurate measurement of nosocomial bloodstream infection rates. Automated approaches to this task have been shown to perform very well compared with infection control practitioners (ICP) applying the traditional NNIS criteria (56, 141, 161). Yokoe et al. demonstrated that an automated approach for detecting nosocomial infections that relied solely upon microbiology data agreed with an NNIS-based retrospective assessment by ICP 91% of the time for cultures of adult patients (161). Disagreements were due primarily to situations in which only a single positive culture had been identified. In this scenario, CDC definitions rely on additional clinical data such as patient findings or treatment information, while the automated approach relied on a subsequent positive culture within a 5-day period. As a result of this difference in approach, 5/65 cultures were labeled as contaminated by the automated approach and as true bacteremia by the NNIS definition. In pediatric patients, agreement was found only 50% of the time, suggesting that its utility in this population may be limited. Graham et al. specifically studied the ability of a similar system in the neonatal population (47). They examined the performance of an automated system for detecting nosocomial bloodstream infections in two neonatal intensive care units in support of infection control activities. They found that their sensitivity and specificity for detecting such infections were 79% and 96%, respectively, although when coagulase-negative staphylococci were excluded, those numbers rose to 84% and 99%.

Trick et al. focused on the evaluation of a computer-based approach for detecting hospital-acquired, CVC-associated bloodstream infections (141). A comprehensive comparison of prospective ICP review, retrospective investigator assessment, and various computer algorithms was conducted on positive blood cultures from adult patients. Making this determination required several specific steps, including (i) the appropriate classification of hospital-acquired infection versus infection present upon admission, (ii) the correct ascertainment of true bacteremia versus contamination, (iii) distinguishing primary versus secondary infections, and (iv) detection of CVC use. The automated rules varied with respect to the inclusion of medication data and the time period over which data were used by a given rule. Those authors found that their computer-based algorithms performed at least as well as the ICP assessment and in fact outperformed them when combined with a manual determination of CVC use. When they looked specifically at the classification of pathogens versus contaminant organisms, a computer-based algorithm that included both microbiology data as well as pharmacy data had a sensitivity and specificity of 77% and 73%, respectively. The use of microbiology data only resulted in a drop of sensitivity to 55%.

Other investigators focused on the automated classification of blood culture results in order to provide clinical decision

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support by estimating probabilities of contamination and displaying this information to clinicians at the point of care. Wang et al. utilized a previously validated prediction model (14) and revised it to include only readily available electronic data (146). By eliminating clinical data such as blood pressure, temperature, etc., they found only a slight degradation in the performance of the model. They then implemented a clinical rule into the laboratory information system to display the probability information along with blood culture results. In a subsequent house staff survey, they found that half of the respondents indicated that the results had influenced their assessment of the probability of true bacteremia, and 98% indicated a desire to continue to receive the reports. These findings suggest that computer-based approaches offer not only benefits for surveillance activities but also an opportunity to change physician behavior for individual patients. Other investigators have also shown that models that use only readily available electronic data perform well in correctly predicting contamination (100).

PREVENTING CONTAMINATION

By definition, the specificity of the blood culture is directly related to the rate of false-positive results, which are caused primarily by contamination. Reducing contamination rates would lead to improved specificity and better performance of this important test. Unfortunately, there has been a dearth of blinded, randomized, controlled trials that might provide clear and compelling guidance on the best methods for the prevention of contamination. While few would claim that the complete elimination of contamination is possible, a number of efforts to reduce contamination rates have been explored, advocated, and utilized. Factors that have been explored for reducing contamination include skin preparation, culture bottle preparation, single versus double needle for bottle inoculation, source of culture (catheter versus percutaneous), the use of dedicated phlebotomy teams, and the use of commercial blood culture collection kits.

Skin Preparation

The most common source of contaminated percutaneous blood cultures is often thought to be the skin of the patient at the site where the cultures are obtained. One study attempted to find the source of coagulase-negative staphylococcal contaminants by performing molecular analysis to compare each blood isolate to isolates obtained from swabs of the patient and from the individual who obtained the cultures (144). Of 19 patients with contaminated cultures, six of the isolates were able to be matched to swabs, and all six matching swabs came from the patient, implying that the most common source of contamination is the patient's own skin flora. However, it is important that no matching sources were found for 13 of the 19 isolates.

Skin antisepsis cannot entirely prevent the contamination of blood cultures from skin flora because as many as 20% of skin-associated bacteria have been found to survive disinfection, as found by culturing skin samples harvested with a sterile surgical technique (21, 116). These skin bacteria can be located in deep layers of the skin or in other structures that antiseptics cannot penetrate. Nonetheless, inadequate skin preparation is thought to be the most common cause of blood culture contamination (30, 89, 147).

Many studies have been performed to determine the best skin antiseptic product to use for blood culturing. Perhaps the most commonly studied and traditionally used skin antiseptic for blood culturing is povidone-iodine, an iodophor. Three studies have found significantly lower contamination rates using iodine tincture compared with povidone-iodine (67, 113, 131), although two of those studies did not have standardized phlebotomy protocols and drying times for the antiseptics. The CAP Q-Probes study investigators found that the median contamination rate was significantly lower in settings where tincture of iodine was used (2.1%) versus an iodophor (2.6%) ($P = 0.036$), but these differences were not found in organizations that relied on a dedicated phlebotomy service, suggesting that contamination may be more related to technique than the actual antiseptic used (113). One study of chlorine peroxide versus povidone-iodine found contamination in 22 (1.3%) of 1,639 cultures in the chlorine peroxide group compared to 37 (2.3%) of 1,637 in the povidone-iodine group ($P = 0.065$) (125). Another study found that 0.5% chlorhexidine plus alcohol had significantly lower contamination rates than standard povidone-iodine (82). In contrast, two studies that compared chlorhexidine to tincture of iodine did not find a statistically significant difference in contamination rates between the two products (11, 140).

Alcohol-based products are also frequently utilized for skin preparation for blood cultures. Calfee and Farr performed a randomized comparative trial of four skin antiseptics for 12,692 percutaneous blood cultures—10% povidone iodine, 70% isopropyl alcohol, tincture of iodine, or povidone-iodine plus 70% ethyl alcohol (25). The overall contamination rate was 2.62% during the study period. The contamination rates were 2.93% with povidone-iodine, 2.58% with tincture of iodine, 2.50% with isopropyl alcohol, and 2.46% with povidone-iodine plus 70% ethyl alcohol ($P = 0.62$). Although there were no significant differences between the groups, those authors concluded that the antiseptics that contained alcohol may have had greater efficacy. Other studies that examined the difference between alcohol solutions and iodine were unable to detect a statistically significant difference in contamination rates (64, 119).

Several barriers can prevent the skin antisepsis technique from being effective for preventing contamination. The time required for the antiseptic to have maximal effect is an important consideration, since the agent with the most efficacy will not be effective if the time required to become effective is longer than clinically feasible. Individuals who draw blood cultures may not have knowledge of the minimum contact time for their chosen skin antiseptic, or circumstances may not allow a sufficient drying time. For example, povidone-iodine preparations require 1.5 to 2 min of contact time to have a maximal antiseptic effect, whereas tincture of iodine requires 30 s (151). This difference in time to effect may account for differences seen in many of the aforementioned studies as opposed to a clear difference in efficacy. Although controversial, some experts recommend that the culture site be prepped with 70% isopropyl or ethyl alcohol and allowed to air dry and that a

second prep should be performed using 1 to 2% tincture of iodine or 10% povidone-iodine (30, 71).

Culture Bottle Preparation

Although data are limited, it is standard practice to disinfect the tops of the culture bottles before inoculating them with blood (30). The rubber stopper on each bottle is not sterile despite being covered with a lid that requires removal prior to inoculation. In the CAP Q-Probes study of 640 institutions, investigators found that 95.5% of organizations routinely applied an antiseptic to the top of the culture bottle before inoculating the bottle (113). Those institutions that prepped the bottle tops had significantly lower contamination rates (2.3%) than those that did not prep the bottle tops (3.4%) ($P = 0.018$).

It has been recommended that individuals should not use iodine alone because it may cause erosion of the rubber stopper during incubation, thereby introducing contaminants. Some institutions use alcohol, whereas others use an iodine solution that is allowed to dry and is then wiped off with fresh alcohol prep prior to inoculating the bottle (36).

Single Needle versus Double Needle

Until the late 1980s, discarding the needle used to draw blood cultures and using a new, different needle to inoculate the bottles (double-needle technique) was standard practice. This was based on the theory that the needle used for phlebotomy may be contaminated, thereby leading to blood culture contamination. However, with the emergence of human immunodeficiency virus, this practice became questionable, as the process of changing needles was felt to increase the risk of needlestick injuries to phlebotomists. Confirmation of the risk associated with this procedure was shown in studies revealing that most (42%) needlestick injuries occurred after use and before disposal of the naked needle, and transferring specimens from one container to another with a hollow-bore needle has been responsible for 5% of needlestick injuries (134). Subsequently, since 1990, the double-needle technique has been discouraged in favor of using the same needle to draw blood and to inoculate the culture bottles (single-needle technique).

The effect of the double-needle technique versus the single-needle technique on blood culture contamination rates has been evaluated by several controlled studies (7, 31, 54, 60, 66, 114, 124, 136). For each of these studies, the authors admitted to inadequate power to detect the level of difference that was actually observed between the two techniques. In order to improve power, a meta-analysis of these studies was performed, and it was concluded that the double-needle technique did in fact decrease contamination rates from 3.7% to 2.0% ($P < 0.001$) (126). Furthermore, the 1997 CAP survey of 640 institutions found that the median contamination rate was 2.2% in settings where the double-needle technique was used (42% of institutions), compared to 2.7% in settings where a single needle was used, but this difference was not statistically significant (112).

At the time of publication, each study's authors reasonably concluded that any benefit from the double-needle technique did not outweigh the risk of needlestick injuries. However, since the publication of those studies, the risk of needlestick injury during phlebotomy has decreased, partially due to modern safety needles (134). Additionally, vacuum-activated transfer devices have been developed to prevent the necessity of using a hollow-bore needle to inoculate blood culture bottles, which allows phlebotomists to engage the safety mechanisms on safety needles immediately after withdrawal from the patient. It remains to be seen whether these newer, safer technologies will reinvigorate the controversy about any potential relative benefits of the double-needle technique.

Obtaining Cultures Percutaneously instead of via Vascular Catheters

As stated above, cultures obtained from vascular catheters can be quite difficult to interpret. However, this technique remains a very common practice for many reasons. Many clinicians seek to prevent inflicting pain on patients by drawing cultures from a catheter instead of percutaneously. Others may wish to decrease the likelihood of inducing transient bacteremia by phlebotomy, especially for highly immunosuppressed patients. For the neonatal population, the difficulty of venous access is a real problem. Finally, practitioners may fear causing nosocomial volume depletion or anemia by drawing too many blood cultures, a potential issue with neonates or profoundly anemic patients.

Despite these good intentions, there are many undesirable consequences of this practice. The consequences could include the requirement for more cultures for clarification, more diagnostic studies, or the unnecessary use of antibiotics with the associated potential for allergic reactions, unanticipated drug interactions, or adverse drug events. Additionally, if falsely positive culture results from vascular catheters are misinterpreted, unnecessary and prolonged vascular access for intravenous antibiotics may be a consequence.

Phlebotomy Team

Trained phlebotomy or blood culture teams have been found to decrease blood culture contamination rates (132, 150, 151). In one study at a community teaching hospital, blood cultures drawn by a dedicated blood culture team using a commercially available kit had a contamination rate of 1%, as opposed to cultures drawn by resident physicians, which had a contamination rate of 4.8% using the same kit. They compared the costs of this team to the cost savings associated with a reduction in contamination rates and reported a net savings of $40,000 over a 6-month period (150). Investigators in the CAP Q-Probes study found that contamination rates were 3.9% at institutions where more than half of all blood cultures were collected by resident physicians, versus 2.2% at institutions where less than half of all blood cultures were obtained by resident physicians (112). In the more recent Q-Tracks study, there was a statistically significant difference in contamination rates between institutions that utilized a dedicated phlebotomy team versus other staff for culture collection. Institutions in which the large majority of cultures were drawn by nursing staff had a contamination rate of 4.21%, while those institutions in which those same individuals did not collect any culture specimens had a contamination rate of 2.17% (17). Dedicated

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phlebotomy teams are increasingly common in the inpatient setting; in a study of 640 institutions, Schifman et al. noted that, on average, 70% of cultures were collected by phlebotomy teams at teaching institutions, while 85% of cultures were collected by such teams at nonteaching hospitals (113).

For those facilities that have not invested in the establishment of a dedicated phlebotomy team, another method that could be used is monitoring and feedback of contamination rates to the collectors. Weinstein performed a pilot study that monitored phlebotomists' contamination rates on a monthly basis. Those results revealed a contamination rate of 3% for phlebotomists compared with nearly 11% for blood cultures obtained by resident physicians, nondegree nursing assistants, and nurses (151). Monitoring and feeding back contamination rates to individuals who obtain blood cultures were used successfully in at least one other institution that achieved a 50% reduction in contamination rates using this methodology (45). Many institutions are using this technique, as indicated in the CAP Q-Probes survey, which found that 47% of laboratories stratified contamination rates on the basis of individual phlebotomists (112).

Commercial Blood Culture Collection Kits

Whether commercially marketed blood culture collection kits reduce infection rates has been debated. In one teaching hospital, cultures drawn by resident physicians who used a commercial kit had a contamination rate of 4.8%, compared to 8.4% for residents who did not use the kit (150). Kits have been found to be beneficial in other studies as well (112). Another study compared povidone-iodine pledgets and alcohol pledgets to a collection kit containing breakable ampules of alcohol and 2% iodine tincture and found no difference in contamination rates when commercial kits were used (156).

SUPPORTING OPTIMAL USE OF BLOOD CULTURES

Blood cultures are frequently ordered tests. Unpublished data from our own academic health center, which includes a 565-bed tertiary hospital with approximately 30,000 admissions per year, suggest that over 20% of our hospitalizations involve at least one blood culture. The high utilization of blood culture testing can be partially attributed to two important reasons: the difficulty that most clinicians have in predicting the risk of bacteremia (72, 80, 97) and their low threshold for ordering the test, given the significant risk of morbidity and mortality associated with this condition (15, 147, 155). Additionally, for some specific clinical conditions, such as patients admitted to the hospital with community-acquired pneumonia, professional or governmental organizations have recommended universal blood culture testing (73). As discussed above, the pretest probability for bacteremia greatly influences the positive predictive value of a blood culture result. Accordingly, several investigators have developed and evaluated clinical prediction rules for bacteremia in a wide variety of patient populations in an effort to assist decision-making regarding diagnostic workup and management. The scientific community has also assessed the rates of bacteremia in a wide variety of patient populations to better understand disease prevalence, potentially allowing the development and refinement of consensus guidelines for specific clinical scenarios.

Clinical Prediction Models

Accurate clinical bacteremia prediction models have the potential to improve the use of blood culture testing and to aid in the interpretation of indeterminate culture results by providing pre- and posttest probabilities (12). Prediction models are generally developed using two consecutive analyses: an initial derivation step that is used to determine the independent predictors of the outcome of interest, which is followed by a validation set that is used to test the model in another population. For a prediction model to be maximally useful, it should be applicable to other settings (148). Researchers have developed or studied models for predicting bacteremia in hospitalized adults (12, 65, 72, 80, 85, 88, 160) and adult patients seen in emergency departments (40, 120, 159). Similar efforts have been explored in pediatric populations, although the motivation for many of these models is targeted primarily at decision-making regarding hospital admission versus outpatient management and initiation of empirical therapy and not whether or not to obtain blood cultures (3, 4, 8, 61, 70, 99). In recent years, greater attention has been paid to the impact of contamination rates on the utility and effectiveness of the blood culture test and the implications for its use in pediatric patients (9, 63, 115, 130, 138).

In hospitalized adults, clinical prediction rules for bacteremia have been found to have mixed results, at least from the perspective of the potential for reducing unnecessary blood cultures. Bates et al. developed a model that grouped patients into four different levels of bacteremia risk based on a combination of clinical and laboratory findings (12). In this prospective cohort study, they found that patients in the lowest risk category had a 1% chance of having bacteremia in the derivation set and a 2% chance in the validation set. In this low-risk group, the positive predictive value of a positive culture was 18%. Leibovici et al. developed a similar model that focused on evaluation of newly admitted febrile adults and found the prevalence of bacteremia in the low-risk groups to be 5% in the derivation set and 1% in the validation set (65). In an attempt to test these models outside their originating institutions, Yehezkelli et al. studied the accuracy of both the Bates and Leibovici prediction models in two hospitals (academic and community) in Israel. They found that the accuracy of both models "deteriorated significantly," with misclassification rates in the low-risk groups of 13 to 15% using the Bates model and 7 to 8% using the Leibovici model (160). Mylotte et al. attempted to validate Bates' model in a different institution with similar patients and found a slight degradation in performance, with a 3% misclassification rate for low-risk patients (88). Misclassification rates for low-risk groups in models developed by other investigators ranged from 4.6 to 5.1% (80, 85, 148). As several of the authors of those studies acknowledged, such results may be insufficient for reducing blood culture testing. Indeed, based on one survey of 149 physicians that included house staff and infectious disease specialists, investigators concluded that the sensitivity of a clinical prediction rule for bacteremia would have to be extremely high (99 to 100%) to be widely accepted.

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Bacteremia prediction modeling in the emergency department setting has been studied as well (40, 120, 159). Shapiro et al. described a general clinical prediction rule for bacteremia in the emergency department setting that identified low-risk groups that were associated with a 0.8% and 1.8% risk of bacteremia (derivation and validation populations, respectively) (120). The sensitivity of the model was 98% in the derivation model and 96% in the validation model. While such prediction rules may well prove clinically useful for decision-making regarding hospitalization or the initiation of empirical antibiotic therapy, it remains unclear whether or not such tools will reduce unnecessary blood culture use.

Population Studies of Bacteremia Prevalence

Efforts to ascertain bacteremia prevalence in specific subpopulations have the potential benefit to inform the appropriate use of diagnostic tests such as blood cultures. In the pediatric population, investigators have studied the risk of occult bacteremia, given the widespread adoption of vaccinations to prevent infection caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (1, 9, 130). In a study of well-appearing, highly febrile children aged 2 to 36 months, Stoll and Rubin found that the incidence of occult bacteremia was 0.91% (95% confidence interval, 0 to 1.9%) and concluded that universal blood culture testing in this population may be unnecessary (130). In a recent similar study, Herz et al. conducted a retrospective review of blood cultures obtained from children aged 3 to 36 months during a 5-year period from 1998 to 2003 at Kaiser Permanente Northern California ambulatory facilities (52). Bacteremia rates dropped from 1.62% to 0.71% from the first year to the last year of the study period, while the contaminant-to-pathogen ratio increased from 1.2:1 to 2.3:1, leading the authors to agree with Stoll and Rubin about the decreased role for blood culture testing in highly febrile children in this age group, who are otherwise well-appearing and were previously healthy. The necessity of blood cultures remains controversial, however. Other investigators who studied occult bacteremia rates in similar age groups (although using somewhat different inclusion/exclusion criteria) found slightly higher rates of 1.9 to 3%, prompting them to suggest obtaining blood cultures and deferring treatment pending culture results (9).

The emergency department is another setting that has received significant attention in terms of blood culture utilization, bacteremia prevalence, and the impact of blood cultures on patient management. Innes et al. (53a) found that during a 6-month period at a hospital in British Columbia, blood culture results for patients seen in the emergency department were rarely helpful, with only 2.1% of 767 culture episodes yielding "potentially helpful" information. Similarly, in a retrospective study of 1,350 patients who had blood cultures taken in the emergency department (and who were subsequently discharged) of a large U.S. urban teaching hospital, only 0.52% had results that potentially affected their management. The prevalence of bacteremia in that population was 1.8%, leading those authors to conclude that specific criteria were needed to help guide the decision regarding blood culture testing (131a).

Finally, the question of whether or not all patients hospitalized for community-acquired pneumonia require pretreatment blood cultures, as recommended by consensus guidelines (73, 91), has become intensely debated in recent years (20a, 52a). Fueling the controversy are increasing reports suggesting that due in part to a combination of high contamination rates and low bacteremia risk, the PPV for blood cultures is low and test results are often clinically unhelpful (26, 27, 29, 33, 137). Consequently, investigators have attempted to develop specific bacteremia prediction rules for community-acquired pneumonia patients to help guide decision-making surrounding the use of blood cultures (81, 149). Metersky et al. developed a model that stratified patients into three different groups on the basis of their bacteremia risk and concluded that their tool would lead to a 38% reduction in blood culture utilization while missing 11% of individuals with true bacteremia (81). It remains to be seen whether such a model can be incorporated into routine practice.

While controversy remains in each of these areas about the proper criteria for blood culture testing and initiation of antibiotic therapy, many agree that the combination of low pretest probability (i.e., disease prevalence) with high contamination rates often leads to unhelpful culture results.

BLOOD CULTURE CONTAMINATION IN THE PEDIATRIC POPULATION

Contaminated blood cultures are a particular challenge for infants and children for several reasons. While an in-depth discussion of the topic is beyond the scope of this review, evidence suggests that contamination occurs more frequently in this population, particularly in young infants (78, 92, 101, 135). In addition, concerns about the risk of occult bacteremia have led to guidelines recommending the use of blood cultures and empirical therapy, particularly in children less than 3 years of age (10). As described above, however, the tides may be starting to turn, as the past decade has seen multiple studies suggesting that in the current era of influenza and pneumococcal vaccination, the risk of occult bacteremia has significantly lowered. As a result, the use of blood culture testing in this patient population is associated with a lower positive predictive value. Moreover, analysis of current practice patterns reveals that in most cases, only single blood cultures are collected (93, 105, 111). In an effort to reduce unnecessary discomfort, pediatricians often use existing intravenous catheters for obtaining cultures instead of peripheral venipuncture (105). The data on the impact of this practice on contamination rates are mixed. In a 2-year observational study comparing contamination rates for culture specimens drawn via venipuncture to those for culture specimens drawn via intravenous catheters in children, Norberg et al. found a large, statistically significant decrease in the rate of false-positive blood cultures (9.1% to 2.8%) after their institution adopted a policy eliminating the use of intravenous catheters for this purpose (92). While compelling, conclusions based on that study are limited by its design, which lacked a control group to account for any potential confounders such as temporal trends. Ramsook et al. found similar results in a 6-month study of 2,431 pediatric blood cultures, with contamination rates of 3.4% for specimens collected via intravenous catheters versus 2.0% for those obtained by separate venipuncture ($P = 0.043$) (101). While

that study used a large sample size, details of the study design and methods are somewhat unclear, making it difficult to ascertain both internal and external validity. Other studies have shown no difference in contamination rates according to specimen collection routes (55, 124). Given pediatricians' disinclination to subject children and infants to unnecessary painful procedures, and the lack of clear evidence on which approach best prevents specimen contamination, the use of existing catheters for blood culture collection continues in this patient population (79). As described above, single blood cultures are particularly common in pediatric patients; this fact, combined with the increased utilization of catheter-based culture specimens, makes discrimination between true bacteremia and contamination challenging, particularly when coagulase-negative staphylococci are grown in culture (24). To combat this challenge, investigators have explored multiple avenues, including the use of C-reactive protein, time to positivity, quantity of growth, and clinical status (3, 18, 19, 32, 44, 98, 110, 129). While none of these factors have performed well enough individually to warrant widespread adoption, they continue to be under investigation.

CONCLUSION

Clearly, progress has been made on several fronts in the battle against blood culture contamination. Better strategies for preventing contamination in the first place are being established, and we are improving our ability to distinguish contamination from true bacteremia. New research on measures to estimate the pretest likelihood of bacteremia offers promise in reducing unnecessary blood culture utilization. Despite the progress that has been made, however, significant barriers remain. Without a gold standard for truly distinguishing contaminant organisms from true pathogens, studies that seek to measure the success of prevention strategies are inherently limited. Similarly, efforts to help establish the posttest probability of bacteremia given a positive result are restricted. Genomic and proteomic approaches for identifying bacteremia are being explored but remain in the early stages (96, 122, 123). There is evidence, however, to suggest that even these methods can be hampered by problems with contamination (95). Furthermore, additional research on the value of time to positivity and quantity of growth for differentiating culture contamination from bacteremia is necessary. Of the various prevention strategies, additional investigation would help to determine the relative effect of each strategy on overall contamination rates. In the meantime, information technology may have a role in facilitating the detection of contamination, assisting clinical decision-making, and enabling better systems for tracking contamination rates both within and between institutions. Additional research on how to make these tools more useful and more acceptable in the clinical work environment is needed. Similarly, while clinical prediction rules for bacteremia have received much scrutiny in the past 15 years, it remains unclear whether they perform at a level that is accurate enough to influence physician behavior and affect blood culture utilization. More research is needed to refine these models and test them in other settings. In the pediatric arena, additional studies are clearly needed to help physicians interpret the results of single blood cultures that grow coagulase-negative staphylococci, a persistent challenge. Ultimately, blood culture contamination is a complex, challenging problem that requires a multidisciplinary approach. Well-conceived and effectively implemented strategies are important for reconciling the sometimes contradictory requirements of individual patient care, population health, and effective resource allocation.

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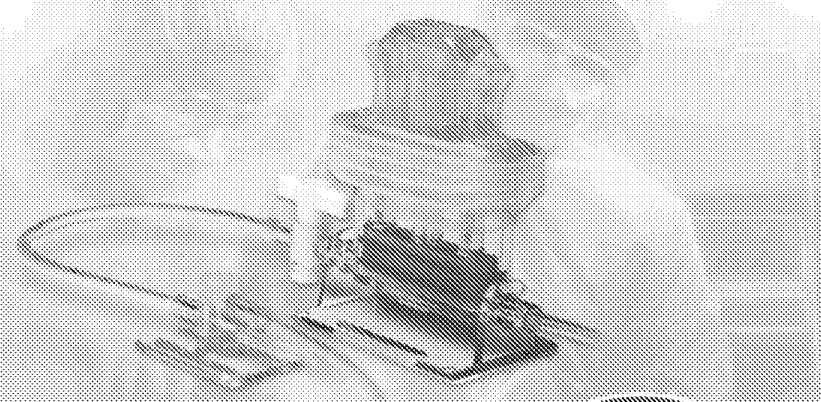
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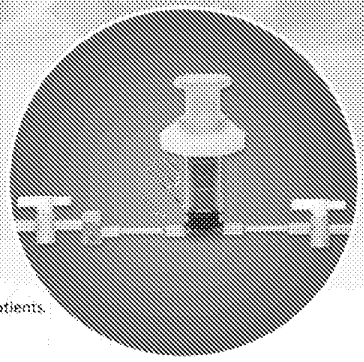
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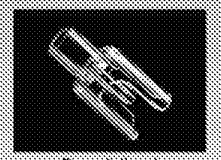


Figure 1 Luer-lok

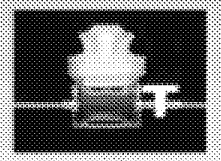


Figure 2 VAMP Reservoir

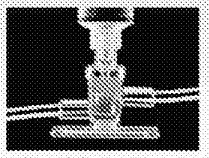


Figure 3 Z-site sampling port

VAMP Kits

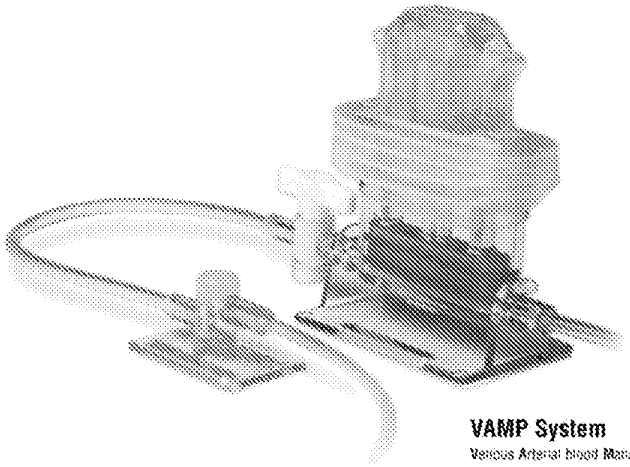
The closed blood sampling system that protects patient from the Edwards TruWave Disposable Pressure Transducer. The Edwards VAMP system provides the safest and easiest method of needleless blood sampling. The blunt cannula design (figure 1) provides safety by eliminating the needlesticks associated with 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.

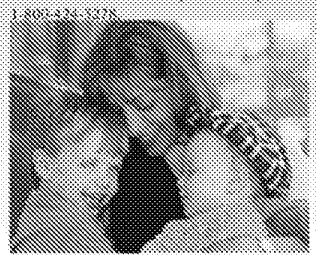
A unique in-line reservoir puts safety first.

Blood conservation and consistent sampling are critical for optimal pediatric and neonatal care. The VAMP Jr. reservoir is designed with "kg" 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.

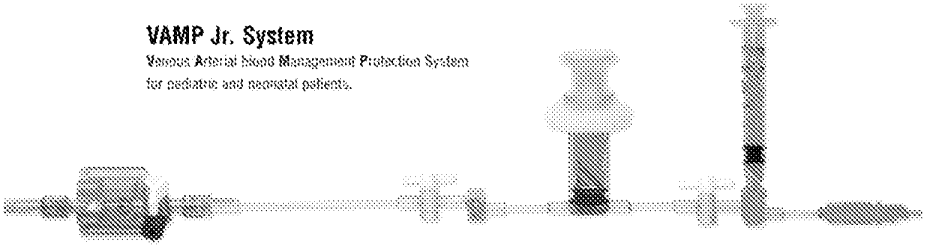
The VAMP Jr. system fits the special needs of your special patients.

The VAMP Jr. system is designed to require decreased volume over a smaller circuit for more accurate sampling and flushing to 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 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 2" proximal, 4" distal for neonatal application	VMP306PX 3cc TruWave DPT with 2" proximal, 4" 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

Conformité européenne

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Caution: Rx only. In accordance with applicable country laws, prescription (or physician order) is required. Refer to applicable instructions for use.

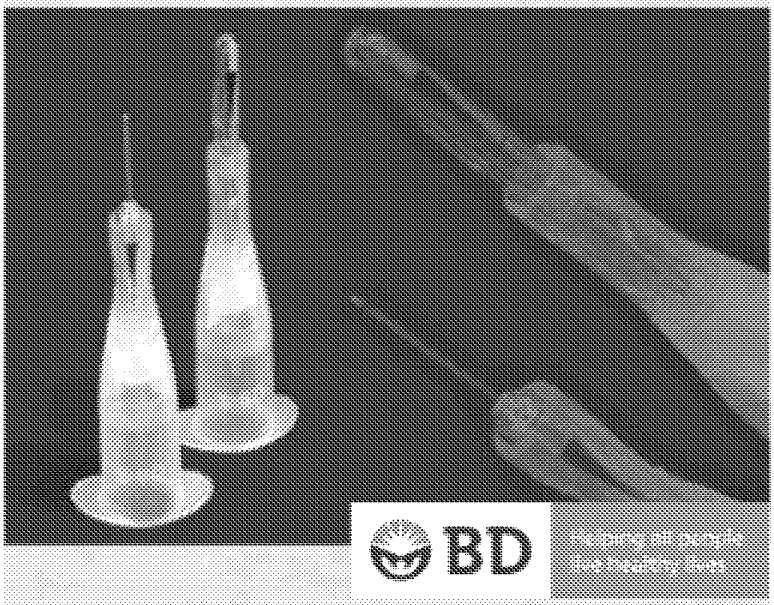
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Edwards Lifesciences

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Edwards Lifesciences Japan - 2-8 Nakanoshima - Kita-ku, Tokyo 102-0083 - Japan - Phone 81.3.6213.5700

Venous Blood Collection

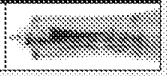
BD Vacutainer® Passive Shielding Blood Collection Needle

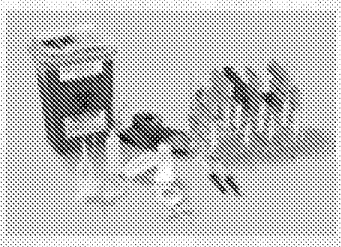


A New Generation of Safety from BD, the leader in safety-engineered technology

The BD Vacutainer® Passive Shielding Blood Collection Needle is designed to provide the highest amount of protection against needlesticks during a blood draw. The needle's safety shield releases automatically upon insertion of the first tube, providing protection from the time the first tube is inserted through product disposal.

BD Vacutainer® Passive Shielding Blood Collection Needle

Ordering Information				
[illegible]	Passive Shielding Blood Collection Needle	21g x 1" needle	25/Box 200/Case	
[illegible]	Passive Shielding Blood Collection Needle	22g x 1" needle	25/Box 200/Case	



A part of the BD Vacutainer® Family of Venous Blood Collection Products

CAUTION: Handle all biologic samples and blood collection "sharps" (lancets, needles, luer adapters, and blood collection sets) in accordance with the policies and procedures of your facility. Obtain appropriate medical attention in the event of any exposure to biologic samples (e.g., through a puncture injury) since samples may transmit viral hepatitis, HIV (AIDS), or other infectious diseases. Utilize any safety-engineered feature if the blood collection device provides one. Discard all blood collection "sharps" in biohazard containers approved for their disposal.

BD Global Technical Services
1.800.631.0174

BD Customer Service
1.888.237.2762

www.bd.com/vacutainer

BD

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/898,239	**09/27/2024 04:54:19 PM Z ET**	**069366-0581370_KUR2C07US**

Title of Invention

BLOOD SAMPLE OPTIMIZATION DEVICE

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7801	FILED BY	Trent Tercenio
PATENT CENTER #	67356484	FILING DATE	-
CUSTOMER #	27500	FIRST NAMED INVENTOR	Bobby E. Rogers
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Benjamin Hudson

Documents

TOTAL DOCUMENTS: 100

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
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069366-0581370_KUR2C07US-A-Foreign-025-FOR.pdf	95392F89415ED312336B4CABF9F970864656A4DF74AB1A36077670ACDDF822CF5D4FB8F451E85BDAA4141EE0FAE6B6F5029DC3B46D07D22B37A0A09EF376EE70
069366-0581370_KUR2C07US-A-Foreign-023-FOR.pdf	2946827C5D21D8E982C3E7CFD7A69FD5EAC3BAED37C0CCBB1E74E7928396C7E8961F8BB37AC93339FECAD2D23F9C6FBD619041B0823D0314EF0FE8E060857934
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Foreign-030-FOR.pdf	575FEB2D8B06350F7A4D42D0FA24582
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069366-0581370_KUR2C07US-A-Foreign-034-FOR.pdf	FBE1BE897C66E2FE5785E9EBCC7A00BBDE2EBD3D44F108D238114263CAB795DE921CB0B60BF045BD0030060F0B1D3B21B375CFF96D756BF9012ACEF032DBFB94
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069366-0581370_KUR2C07US-A-Foreign-041-FOR.pdf	60CB58B519E9813D6A385B4756AA8C615169EAF3D438B3233F667DCB99EBADBC5B8A313F032FC9E93AD6F6FCBC0C5299A3EA563D4B14014D81C826B31BAD8BEC
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069366-0581370_KUR2C07US-A-Foreign-045-FOR.pdf	9EE9CC5216E1ECF3A117CE9EEE043F8E73F3D2B9275E61DB57B28CD69EA52C83113FC7C8F9D535F5F8D041191A23E4939C3C71F00EB7137DB555ABF3DB4B5F13
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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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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.

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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.

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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

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.

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Retractable Technologies, Inc. v. Becton Dickinson & Co.

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Bacterial Contamination of Blood Components

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INTRODUCTION

Allogeneic blood for transfusion is a potential source of infection by a variety of known and unknown transmissible agents. Since the 1980s, with the recognition of human immunodeficiency virus contamination of the blood supply, only a blood supply with a zero risk to recipients has been politically acceptable (67). This approach has led to the concept of "creeping precautionism" in the blood supply (46). The precautionary principle has grown out of the environmental movement. Briefly, it states ". . .where there are threats of serious or irreversible damage to the environment, lack of full scientific certainty should not be used as a reason for postponing cost-effective measures to prevent environmental degradation. . ." (46). To this end, astounding reductions in the viral risk of allogeneic blood has been accomplished (27). However, a number of transfusion safety measures have been implemented to achieve this level of safety, despite relatively poor cost-effectiveness, in order to assuage the public's fears (32).

Given the reduction of viral transmission via allogeneic blood, the low but known risk of bacterial contamination has emerged as the greatest residual threat of transfusion-transmitted disease (Fig. 1).

TRANSFUSION-TRANSMITTED BACTERIAL INFECTION OF RED CELLS

Each year, approximately 13,898,000 units of red cells or whole blood are transfused in the United States alone (1). This equates to one unit being transfused every 2.3 s. Despite this large number, sepsis associated with the transfusion of bacterially contaminated red cell blood components is generally regarded as a very rare event. From 1976 through September 1998, 26 fatalities thought to be secondary to contaminated whole blood or red cells were reported to the U.S. Food and Drug Administration (FDA) (36). Thus, approximately one red cell-related death per year has been reported. The majority of deaths reported to the FDA involved *Yersinia enterocolitica*. The highest reported incidence of *Y. enterocolitica* contamination was reported in New Zealand, with an incidence rate of 1 in

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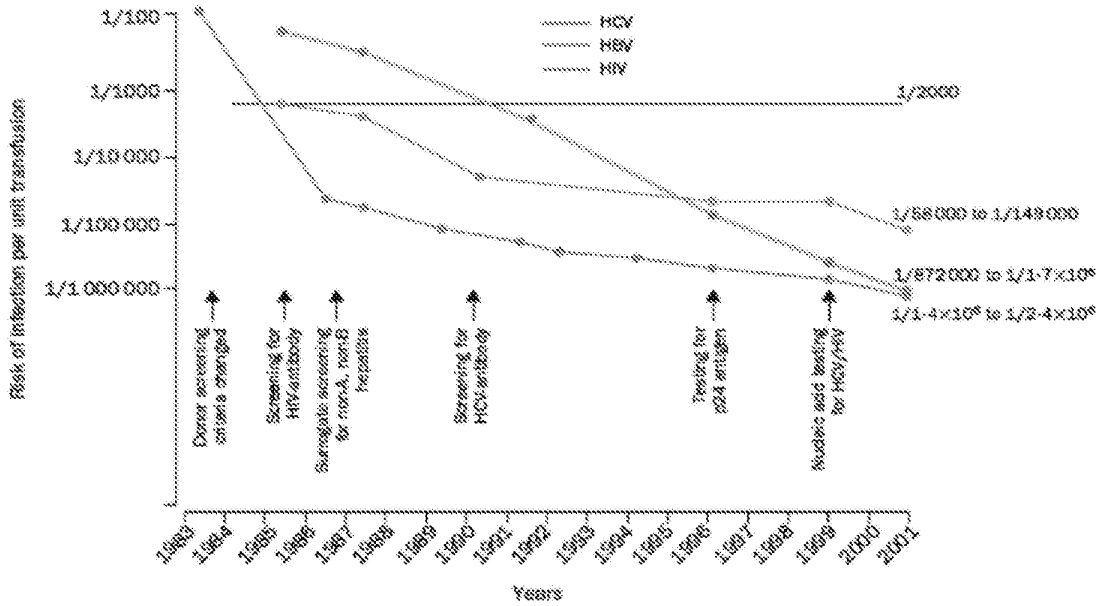


FIG. 1. Risk of infectious disease transmission per unit transfused by year, 1983 to 2001. Reprinted from reference 27 with permission of the publisher.

65,000 and a fatality rate of 1 in 104,000 red cell units transfused (59). Unrecognized cases, underreporting, and regional variation may account for observed differences in this incidence.

Interestingly, more recent passive reporting studies of bacterially contaminated red cells from the United States, France, and the United Kingdom that caused symptoms of infection show a relative paucity of *Yersinia* cases (Table 1) (35, 51, 57). Of the reported deaths, one was due to a coagulase-negative

TABLE 1. Organisms isolated from red cells implicated in transfusion-associated infections[a]

Organism	No. of contaminated units in:			Total no.
	United States	United Kingdom	France (29 isolates, 25 implicated units)	
Gram positive				
Coagulase-negative staphylococci	2 (1)	2	3	7 (1)
Streptococcus spp.			4[d]	4
Staphylococcus aureus			2[b]	2
Enterococcus faecalis			1[c]	1
Bacillus cereus			2	2
Propionibacterium acnes			1	1
Subtotal	2 (1 or 50%)	2 (0 or 0%)	13 (0 or 0%)	17 (1 or 6%)
Gram negative				
Serratia liquifaciens	2 (2)	1	2 (1)	5 (3)
Serratia marcescens	1			1
Yersinia enterocolitica		1 (1)	1	2 (1)
Enterobacter spp.			1 (1)	1 (1)
Acinetobacter spp.			5 (1)[b]	5 (1)
Pseudomonas spp.			2 (1)	2 (1)
Escherichia coli			3[c]	3
Klebsiella pneumoniae			1	1
Proteus mirabilis			1	1
Subtotal	3 (2 or 67%)	2 (1 or 50%)	16 (4 or 25%)	21 (7 or 33%)
Total	5 (3 or 60%)	4 (1 or 25%)	29 (4 or 14%)	38 (8 or 21%)

[a] Summary of organisms identified in the BACON, SHOT, and BACTHEM studies (35, 51, 57). Numbers and percentages of fatalities are given in parentheses.
[b] In one case, *S. aureus* and *A. baumannii* were both isolated from the implicated bag.
[c] In one case, *E. faecalis* and *E. coli* were both isolated from the implicated bag.
[d] In two cases, two isolates of *Streptococcus* were isolated from the implicated bag. Of the eight reported fatalities, seven (87.5%) were due to gram-negative organisms.

TABLE 2. Organisms implicated in infections associated with platelet transfusions[a]

Organism	No. of contaminated units in:			Total no.
	United States	United Kingdom	France	
Gram positive				
Bacillus cereus	1	4 (1)	2	7 (1)
Coagulase-negative staphylococci	9	6 (1)	5	20 (1)
Streptococcus spp.	3 (1)	2		5 (1)
Staphylococcus aureus	4	2 (1)		6 (1)
Propionibacterium acnes			3	3
Subtotal	17 (1 or 6%)	14 (3 or 21%)	10 (0 or 0%)	41 (4 or 10%)
Gram negative				
Klebsiella spp.			2 (1)	2 (1)
Serratia spp.	2 (2)		1 (1)	3 (3)
Escherichia coli	5 (1)	2 (1)	1	8 (2)
Acinetobacter spp.			1	1
Enterobacter spp.	2 (1)	1 (1)	1	4 (2)
Providencia rettgeri	1 (1)			1 (1)
Yersinia enterocolitica	1			1
Subtotal	11 (5 or 45%)	3 (2 or 67%)	6 (2 or 33%)	20 (9 or 45%)
Total	28 (6 or 21%)	17 (5 or 29%)	16 (2 or 13%)	58 (11 or 19%)

[a] Summary of organisms identified in the BACON, SHOT, and BACTHEM studies (35, 51, 57). Numbers and percentages of fatalities are given in parentheses.

Staphylococcus strain and seven were due to a variety of gram-negative organisms (including *Serratia liquefaciens* in three cases). These organisms are all capable of growth at 1 to 6°C. Sepsis associated with the transfusion of red cells contaminated with gram-negative bacteria is typically severe and rapid in onset. Patients frequently develop high fever (temperatures as high as 109°F have been observed) and chills during or immediately following transfusion. From 1987 to February 1996, 20 recipients of *Yersinia*-infected red cells were reported to the Centers for Disease Control (S. T. Cookson, M. J. Arduino, S. M. Aguero, W. R. Jarvis, and the *Yersinia* Study Group, Program Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 237, 1996). Twelve of the 20 recipients died, and the median time to death was only 25 h. Of the seven who developed disseminated intravascular coagulopathy, six died.

Prospective bacterial cultures of whole blood or red cells, however, have shown a much higher incidence of bacterial contamination (2 to 4 per 1,000 units); however, the organisms commonly cultured are *Staphylococcus* or *Propionibacterium* spp., which generally proliferate poorly during storage at 1 to 6°C (4).

TRANSFUSION-TRANSMITTED BACTERIAL INFECTION OF PLATELETS

Each year, within the United States approximately 4 million platelet units are transfused (1×10^6 single-donor apheresis platelets and 3 million whole-blood-derived platelet concentrates) (1). This equates to one platelet unit being transfused every 8 s. Unlike red cell or whole-blood components, which are stored at 1 to 6°C, platelets are stored at 20 to 24°C to preserve function and survival. Such storage makes them an excellent growth medium for a broad spectrum of bacteria. Multiple aerobic-culture surveillance studies have demonstrated that 1 in 1,000 to 2,000 platelet units are bacterially contaminated (4). Thus, 2,000 to 4,000 bacterially contaminated units would be expected to be transfused per year. Estimates of the fraction of cases that result in patient symptoms have been as low as 1 in 10 cases. However, in the only study that has prospectively cultured platelets that were transfused, eight culture-positive but Gram stain-negative platelet pools that were bacterially contaminated resulted in symptoms in three patients (37.5%) [A. Dykstra, G. Hoeltge, M. Jacobs, J. Miller, R. Domen, and R. Yomtovian, Transfusion 38(Suppl.): 104S, 1998]. Notably, six Gram stain-positive pools (which would be expected to have had the highest bacterial load) were interdicted and never transfused.

Thus, clinical sepsis would be expected in at least 1 in 10 to 2 in 5 contaminated transfusions (200 to 1,600 cases). National passive-reporting studies from the United States, the United Kingdom, and France (Table 2) suggest that one-fifth to one-third would result in death (40 to 533 deaths per year) (35, 51, 57). This translates to a risk of death from a transfusion of a bacterially contaminated platelet unit of between 1 in 7,500 and 1 in 100,000. Clinical observations from university hospitals actively pursuing suspected cases of platelet-related sepsis confirm these estimates. Ness et al. from Johns Hopkins University, reported a fatality rate of 1 in 17,000 with pooled whole-blood-derived platelets and 1:61,000 with single-donor-apheresis-derived platelets (48). Similarly, University Hospitals of Cleveland observed a fatality rate of 1 in 48,000 per random platelet unit (21). The French BACTHEM study documented a fatality rate due to bacterially contaminated platelets of 7 per 10^6 (1 in 140,000) (51).

From 1976 through September 1998, 51 fatalities thought to be secondary to contaminated platelets were reported to the U.S. FDA (36). Gram-negative organisms accounted for the majority of deaths (59.7%). Similarly, passive surveillance studies from the United Kingdom, the United States, and France show that gram-positive organisms were implicated in 41 (71%) of 58 of cases but gram-negative organisms (mostly members of the *Enterobacteriaceae*) account for the majority (9 [82%] of 11) of the fatalities (Table 1) (35, 51, 57).

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Clinical Presentation

Clinical sequelae of the infusion of bacterially contaminated platelets are variable and may be acute or delayed (contributing to missed diagnoses). Ironically, the majority (85%) of platelets are transfused to patients in the medical oncology, hematology, pediatric hematology/oncology, and bone marrow transplantation settings, all typically immunosuppressed patients (61). A study of platelet transfusions in autologous bone marrow transplant patients found that 1 in 2,000 units of platelet concentrates associated with a febrile episode (within 24 h of transfusion) were linked to bacterially contaminated platelets (16). Of the 10 patients known to have received a bacterially contaminated unit, 4 experienced septic shock.

Because of the severity of the patient's underlying disease and the variability in presentation and timing, sepsis resulting from bacterially contaminated platelets may go unrecognized. For example, an outbreak of *Salmonella enterica* serovar Choleraesuis sepsis in seven patients was traced to one repeat platelet donor, subsequently found to have occult chronic osteomyelitis (52). One patient died, and two had long-term recurrences of *Salmonella* sepsis. The time to the onset of illness ranged from 5 to 12 days (mean, 8.6 days). In many cases, the platelet-related bacterial sepsis is discovered only in retrospect. Investigations of two *Serratia liquefaciens*-contaminated red cell units led to platelet products from the whole-blood donations and to the recognition of an associated septic death in one recipient and bacteremia in the other recipient (53).

TRANSFUSION-TRANSMITTED BACTERIAL INFECTION OF PLASMA AND CRYOPRECIPITATE

Cell-free products such as plasma and cryoprecipitate are stored frozen and thus are rarely associated with contamination. However, in some cases *Pseudomonas cepacia* and *P. aeruginosa* have been cultured from cryoprecipitate and plasma thawed in contaminated water baths.

SOURCES OF CONTAMINATION

Gram-positive skin commensals such as *Staphylococcus epidermidis* and *Bacillus cereus* are the organisms most often recovered from donated blood (and implicated in bacterial contamination of platelets). Such contamination is thought to occur principally during phlebotomy, as a result of incomplete disinfection and/or skin core removal (including skin appendages where the skin disinfectants may not penetrate) by the collection needle (25). These organisms typically do not grow at 1 to 6°C but survive and multiply readily at the platelet storage temperature of 20 to 24°C.

In the case of gram-negative bacterial contamination, asymptomatic donors with transient bacteremia are presumed to be responsible for most cases of contamination. For example, in the case of *Y. enterocolitica* contamination of red cells, implicated donors typically are found to have elevated antibody titers (immunoglobulin M or G) to *Y. enterocolitica*, implying a recent infection (38, 39, 60).

An outbreak of *Serratia marcescens* contamination of red cells in Denmark and Sweden (29, 30) was thought to involve the manufacturing process since the sterile bag sets were autoclaved and put in a clean but not sterile outer plastic package. It was thought that *S. marcescens* present in the dust in the factory contaminated the outside of the containers and that in the presence of moisture and a nutrient (the plasticizer diethylhexyl phthalate) the bacteria proliferated and gained entry into the bag (58).

In rare cases, unusual circumstances have been identified as the source of bacterial contamination. For example, a donor with a pet boa constrictor, who reported fever and bloody diarrhea treated with antibiotics 13 days prior to his donation, was linked to *Salmonella enterica* platelet sepsis in two patients (33). Scarring or dimpling of the venipuncture site (due to prior donations) can result in recessed pits that are difficult to adequately sterilize (3). A repeat single donor with a "dimpled" venipuncture site resulted in four cases of gram-positive bacterial platelet sepsis in recipients (3). Another unusual association was made between one donor in a platelet pool and the death of a leukemic recipient from septic shock. The contaminating organism was identified as *C. perfringens* and was thought to originate from a donor who had two young children and frequently changed their diapers (42). As stated above, an outbreak of *S. enterica* serovar Choleraesuis platelet sepsis in seven patients at the National Institutes of Health Clinical Center was traced to a repeat platelet donor with an occult osteomyelitis (52). However, in most cases the source of the bacterial contamination remains unidentified.

METHODS TO REDUCE THE RISK OF POST-TRANSFUSION SEPSIS

There are multiple strategies to reduce transfusion-related bacterial infection. The various approaches can be grouped into four major categories: avoidance, bacterial detection, bacterial elimination, and growth inhibition.

Avoidance

Donor screening. Screening of donors to detect a possible risk of infection or transient bacteremia (e.g., from recent dental procedures) is routinely performed. However, questioning about symptoms suggestive of infection are often problematic; for example, gastrointestinal symptoms have not been a specific predictor (13% of donors have had gastrointestinal symptoms in the previous 30 days) (28). Such questioning also lacked sensitivity, since only 13 of 20 donors associated with *Y. enterocolitica*-contaminated red blood cells recalled a history of gastrointestinal symptoms (38, 39, 60; Cookson et al., Prog. Abstr. 36th ICAAC, 1996).

Skin preparation. Skin disinfection reduces the skin bacterial load (65), but a sterile venipuncture cannot be guaranteed due to inaccessibility of organisms present in sebaceous glands and hair follicles; organisms present in skin fragments may be drawn into the component bag (25). Multiple studies have evaluated skin disinfection in the context of blood donation (25, 26, 43). A summary of the effectiveness of some of the more commonly used skin disinfection methods is given in Table 3 (43). In general, either iodine or povidone iodine are used. In donors with allergies to iodine, chlorhexidine or double isopropyl alcohol skin disinfection is employed. The differ-

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TABLE 3. Percentage and mean count of donors with bacteria after skin disinfection[a]

No. of CFU/plate	% of contaminated donors after disinfection with:			
	Povidone iodine × 2	IPA[b] and iodine	IPA × 2 (sponge)	IPA × 2 (swab)
0	39	79	0	29
≤10	57	93	69	50
≤100	75	100	86	68
≤1,000	96	100	97	89
Mean count	175	3	161	237

[a] Data are from reference 43.
[b] IPA, isopropyl alcohol.

ence noted in Table 3 for two different isopropyl alcohol scrubs was attributed to the abrasive nature of the sponge used in one of the preparations.

Diversion of the initial blood draw. Several studies have demonstrated the partial effectiveness of diverting the first 10 to 30 ml of blood from the initial collection. A study performed with 22,000 samples of donated blood by the Red Cross in The Netherlands, in which the first 10 ml of donor blood was diverted from the primary bag, showed that 16 of the first 5-ml aliquots were bacterially contaminated while only 2 of the second 5-ml aliquots were positive after culture (19). A second study in France showed that removal of the first 10 ml of donor blood was associated with a significant decrease in bacterial contamination (18,263 collections with 0.39% contamination compared with 7,115 collections with 0.21% contamination; $P < 0.05$) (12).

Such methods are most effective with respect to skin contaminants (12, 19). However, it has been said that "one should not be diverted by diversion," since most fatal cases of bacterial contamination involve gram-negative organisms and thus would not minimized by diversion. Interestingly, the addition of a diversion bag to whole-blood collections in the United States has been initially complicated by hemolysis with certain sample tubes (from Pall, East Hills, N.Y.) and dilution of the sample with anticoagulant (from Baxter, Round Lakes, Ill), requiring redesign of both diversion systems (data presented at the HHS Advisory Committee on Blood Safety and Availability, Washington, D.C.; http://www.hhs.gov/bloodsafety/pastmeetings.html#n).

Apheresis versus whole-blood-derived platelet concentrates. Therapeutic doses of platelets can be obtained from two sources. Platelets can be collected from a donor by the use of an automated cell separator (apheresis); such collections can yield one to three therapeutic doses. Alternatively, platelets can be obtained from whole-blood donations (whole blood platelet concentrates [WBPCs]); however, a therapeutic dose requires the pooling of four to six WBPCs. Current estimates suggest that 69% of all therapeutic doses of platelets transfused in the United States are apheresis derived (1). Usage varies considerably by country.

Since bacterial contamination may result from a contaminated venipuncture or an asymptomatic bacteremic donor, it would be expected that pooled platelet products would be associated with a higher risk of contamination than a single donor product. From 1986 to 1998, the incidence of septic events related to platelets at Johns Hopkins University Hospital decreased from 1 in 4,818 to 1 in 15,098 as the hospital went from transfusing 51.7% to 99.4% single-donor apheresis units (48). The overall clinical sepsis rate was approximately 1 in 2,500 for WBPC pools and 1 in 13,400 for single-donor apheresis transfusion. The related mortality rate was approximately 1 in 17,000 for WBPC pools and 1 in 61,000 for single-donor apheresis platelets. It was concluded that the use of single-donor apheresis platelets is a simple means of reducing septic platelet transfusion reactions. Similarly, the University Hospitals of Cleveland have monitored the contamination rates of both single-donor and whole-blood-derived concentrates [A. Dykstra, M. Jacobs, and R. Yomtovian, Transfusion **38**(Suppl.):104S, 1998]. The rate of bacterial contamination of apheresis-derived platelets was 1 in 2,184. While the rate for random-donor platelets was similar at 1 in 1,861, random-donor platelet concentrates in a pool of six units would be expected to result in a contamination rate of 1 in 310.

Bacterial Detection

Timing of detection. Culture studies performed both on red cell units and platelets have shown that culture on the day of collection invariably misses bacterially contaminated units that would possibly achieve dangerous levels of overgrowth during storage of the blood components [5a, 10; M. A. Blajchman, A. Ali, P. Lyn, L. Bardossy, and H. Richardson, Transfusion 7(Suppl.):7S, 1997]. This is in contrast to viral contamination of blood components, in which the virus or the immune response to the virus (antibodies) is detected from a sample obtained at the time of donation. Bacterial contamination of blood components generally requires time for the organisms to proliferate before being detectable in a small representative sample of the product. Therefore, knowledge of the growth characteristics of bacteria in blood components is essential before one considers implementation of a detection strategy (Fig. 2 and 3).

Growth characteristics of 165 platelet units inoculated (to 1 to 50 or 1,000 CFU/ml) within 1 day of collection with one of the following: *B. cereus*, *P. aeruginosa*, *K. pneumoniae*, *S. marcescens*, *S. aureus*, and *S. epidermidis* showed that after 1 day of storage all samples of *B. cereus*, *P. aeruginosa*, and *K. pneumoniae* had concentrations of ≥10 CFU/ml (the level of detection), while only 71.4 and 84.2% of the *S. marcescens* and *S. aureus* samples were at concentrations of ≥10 CFU/mL (10). By day 3 of storage, all units inoculated with *B. cereus*, *P. aeruginosa*, *K. pneumoniae*, *S. marcescens*, and *S. aureus* contained $\geq 10^5$ CFU/ml. Units contaminated with *S. epidermidis* showed slower and more varied growth.

Bacterial culture. Although there are a variety of automated and semi-automated systems, only two are FDA cleared for quality control of bacterial culture in platelets in the United States. The first is an automated liquid culture system (BacT/ALERT; bioMérieux, Durham, N.C.) that uses broth bottles with a colorimetric sensor which changes color as a consequence of increasing CO_2 produced by bacterial proliferation. The machine monitors both the rate of change of the colorimetric sensor and the absolute color change of the sensor. Generally, one aerobic (and in some cases one aerobic and one anaerobic) bottle is inoculated with 4 ml of the platelet product. This system is not completely closed, since a needle is used

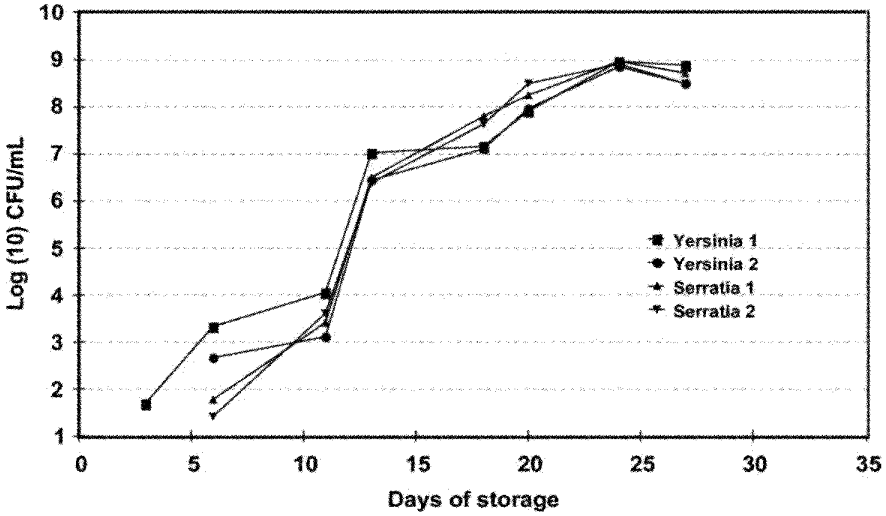


FIG. 2. Growth curves of four units of AS-3 red blood cells inoculated with *S. liqueifaciens* (two units inoculated to 4.2 CFU/ml) and *Y. enterocolitica* (two units inoculated to 11.6 CFU/ml) (5a). Bacteria were not detectable by culture until days 3 to 6. Isolates were from strains actually implicated in post-red-blood-cell-transfusion sepsis (the isolates were kindly provided by M. Arduino, Centers for Disease Control and Prevention, Atlanta, Ga.).

to inoculate the bottles. It has been extensively validated by tests with a wide range of potentially contaminating organisms (7, 8, 11, 44). The method reliably detects contamination of platelets inoculated to 10 CFU/ml and in many cases to ≤5 CFU/ml (e.g., *B. cereus*, *S. marcescens*, *C. perfringens*, *S. epidermidis*, *S. pyogenes*, *E. coli*, *K. pneumoniae*, *S. aureus*, and viridans streptococci) in 12 to 26 h. *Propionibacterium acnes* (which is of questionable clinical significance in this setting) required longer incubations. Recently, our laboratory completed an 11-month pilot program in which we cultured 2,397 apheresis-derived platelets on day 2 of storage (collection day = day 0) and again at the time of issue (or following outdate: days 6 to 8) (6). This study involved the inoculation of 9,588 bottles; one "machine" false-positive bottle (negative subculture, Gram stain, and repeat culture), and one inadvertent contamination false-positive bottle (*Propionibacterium* sp.) were detected. Thus, the overall false-positive rate was 2 in 4,794 samplings (0.04%, or 1 in 2,397 samplings) or 2 in 9,588 bottles (0.02% or 1 in 4,794 bottles). During this period, we successfully interdicted three apheresis-derived units (one collection) contaminated with *S. epidermidis* but were unable to prevent the transfusion of four apheresis units contaminated

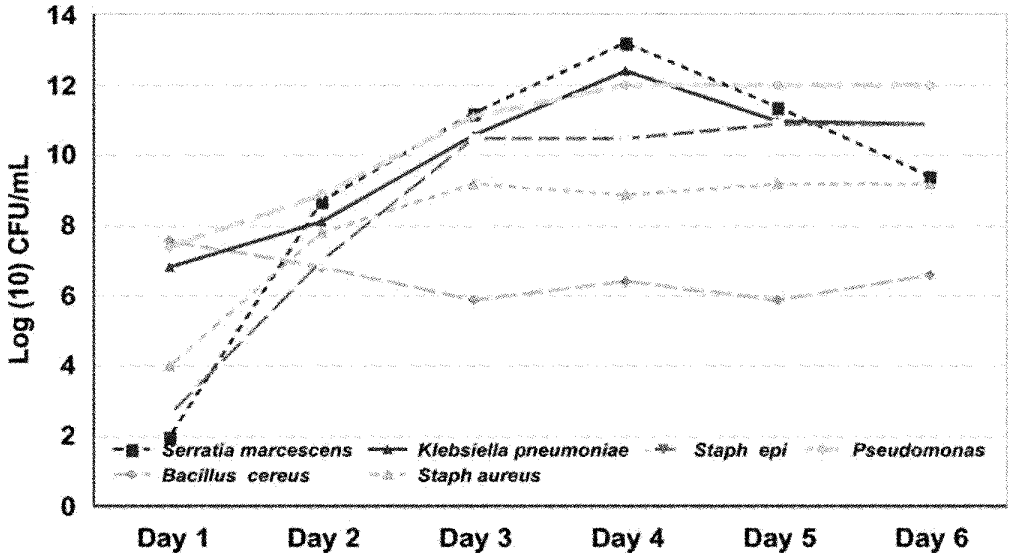


FIG. 3. Growth curves of six bacteria species (*S. marcescens*, $n = 7$; *K. pneumoniae*, $n = 21$; *S. epidermidis*, $n = 21$; *Pseudomonas* sp., $n = 15$; *B. cereus*, $n = 9$; *S. aureus*, $n = 22$) in 95 platelet units. All bacteria were inoculated on day zero at 10–50 CFU/ml (10).

TABLE 4. Summary of recent experiences with culturing of apheresis-derived platelets at three large blood centers[a]

Center	No. (rate) of results[b]		
	True positive	False positive	No. tested
New York Blood Center	5 (1/4,101)	5 (1/4,101)	20,506
Florida Blood Services	6 (1/1,790)	5 (1/2,147)	10,737
Puget Sound Blood Center	5 (1/1,800)	15 (1/600)	8,999
Total	16 (1/2,515)	25 (1/1,610)	40,242

[a] http://www.hhs.gov/bloodsafety/pastmeetings.html#n.
[b] True positive = positive bottles in which an organism was identified and a repeat sample from the bag or a retention sample also contained the same organism. False positive = positive bottles that contained no organism (machine false positive) or from which the organism could not be reisolated from the original bag or a retained sample.

with *Propionibacterium* sp., for which the culture bottles were reactive after 6 days of incubation. Thus, the overall true-positive rate was 7 of 2,397 apheresis units (0.29%), with a true-positive rate for aerobic organisms of 3 of 2,397 (0.13% or 1 of 799 units) and an anaerobic true-positive rate of 4 of 2,397 (0.17% or 1 of 599 units). Within our facility, transition from a research setting to a clinical microbiology laboratory has resulted in a higher false-positive (laboratory contamination) rate of 0.6% per unit (with one aerobic and one anaerobic bottle) (unpublished data). More recent experience from three large blood centers is included in Table 4.

The second culture system is the Pall Bacterial Detection System (BDS) (49). Sampling is obtained so as to maintain an effectively closed system. Approximately 5 to 6 ml of leukocyte-reduced platelet-rich plasma is removed from the bag and passed through a filter that removes residual white cells and platelets but allows approximately 50% of the bacteria (variable by organism) and plasma to pass into an incubation bag. The incubation bag holds 2 to 3 ml and contains sodium polyanethol sulfonate, which facilitates the growth of gram-negative organisms by inhibiting both complement and plasma lysosomal enzymes and by antagonizing the action of growth-retarding lipoproteins normally present in plasma. The incubation bag is then incubated at 35°C for at least 24 h before the oxygen concentration of the bag's headspace is measured with an oxygen analyzer. A decrease in the oxygen concentration to 19.5% or lower is an indication of bacterial growth. Thus, this system does not detect obligate anaerobic organisms. Leukocyte-reduced platelets challenged with 10 known platelet contaminants at doses of 100 to 500 CFU/ml were detected at a rate of 96.5% at 24 h and 100% at 30 h (49). External validation studies have shown lower than expected sensitivity for *S. epidermidis* and *S. agalactiae* [K.-A. T. Nguyen, T. Yamamoto, and N. Hirschler, Transfusion **43**(Suppl.):S63-030K, 2003; H. C. Pleasant, G. A. Geele, and M. P. Holub, Transfusion **43**(Suppl.):S62-030K, 2003 (abstract)]. Most recently, an enhanced version of this system has been cleared by the FDA, it includes modifications to the configuration (with removal of the filter, which removed some bacteria), and the incubation bag now contains a platelet-aggregating agent and tryptic soy medium to enhance the sensitivity and decrease the incubation time (http://www.pall.com/BDS.asp??noleftnav).

Less sensitive methods of detection such as Gram or Wright stains or the use of glucose and pH determination (in some case with multireagent strips) are used for rapid detection of bacteria in platelet components prior to transfusion. However, the overall sensitivity is only 10^6 to 10^7 CFU/ml (13, 62, 63, 66). Werch et al., from the M. D. Anderson Cancer Center, reported on the screening of 3,093 platelet concentrates, in which they found that multireagent strips for 30 bags had glucose levels or pH outside of the reference range (63). Two of these platelet units were culture positive for *B. cereus*. This screening method resulted in 1 unit per 110 being wasted but prevented two patients from receiving contaminated platelets.

Molecular biology techniques. Because of the high sensitivity and specificity and the rapidity of obtaining results, molecular biological approaches are theoretically appealing for the detection of contaminating organisms in blood components. One such approach is the use of a nonamplified chemiluminescence-linked universal bacterial rRNA probe (5, 9). This technique was shown to detect four bacterial species in the range of 10^4 to 10^5 CFU/ml. In some cases, *S. aureus* was detected at levels as low as 10^2 to 10^3 CFU/ml. Other investigators have pursued the use of PCR-based amplification for a limited number of organisms (56).

However, bacterial DNA contamination of nucleotide amplification reagents (particularly the bacterially derived enzymes) and laboratory materials and the presence of bacterial DNA sequences commonly found in human blood complicate the usefulness of universal bacterial amplification techniques (22, 45, 47). It also remains to be seen if complex molecular biology techniques could be successfully deployed to a wide range of transfusion services.

Detection systems recently approved in Europe. Recently, two bacterial detection systems were approved in Europe. The Scansystem (Hemosystem, Marseilles, France) involves a 70-min solid-phase laser cytometry. In a few studies, the Scansystem detected 11 organisms in the range of 10 to 10^3 CFU/ml [P. Morel, M. Deschaseaux, X. Bertrand, C. Naegelen, and D. Talon, Transfusion **43**(Suppl.):SP13, 2003]. Positive samples require a technologist to perform a microscopic confirmation.

A second "rapid" method recently approved detects bacteria by using dielectrophoresis (Cell Analysis, Slough, United Kingdom). Platelet concentrates inoculated with six organisms at concentrations of 10^3 to 10^5 CFU/ml were detected after 30 min of dielectrophoresis by image analysis as they were released from the electrodes when the electric field was discontinued [C. P. McDonald, R. Smith, J. Colvin, S. Robbins, J. Barbara, W. Betts, R. Anthony, K. Chan, A. Brown, and K. Gregory, Transfusion **41**(Suppl.):S119-040H, 2001].

Detection systems under development. Currently, there are at least three other rapid-detection systems under development. Genpoint (Oslo, Norway) has developed a unique system that uses paramagnetic particles to concentrate bacteria (BUGS'n BEADS) coupled with a PCR for highly conserved DNA. The target sensitivity of this assay is 1,000 CFU/ml, and the total time is 2.5 h. Immunetics, Inc. (Cambridge, Mass.) is developing a 96-well 1-h enzyme immunoassay which employs proteins and derived peptides that bind to the peptidoglycan component of the bacterial cell wall. Preliminary results suggest a sensitivity of 10^3 to 10^4 CFU/ml (or lower) for a variety of organisms [L. A. Beausang and A. Levin, Transfusion

43(Suppl.):20A, 2003; D. Kagan, and A. E. Levin, Transfusion 41(Suppl.):S118-040H, 2001]. Verax Biomedical (Worcester, Mass.) is developing an immunoassay embodied in a lateral-flow format. Preliminary results suggest a sensitivity of 10^3 to 10^4 CFU/ml for a variety of organisms [F. Kenny, C. Woodbury, M. Pelak, J. Weinberg, and J. A. Hall, Transfusion 43(Suppl.):10A, 2003].

Implementation of detection systems: problems and considerations. (i) Platelet concentrates and prestorage pooling. Bacterial detection of whole-blood-derived platelet concentrates presents logistical problems for systems that do not allow the prestorage pooling of platelet concentrates (e.g., United States, Canada, and Hong Kong). In Europe, whole-blood-derived buffy coat platelets are prepooled prior to storage; this allows for the culturing of platelets by the methods described above. If prepooling is not allowed, culturing of each individual platelet sample is generally not thought to be practical due to the loss of volume from each bag required per culture and the high cost of culture for each individual bag. In the absence of prepooling, many centers have chosen or are contemplating the use of less sensitive bacterial detection strategies such as Gram stains or glucose or pH measurement (or the use of multireagent strips) (2).

(ii) Anaerobic organisms. Anaerobic organisms such as *Propionibacterium* sp. can be identified in platelets; however, it is not known whether anaerobic organisms such as propionibacteria are clinically significant since growth in the aerobic environment of platelet storage is slow and not favorable. Although a few cases of *Propionibacterium*-contaminated units have been infused into patients, no long-term sequelae have been reported (6, 40, 55). Debate continues as to the value of an anaerobic culture in this context. It is worth noting that some aerobic organisms or isolates (e.g., viridans streptococci) can be more rapidly detected in an anaerobic culture system (7, 8, 11).

(iii) Potential for reduced shelf-life. Some centers have chosen to incubate platelet cultures for 12 to 24 h prior to release. This has in many cases led to a decrease in the available shelf-life of the platelets. Given that the current platelet products have a shelf-life of only 5 days (and that, for 1 to 2 days, such products are not available, pending completion of viral testing), any further reduction in available shelf-life can impact inventory control and hospital supply.

(iv) Use of noncleared detection systems. Use of non-FDA-cleared detection systems (e.g., alternative automated culture systems) would at a minimum require internal validation. Examples of validation of detection systems are available in the literature (7, 8, 11, 44, 49). Patent issues currently preclude certain companies from actively pursing this market. Use of a non-FDA-cleared device for bacterial quality control of platelets, when cleared devices are available, may place an institution at higher legal risk should a patient die after receiving bacterially contaminated platelets.

Bacterial Elimination

Pathogen reduction technologies. Continued efforts to create a "zero-risk" blood supply have led to various pathogen reduction technologies. A variety of photoactive sensitizers have been investigated for use in the reduction of viruses, bacteria, and parasites.

The best studied of these methods is the use of amotosalen HCL (S-59), a synthetic psoralen combined with a photochemical treatment process that causes permanent cross-links in DNA and RNA (INTERCEPT Platelet System; Baxter Healthcare Corp., Round Lake, Ill.) (41, 64). However, organisms capable of spore formation may be resistant to photochemical inactivation (34). The SPRINT trial, a multi-center phase III trial, has evaluated the hemostatic effectiveness of S-59 pathogen-inactivated platelets. Treated platelets were found to be as effective as conventional platelets for the prevention and treatment of bleeding; however, the treated platelets resulted in a lower post-transfusion platelet response, resulting in the need for 35% more platelets to support transfusion-dependent patients (18, 41). Concerns also remain regarding mutagenicity and teratogenicity associated with such technologies.

Growth Inhibition

The addition of antibiotics to blood components has been considered but has not been adopted due to the added risk of drug reactions (trading one infrequent reaction for another) and the potential for the development of antibiotic resistance if small amounts of antibiotics were infused with every transfusion (31).

THE PROSPECT OF SEVEN-DAY STORAGE WITH DETECTION

Currently, within the United States platelet storage is limited to 5 days due to the fear of bacterial overgrowth during storage at 20 to 24°C. In 1983, platelet storage in the United States was extended to 7 days; however, in 1986 the FDA shortened the outdate to 5 days following reports of bacterial sepsis with older units (65). With the prospect of bacterial detection, the possibility of an extended shelf-life is being reconsidered. European reports have described the use of bacterial culturing of platelets on days 1 to 3 of storage in order to extend the shelf-life of platelets to 7 days, thereby reducing the number of outdates [M. Ollgaard, I. Albjerg, and J. Georgen, Vox Sang. 74(Suppl. 1):1126, 1998; D. Vuetic, J. Taseki, B. Balint, and V. Mirovic, Vox Sang. 80(Suppl. 1):P371, 2000]. Within the United States, premarket multicenter studies (or possibly postmarket studies) are currently under discussion to provide data that may allow the extension of storage to 7 days. It would be expected that the cost of culturing would be mitigated by the savings obtained by the extension of platelet storage time (20). For example, in Denmark, when bacterial culture was implemented in 1997, it was anticipated to be cost neutral if the outdating could be reduced from 18 to 8% by extending the storage time to 7 days (24). The actual outdating rate decreased to 3 to 6%.

CONCLUSIONS

Regulatory oversight in the United States and Canada has generally concentrated on new emerging threats such as West Nile virus (leading to nationally mandated efforts to screen the

blood supply with West Nile virus nucleic acid testing). However, there is no similar mandate in these countries for bacterial screening. To place these risks into some perspective, in 2002 23 transfusion-transmitted cases of West Nile virus were identified in the United States (50). Of these 23 recipients, 7 died, but only 5 of these deaths were associated with West Nile virus meningoencephalitis. During the same period, 17 deaths from bacterial contamination of blood components were reported to the FDA (14). Contaminated apheresis-derived platelets and pooled platelets were the products most often implicated. Gram-negative bacteria were the causative agents in the majority of these fatalities. It is perplexing that similar (or greater) government emphasis has not been placed on the detection of bacteria.

In blood banking and transfusion medicine, our paramount concern is to improve transfusion safety for patients, in our attempt to achieve a zero-risk blood supply. Unlike other recent threats (existing or theoretical) to blood safety, the movement for reducing bacterial contamination has come from the blood-banking and the transfusion medicine community. In this case, voluntary accrediting agencies such as the American Association of Blood Banks and the College of American Pathologists have taken the lead by developing standards to reduce the risk of bacterial contamination of blood components (17, 23). Our patients deserve no less.

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Interventions Implemented to Reduce the Risk of Transmission of Bacteria by Transfusion in the English National Blood Service

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Abstract

Summary

Background

Bacterial contamination remains a significant problem in transfusion medicine. A National Health Service Blood and Transplant (NHSBT) study and surveillance data indicated skin commensals derived from the skin of the donor are the major contaminants of blood components. NHSBT therefore explored two interventions: improved donor arm disinfection and diversion.

Methods

Improved donor arm disinfection: Commercial and in-house methods of disinfection were evaluated. Swabs of the venepuncture site were taken before and after disinfection and the reduction in bioburden determined. Diversion: Special collection bags were manufactured to allow the initial volume of blood to flow into a pouch, representing the diversion pouch and then the next flow of blood into another pouch representing the collection bag. Pouches were screened for the presence of bacteria. The reduction in bacterial contamination was then determined.

Results

A two-step commercial procedure (Donor Prep Kit; DPK) consisting of 70% isopropyl alcohol followed by tincture of iodine was shown to be a best practice procedure (2-min procedure). A 99.79% reduction was obtained, and this method was 10 times more effective than current practice at that time. The DPK was shown in a field trial to increase donor waiting time. A second study was initiated to find a more rapid procedure. ChloraPrep®, consisting of 2% chlorhexidine gluconate and 70% isopropyl alcohol, was shown to have equivalent disinfection efficiency as the DPK, but only took 1 min to perform. In 2006, ChloraPrep was introduced as the national method of donor arm disinfection. Diversion was shown to give a 47% reduction in contamination and was introduced nationally in 2002.

Conclusion

Improved donor arm disinfection and diversion are effective, low-cost interventions, but do not eliminate all bacterial transmissions. In 2011, bacterial screening of platelet components was introduced by NHSBT to further increase the safety of the blood supply.

KeyWords: Bacterial contamination, Blood donation, Blood safety, Haemovigilance, Platelet concentrates, Transfusion reaction, Transfusion risks, Transfusion-associated infectious Bacteria, Diversion, Disinfection

Introduction

Since the 1970s, the risk of viral transmission by transfusion has been markedly reduced [1]. Transmission of bacteria by transfusion is not a new problem, having been reported nearly 70 years ago [2, 3]. In the mid 1990s, the attention of the blood community was drawn to bacterial transmissions due to case reports in the literature and the establishment of haemovigilance systems. In 1995 the U.K. Serious Hazards of Transfusion (SHOT) voluntary surveillance system was established, reporting that between 1995 and 2001 bacterial transmissions accounted for 64% (21/33) of microbial transmissions [4]. In this period in the UK, 85% (6/7) of microbial fatalities reported to SHOT were due to transmission of bacteria by transfusion. Platelet concentrates accounted for 81% (17/21) of these transmissions.

From 1994 to 1999, the French haemovigilance surveillance system (a mandatory requirement under French law), attributed 18 deaths (four occurring in 1997) to blood components contaminated with bacteria [5, 6]. Between 1994 and 1999, bacterial transmissions comprised 22% of total transfusion-associated fatalities [7]. Transmission of bacteria by transfusion was reported to the haemovigilance surveillance system as the most frequently identified cause of death [5].

In the USA, from 1985 to 1989 bacterial contamination was second only to haemolytic reactions as the most frequent reported cause of mortality, accounting for over 10% (77/694) of transfusion fatalities [8]. From 2001 to 2003, the transmission of bacteria by transfusion accounted for 37 deaths, amounting to 14.1% of all transfusion fatalities [9].

A National Health Service Blood and Transplant (NHSBT) retrospective monitoring study was established in 1995 to determine the bacterial contamination rate in blood components using an automated microbial detection system [10, 11]. The study was also used to determine the effectiveness of any interventions implemented to reduce bacterial contamination.

Data from this study and SHOT surveillance data indicated that the vast majority of organisms that contaminate blood components are skin commensals derived from the skin of the donor at venepuncture. NHSBT therefore explored two interventions:

– improved donor arm disinfection,
– diversion.

Material and Methods

Improved Donor Arm Disinfection

A study was undertaken to determine the effectiveness of in-house and commercial disinfection protocols [12]. Swabbing of the venepuncture site was performed before and after disinfection. Swabs were inoculated onto agar plates, and the reduction in bioburden pre and post disinfection was determined. A second study was undertaken to derive a disinfection procedure that would only take 1 min to perform [13].

Diversion

In 1995, Olthuis et al. [14] proposed that diversion of the initial volume of blood donation from the collection bag had the potential to dramatically reduce bacterial contamination. The rationale behind this is that (as previously mentioned) the major source of bacterial contamination of blood components occurs at the collection stage, due to inadequate donor arm disinfection and/or a small core of skin entering the collection bag from coring by the phlebotomy needle. Re-direction of the initial flow of blood from the collection bag into a pouch or side arm would thus reduce the risk of bacterial contamination of the donation contents.

Special collection bags were manufactured for a study to determine the effectiveness of diversion [15]. These bags consisted of two sampling pouches attached to the standard collection bag configuration. At donation, blood was made to flow initially into pouch P1, which represented a diversion pouch. Pouch P1 was then closed causing the blood to flow into pouch P2, which acted as a representative sample of the collection bag post diversion. P2 was then closed, and blood was

diverted into the collection bag as in a routine donation. The pouches were sampled and inoculated into culture bottles and incubated on an automated microbial detection system for 7 days. Any bacteria that grew were sub-cultured and identified.

Results

Improved Donor Arm Disinfection

The Donor Prep Kit (DPK) (Ecolab (formerly Medi-Flex), Leadwood, KS, USA) was shown to be a best-practice technique, consisting of an initial application of isopropyl alcohol and tincture of iodine. The procedure took 2 min, with an application time of 30 s and drying time of 30 s for each disinfectant. A percentage reduction of 99.79% ($\log_{10}$ reduction 2.67%) was obtained compared with 78.2% ($\log_{10}$ reduction 1.31%) for the then current method, 0.5% chlorhexidine isopropyl alcohol wipe (Guardpack, Chelmsford, Essex, UK) [12].

The DPK was implemented for apheresis platelet donations in July 2001, and the reduction in the bacterial contamination rate of time-expired platelet donations was shown to be 57% [16]. Previously an experimental study predicted a 57% reduction in contamination [15]. A 67% reduction in clinically apparent cases of bacterial transmission following transfusion of NHSBT blood donations reported to SHOT was observed [17]. In the period 1997 to 2000 prior to implementation, 6 clinical cases (including 2 deaths) were reported. After the introduction of the DPK at apheresis clinics in the 4-year period from July 2001 to 2005, only 2 clinically apparent reactions from transfusion of platelet concentrates manufactured by NHSBT have been reported.

An extensive field evaluation of the use of the DPK procedure has been undertaken at mobile blood donor sessions. It was however, deemed inappropriate for routine use by NHSBT because it would increase donor waiting times. This was due to the additional 3 min that was required with the DPK compared with the routine method in use at that time. The NHSBT National Bacteriology Laboratory (NBL) was therefore tasked with identifying a disinfection procedure that was of comparable disinfection efficacy as the DPK, but was only 1 min in duration.

The ChloraPrep® disinfection method (CareFusion Ltd, Reigate, UK), consisting of a 30-second application of 70% isopropyl alcohol and 2% chlorhexidine gluconate with a 30-second drying time was shown to give equivalent disinfection efficiency as the DPK [13]. In 2006, ChloraPrep was implemented throughout NHSBT for both routine and apheresis donations.

Diversion

A 47% reduction in bacterially contaminated blood donations was observed in our study on the effectiveness of diversion [15]. On the basis of this study, diversion was implemented nationally in 2002. Monitoring data derived from testing outdated platelet concentrates showed a 66% reduction in contamination [16]. Prior to the implementation of diversion in the 3-year period 1999 to 2001, there were 11 clinically apparent cases from NHSBT-produced pooled platelet concentrates (n = 9) and red cell units (n = 2). After the implementation of diversion in the 3-year period 2003 to 2005, there were only 2 reports of clinically apparent transmission of bacteria by transfusion, a reduction of 82% [17].

The NHSBT diversion study also indicated that diversion, together with improved donor arm disinfection, would reduce bacterial contamination by approximately 77% [15].

Discussion

Donor arm disinfection is the first physical intervention applied to prevent microbial contamination of a blood donation. Many blood services have now validated and implemented best-practice procedures [18, 19]. In Canada the DPK system was shown to be a best-practice procedure, a finding confirmed by our studies [20]. Studies in the USA and Canada with the ChloraPrep disinfection device have confirmed the findings of NHSBT [21, 22]. This device has been adopted for use in these countries. Since the work of NHSBT, the evidence-based practice in Infection Control Guidelines Version 2 (epic 2) for National Health Service hospitals in England recommend "a single patient use application of alcoholic chlorhexidine gluconate solution, preferably 2% chlorhexidine in 70% isopropyl alcohol" for central venous access device decontamination [23].

The NHSBT diversion study indicated that a 47% reduction in bacterial contamination would be obtained, although a greater reduction of 66% was observed in the outdated platelet study, and clinically apparent transmissions were reduced by as much as 82%. Studies in the Netherlands by de Korte et al. [24] and by Ohlbius et al. [14] showed a 40% and 82% reduction respectively. Brunead et al. [25] in France reported a 72% and Benjamin et al. in the USA a 54% reduction in bacterial contamination [26]. Diversion has now been widely adopted by blood services.

Improved donor arm disinfection and diversion have been shown to be highly effective, relatively low-cost interventions for reducing the transmission of bacteria by transfusion. An NHSBT study indicated that improved donor arm disinfection in conjunction with diversion would reduce bacterial contamination by approximately 77% [27]. Residual contamination levels of blood units after the introduction of diversion may be in the order of 30–40% [28, 29].

Since 2006, improved donor arm disinfection and diversion have been used for all NHSBT donations. In the period of SHOT haemovigilance 2006–2009, bacterial transmission was reported from 10 NHSBT donations which resulted in 4 deaths [30]. In November 2005 in the UK, it became mandatory to report adverse transfusion reactions, which resulted in an increase in bacterial investigations, revealing more cases of transmission. In 2011, in view of this data, NHSBT implemented bacterial screening of platelet concentrates to further increase the safety of the blood supply.

Disclosure Statement

The author declared no conflicts of interest.

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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.

1

. 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.

"

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

.

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

.

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

.

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

.

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

.

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

.

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 chrom ogenic substrate S2288 (3 mM), followed by measurement of absorbance over time at 405 n m (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 sa mple to which aprotinin was added first was used as a control. Each sample was diluted in tri s 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 S27 65, 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 red uction in blood clotting time. In the example shown here the fibrinolytic effect of the "FVII acti vator" was hidden in the background. The reason for this is that in "normal subjects" the conc entration 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:

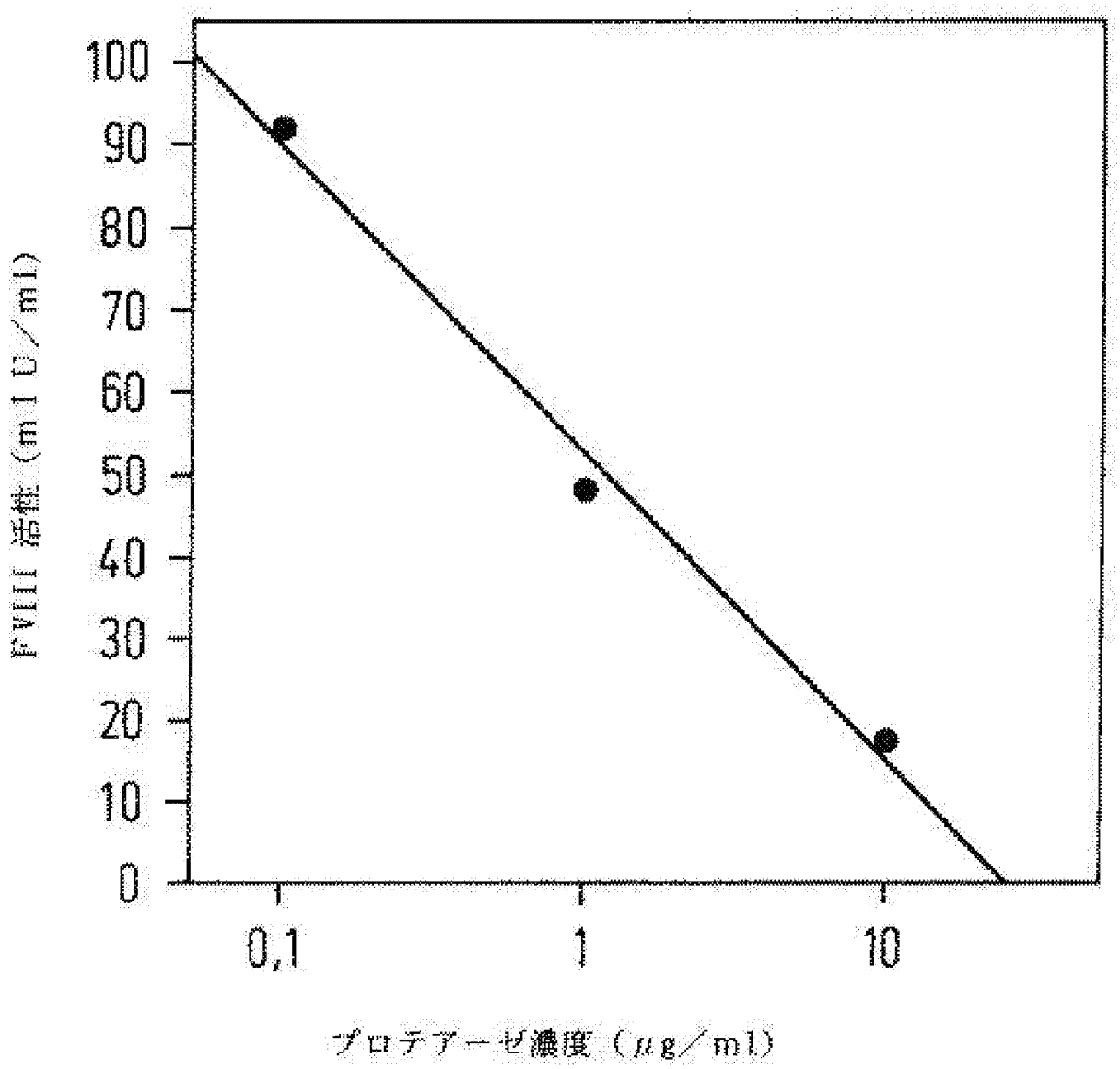
[Table 14]

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

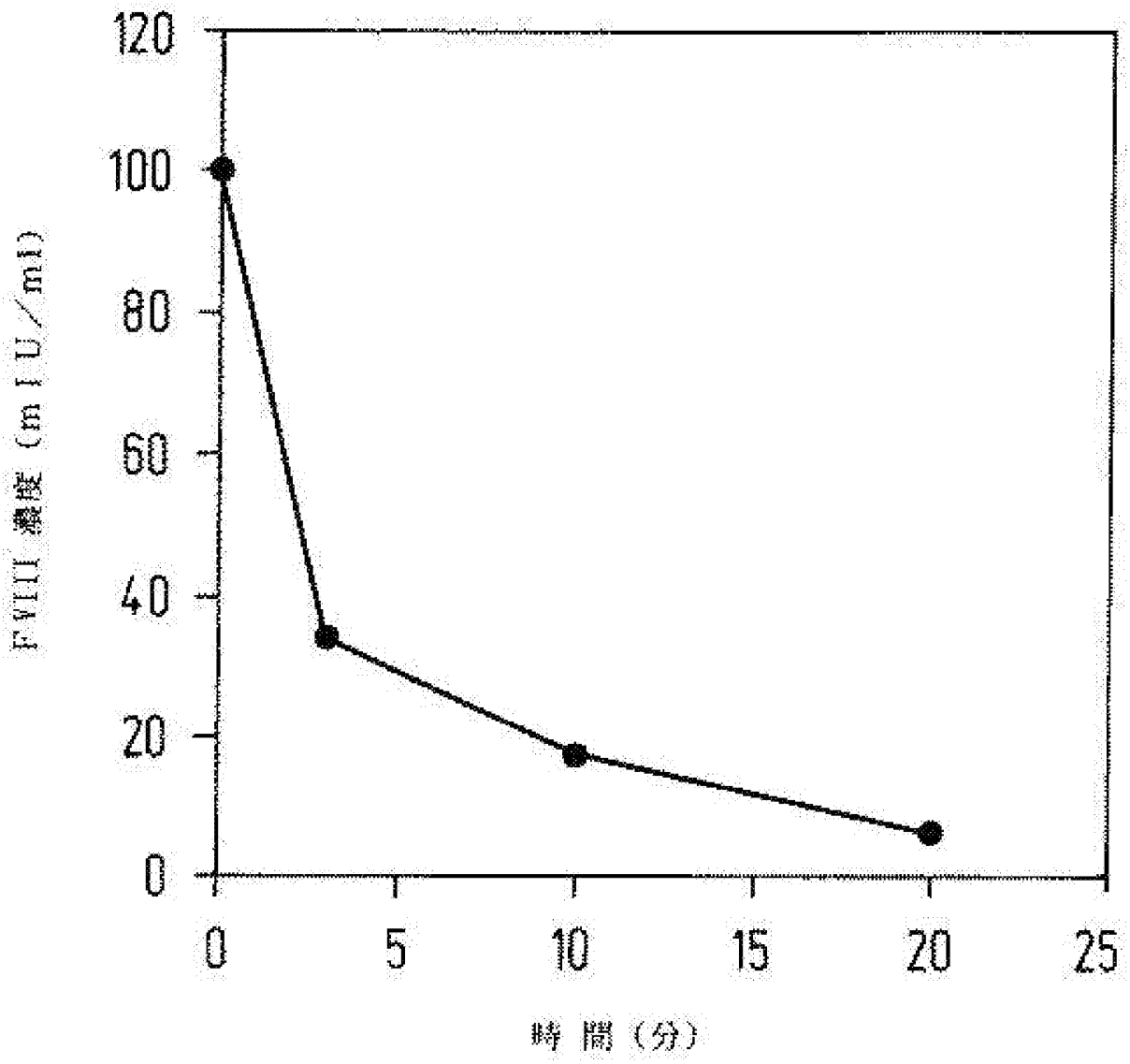
Addition of sucrose and one amino acid in each case demonstrated a significant stabilization of the protease.

drawing open —

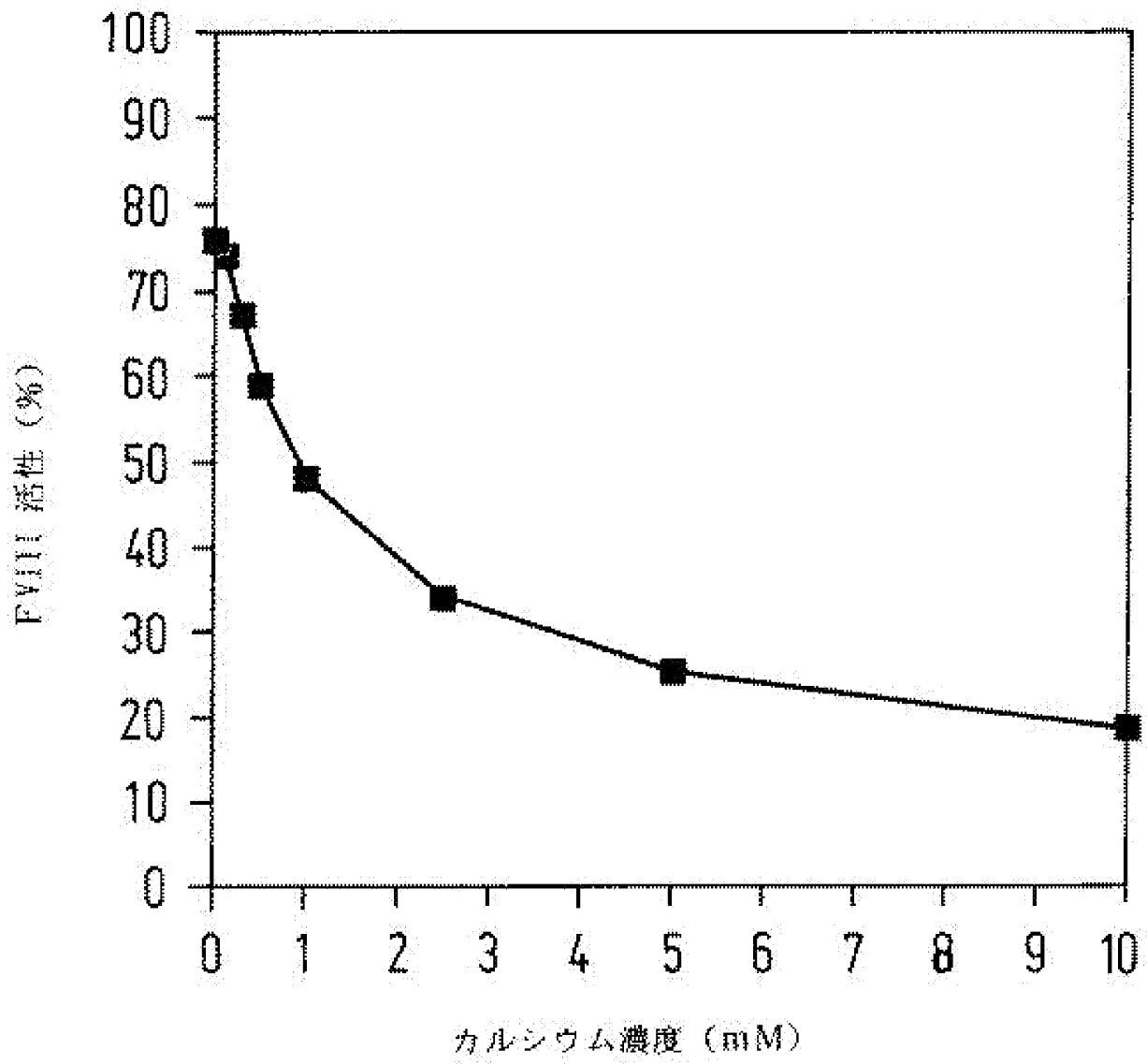
[Fig. 1]



[Figure 2]



[Figure 3]



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1 2 3

Magnify and Rotate

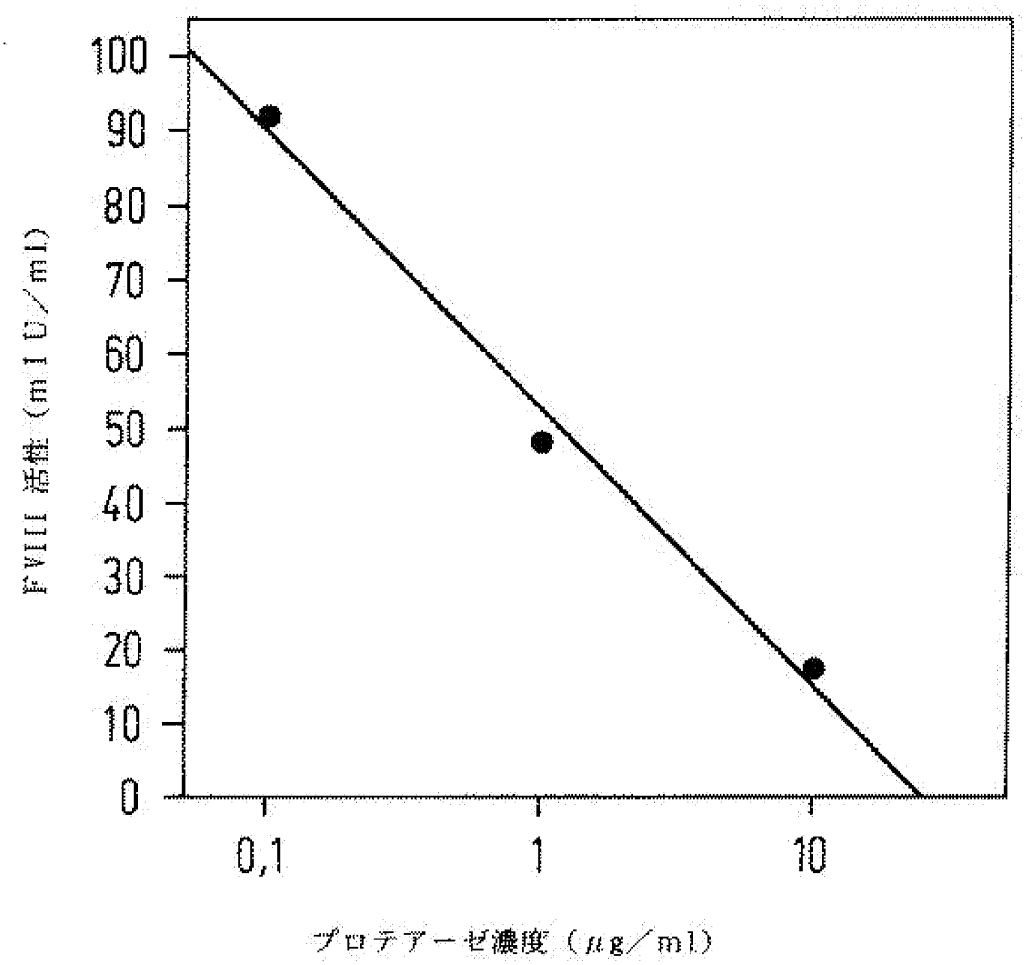


Figure 1

1 / 1 display

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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】

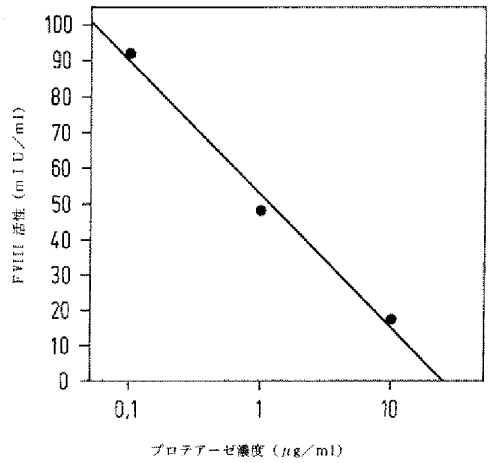
【0009】

【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。

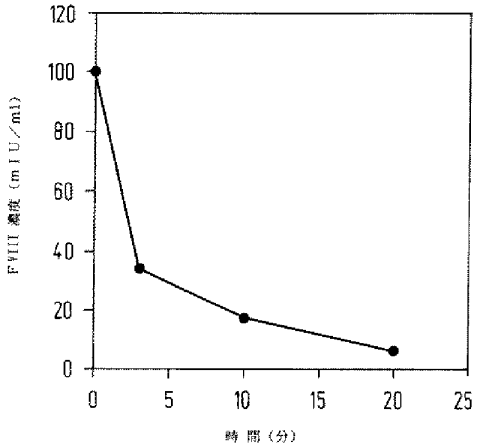
【図2】プロテアーゼ濃度を一定とし、ＦＶＩＩＩを様々な時間インキュベートした場合のＦＶＩＩＩの不活性化を示す。

【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。

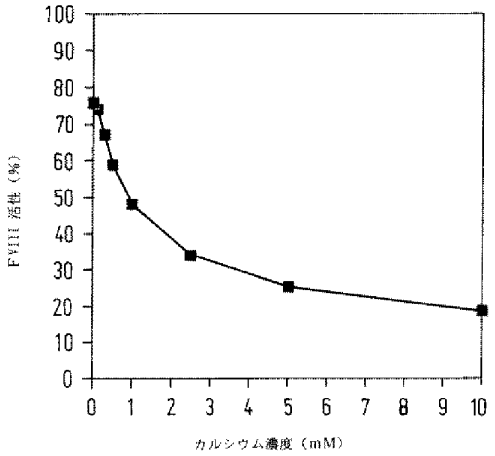
【図1】


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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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

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

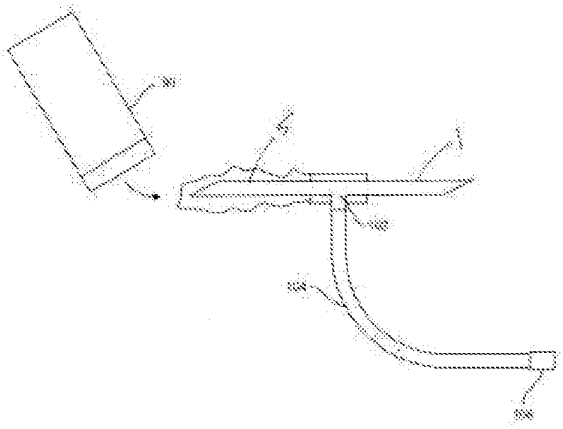
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Blood sample optimization systems and methods are described that reduce or eliminate contaminates in collected blood samples, which in turn reduces or eliminates false positive readings in blood cultures or other testing of collected blood samples. A blood sample optimization system can include a blood sequestration device (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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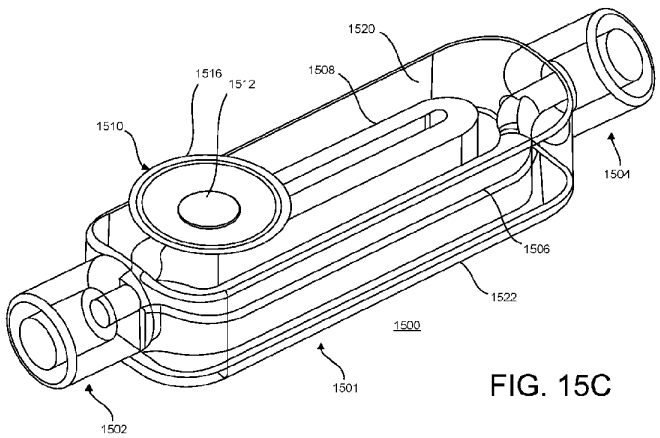


FIG. 15C

(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.

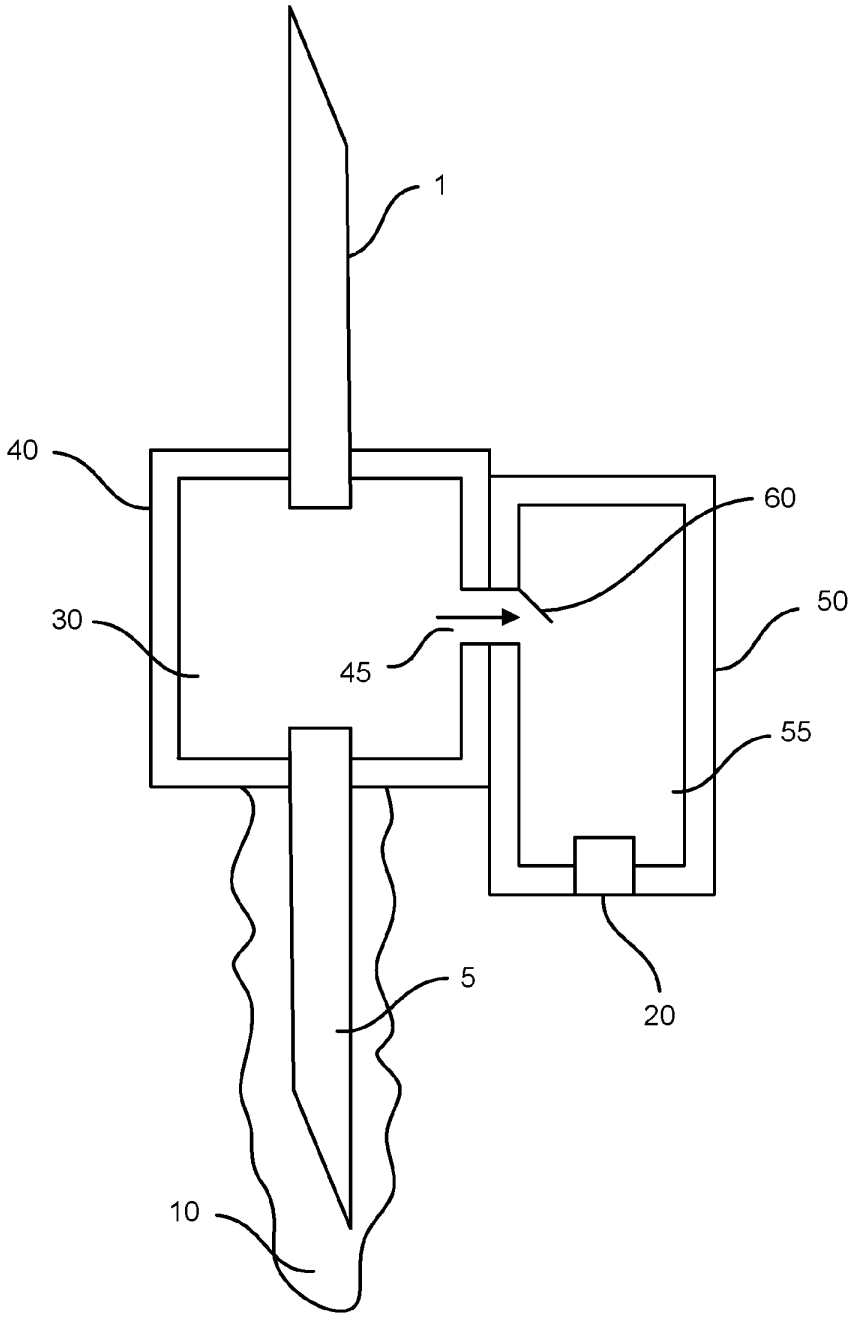


FIG. 1

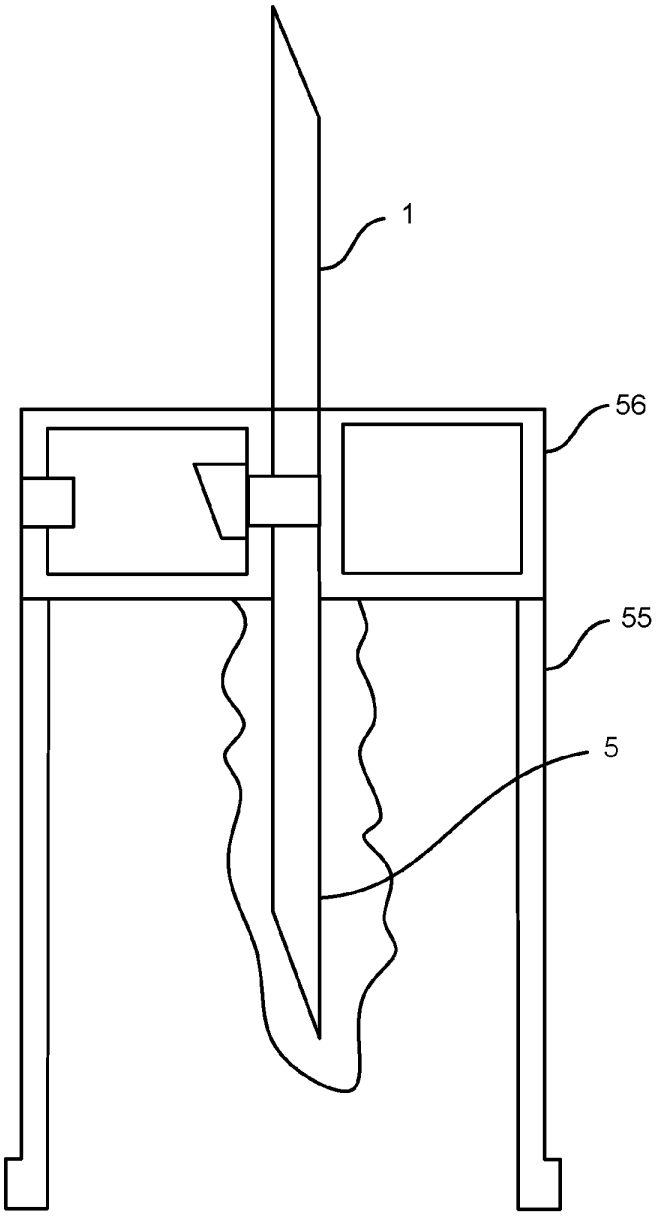


FIG. 2

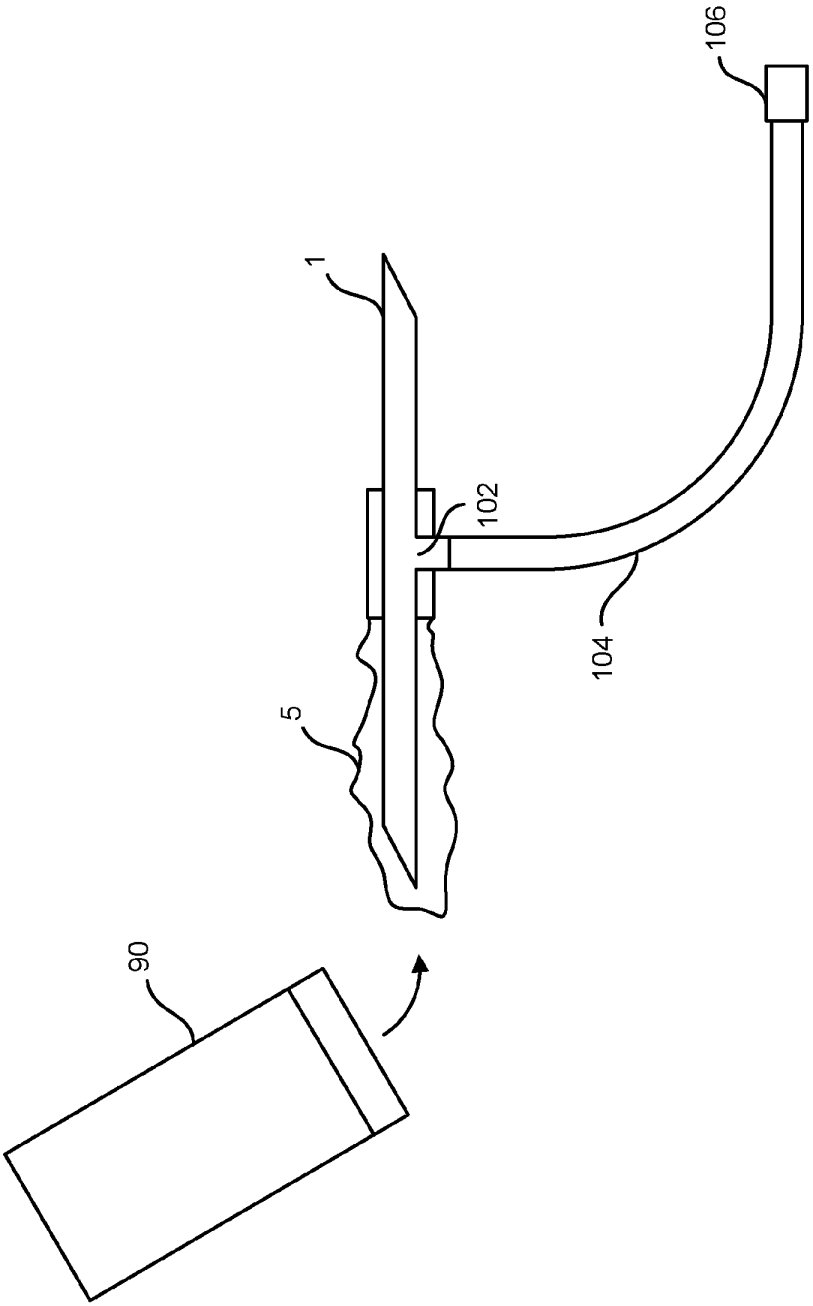


FIG. 3

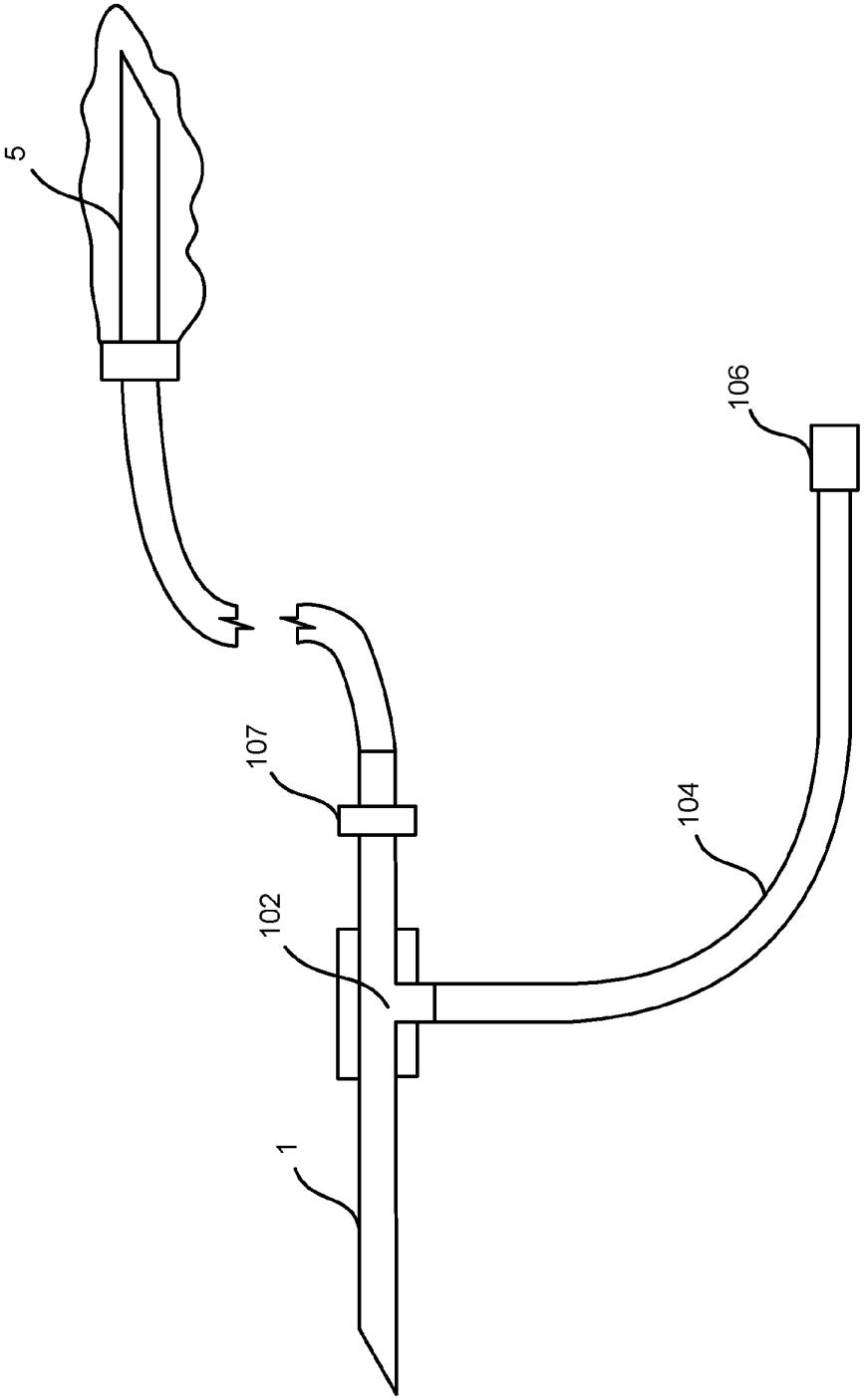


FIG. 4

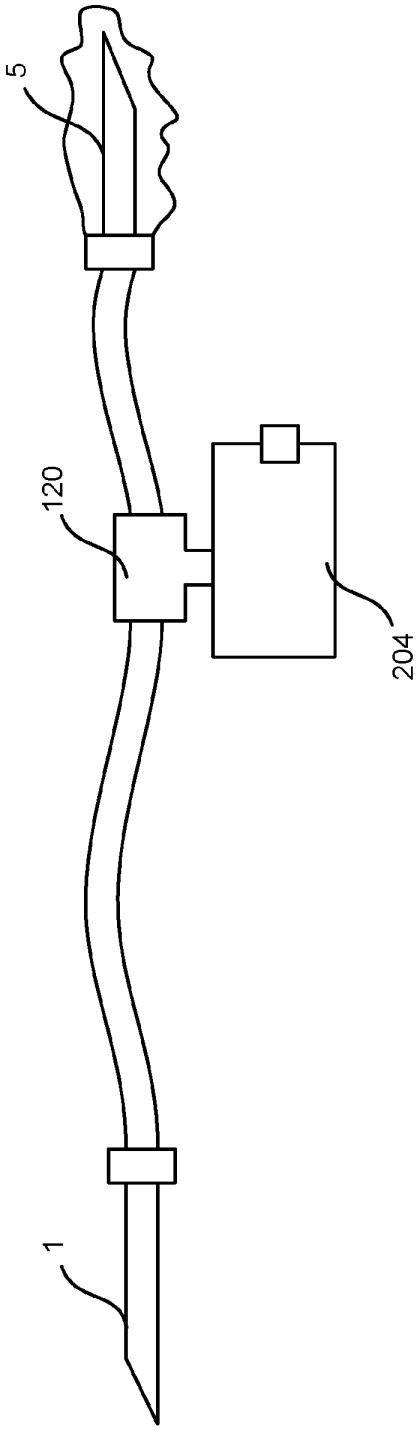


FIG. 5

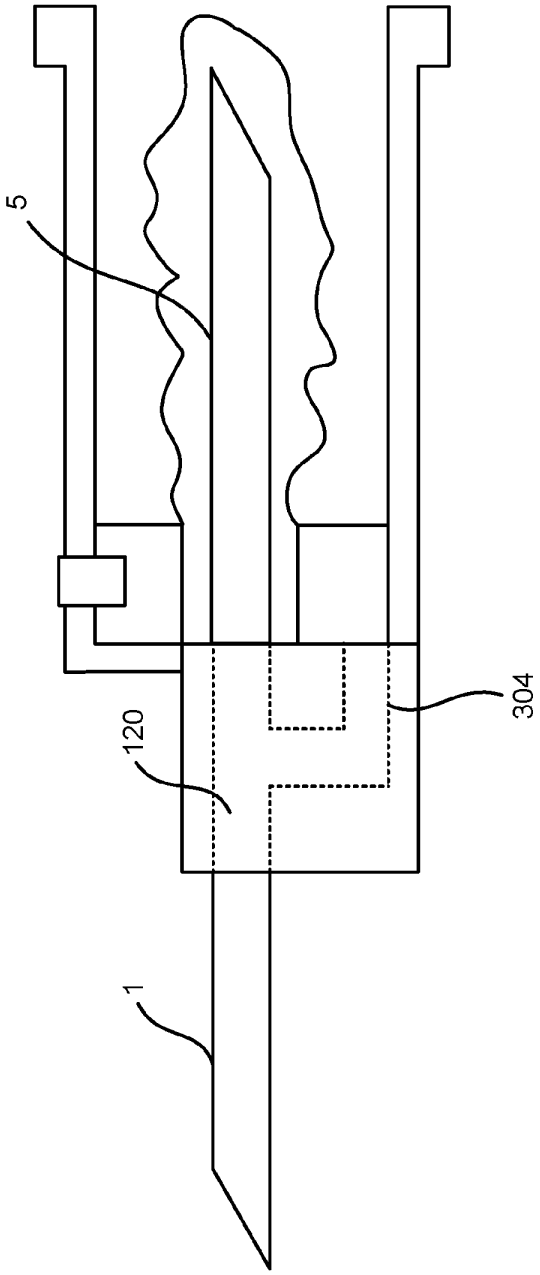


FIG. 6

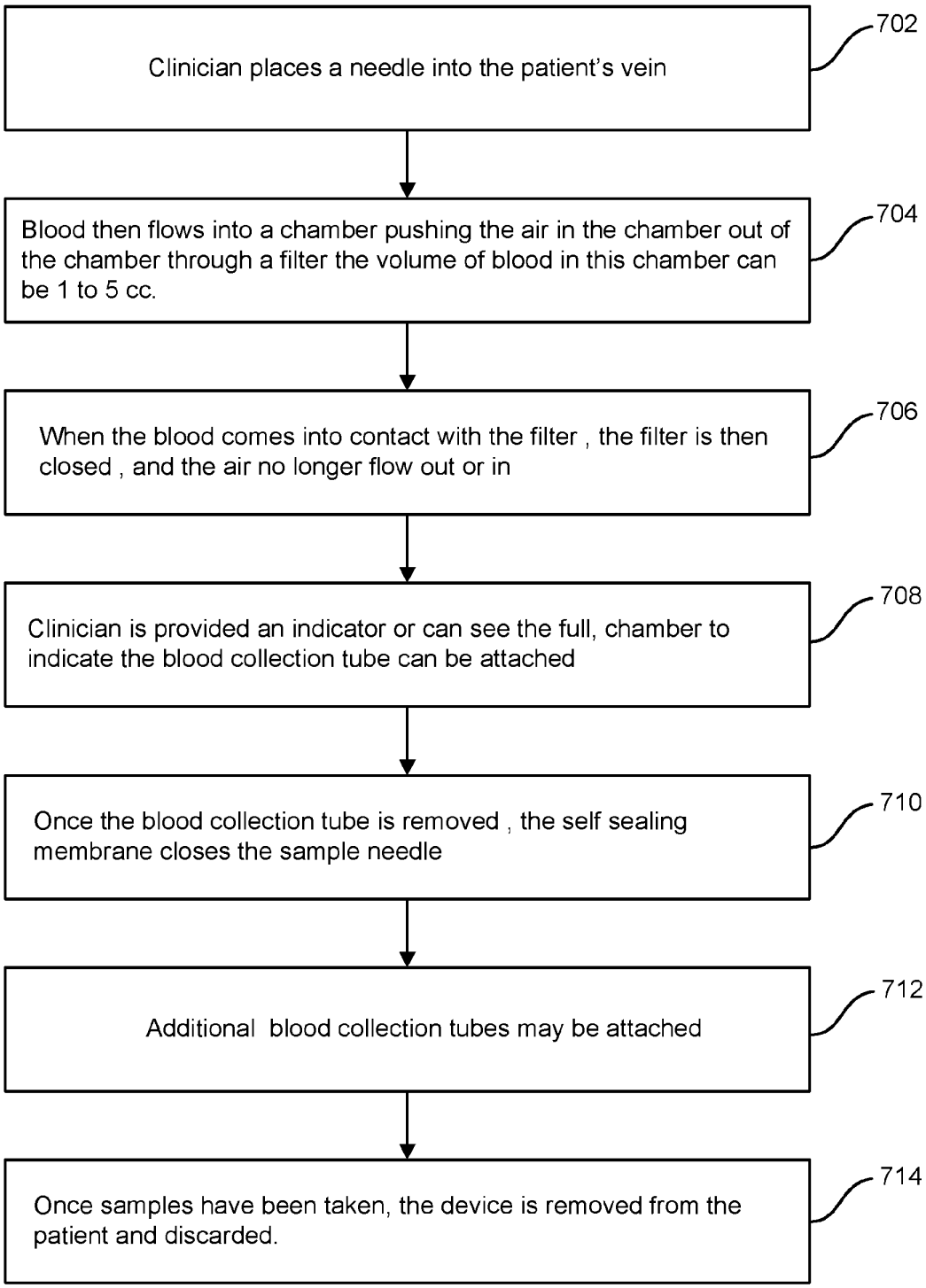

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air 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

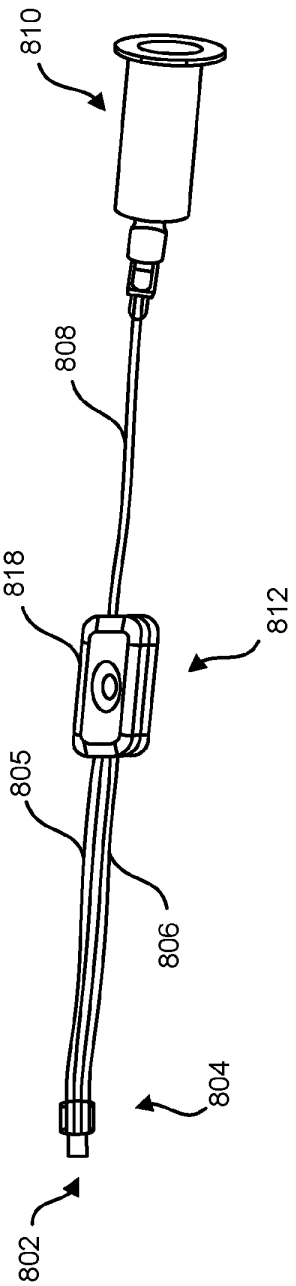


FIG. 8A

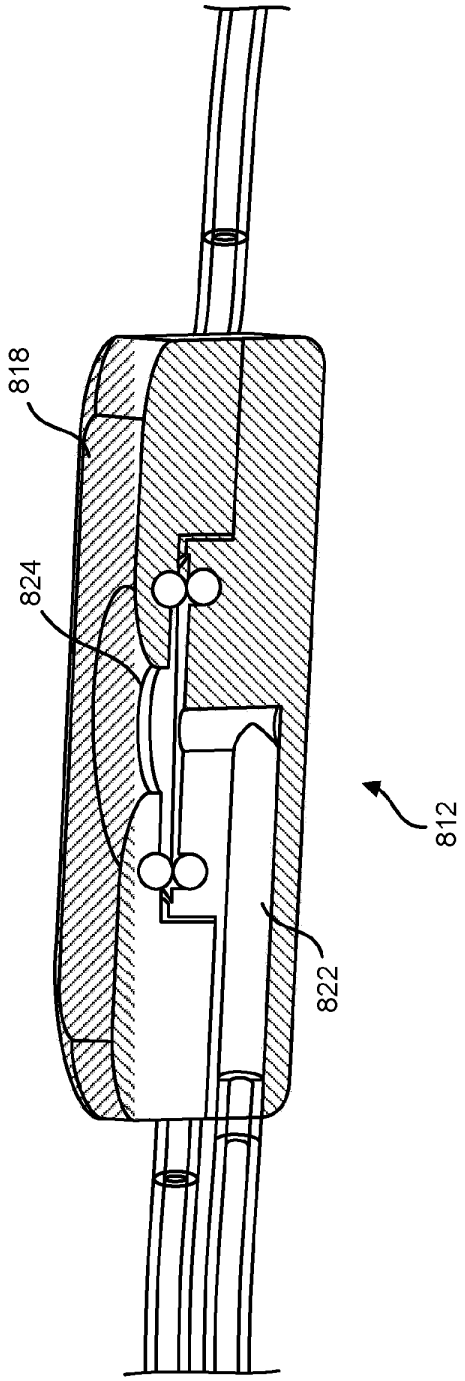


FIG. 8B

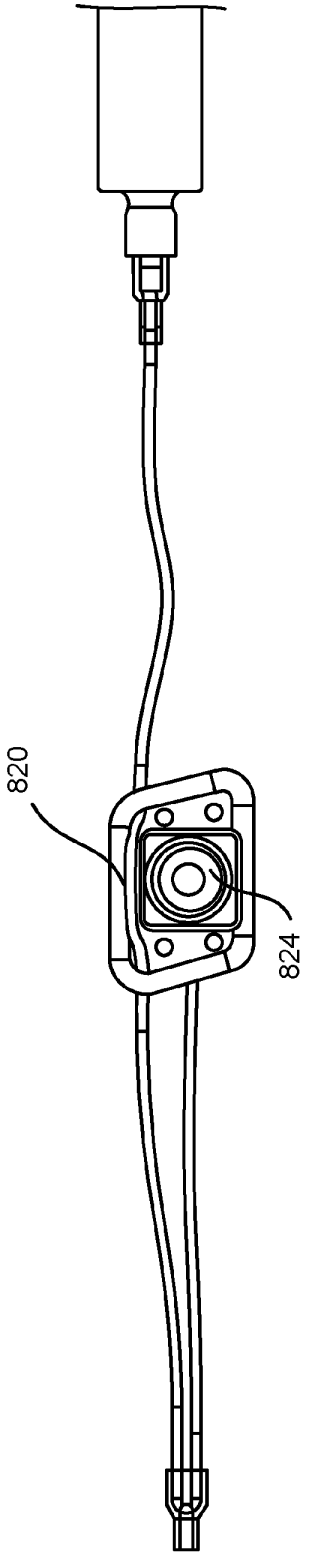


FIG. 8C

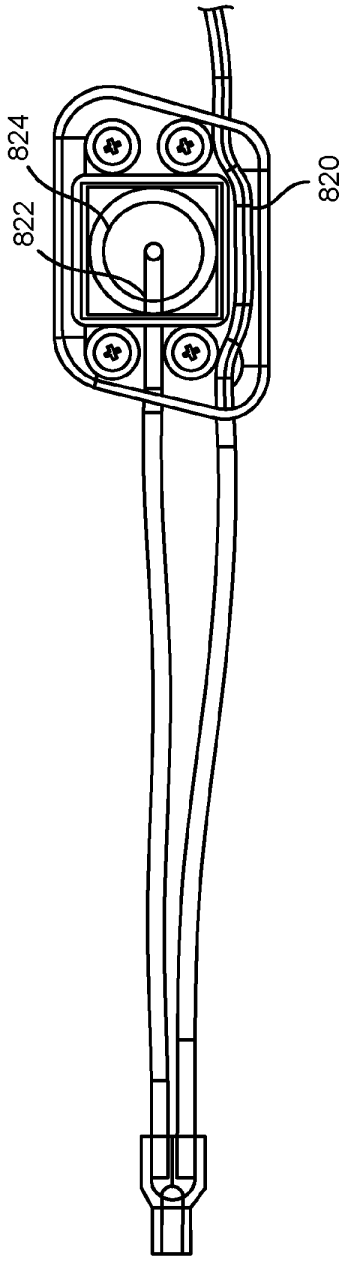


FIG. 8D

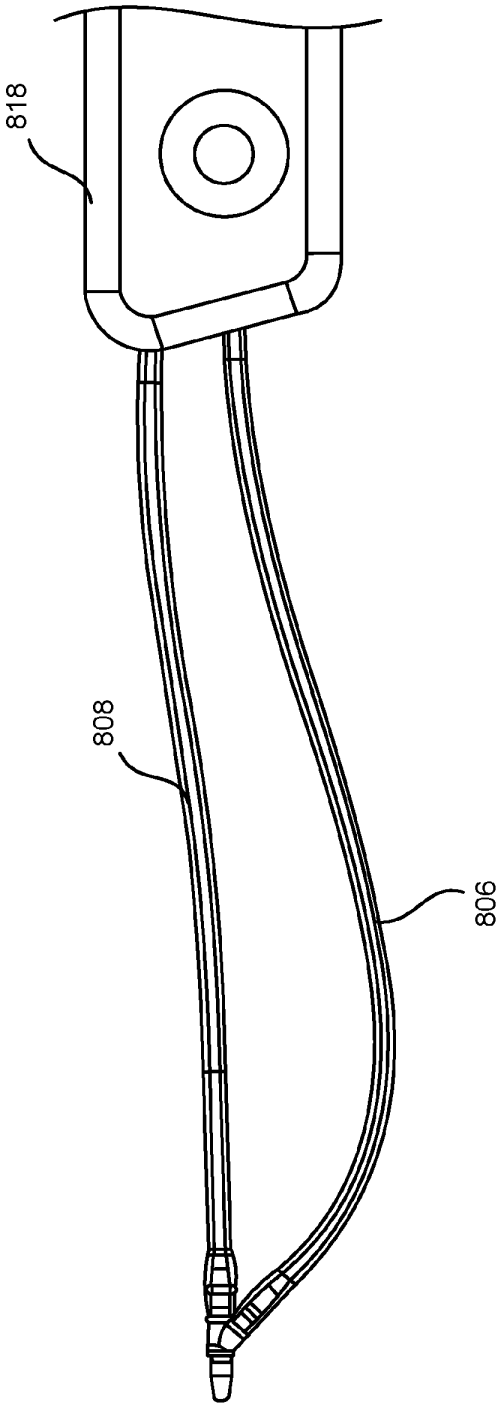


FIG. 8E

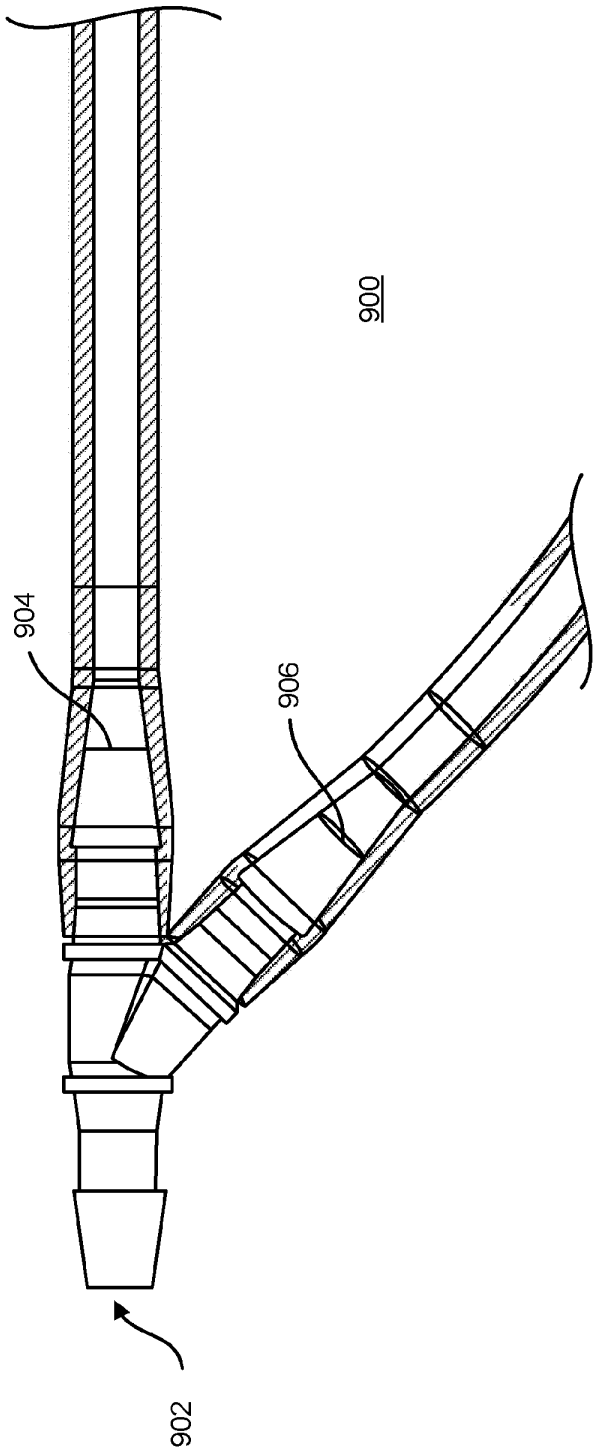


FIG. 9

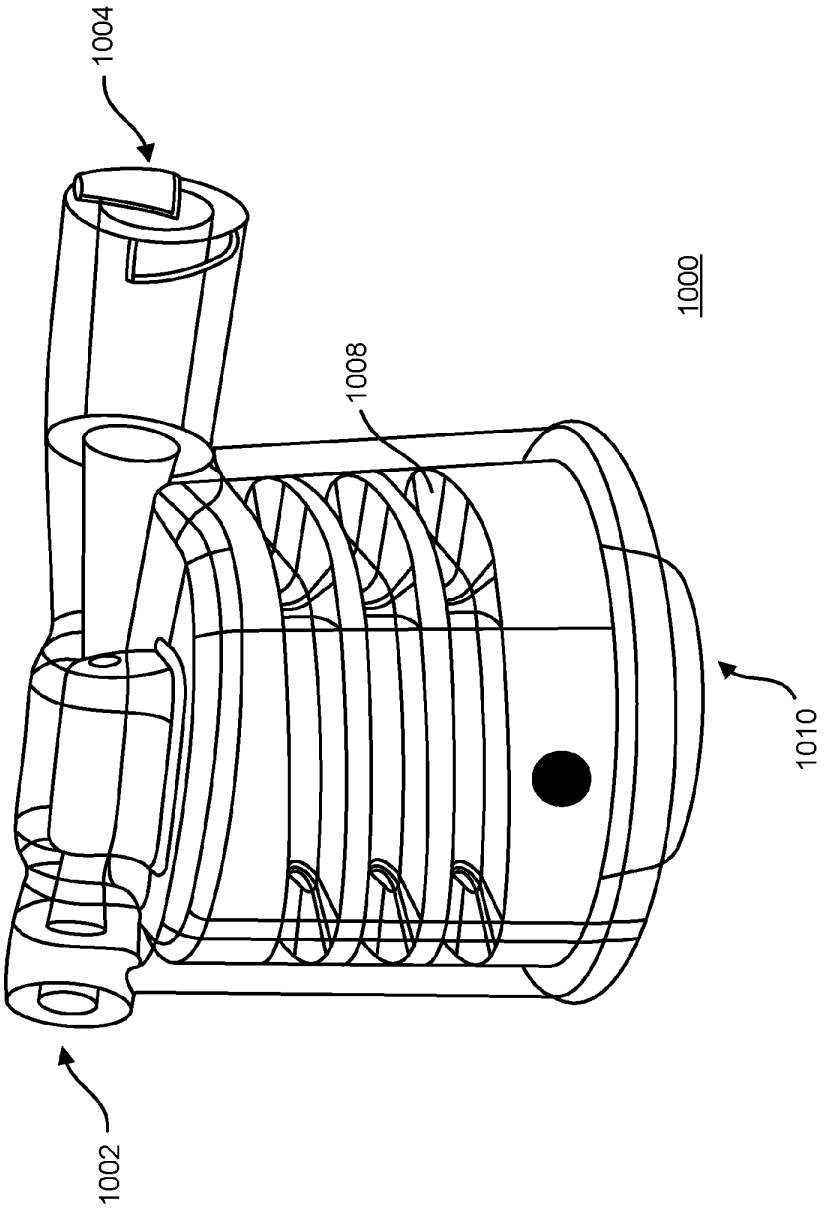


FIG. 10A

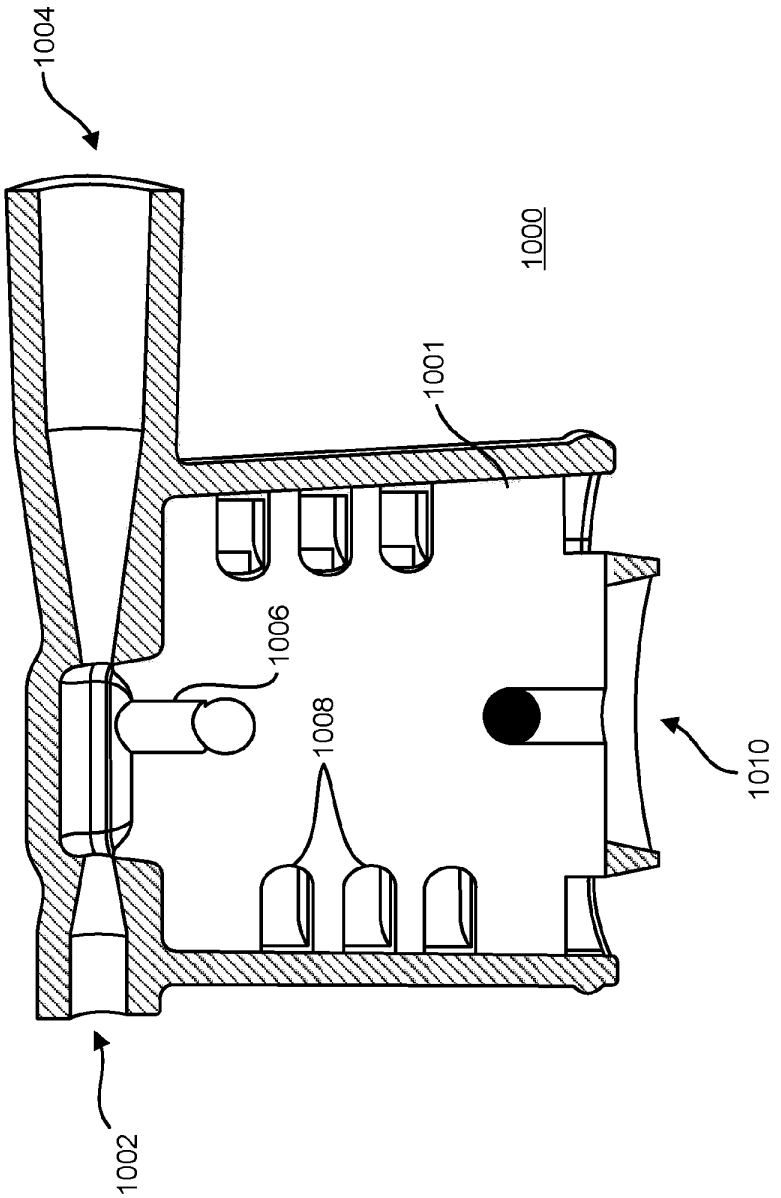


FIG. 10B

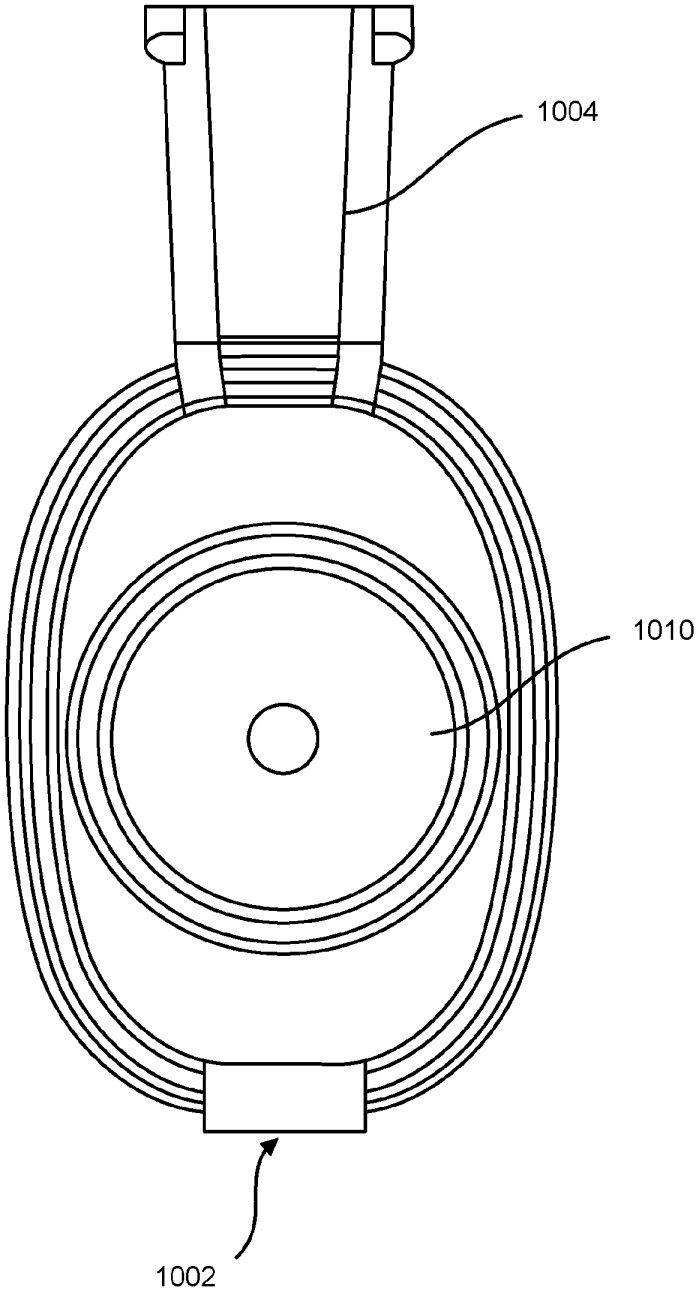


FIG. 10C

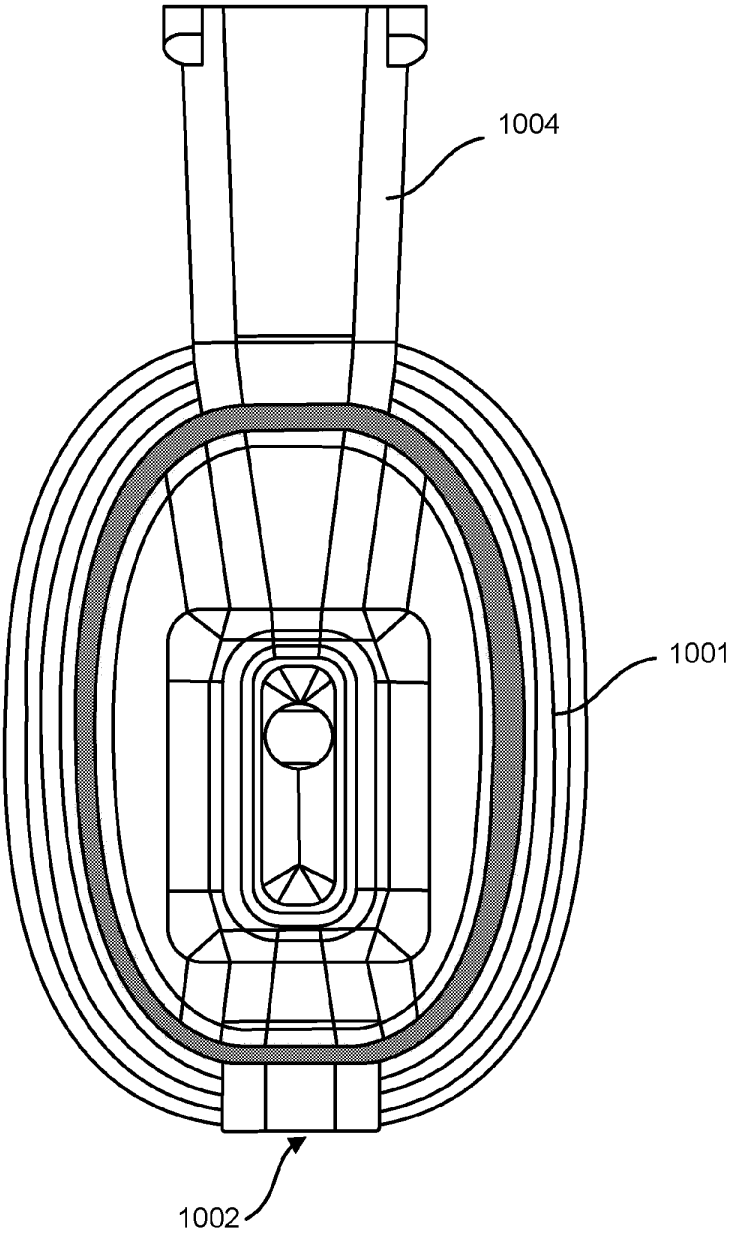


FIG. 10D

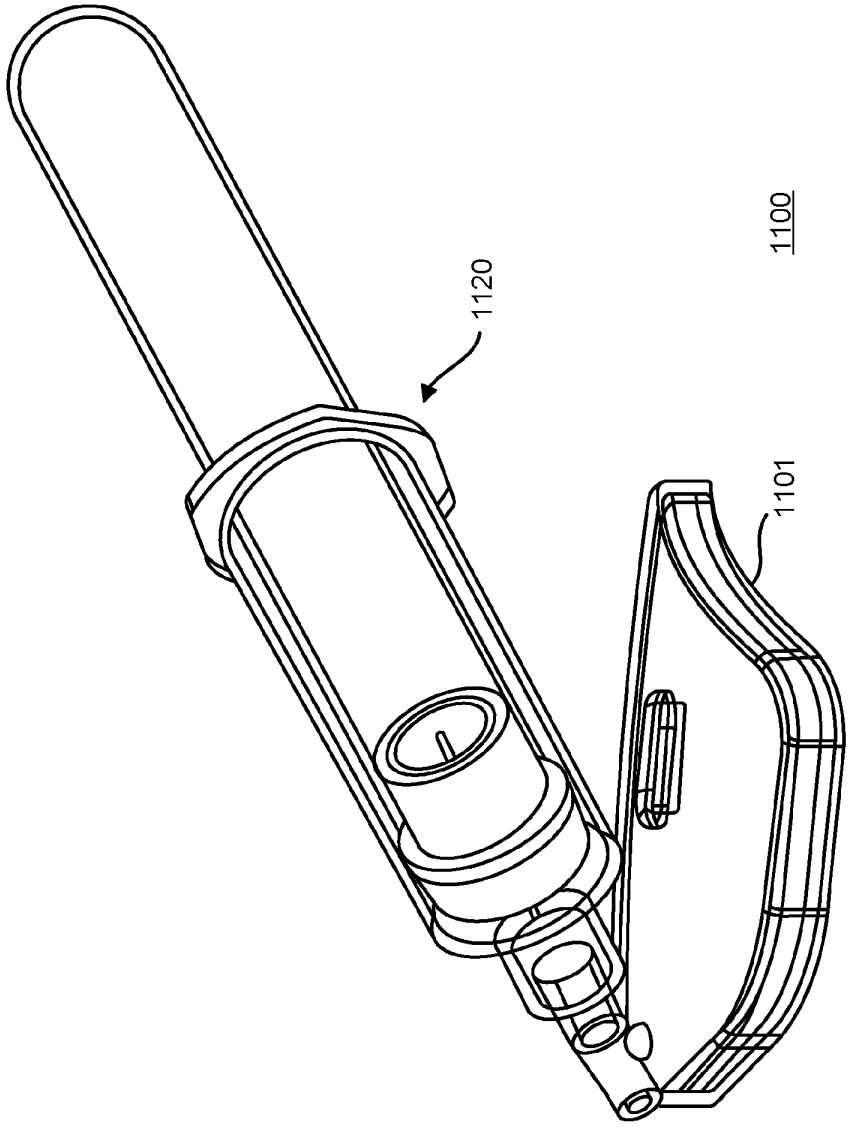


FIG. 11A

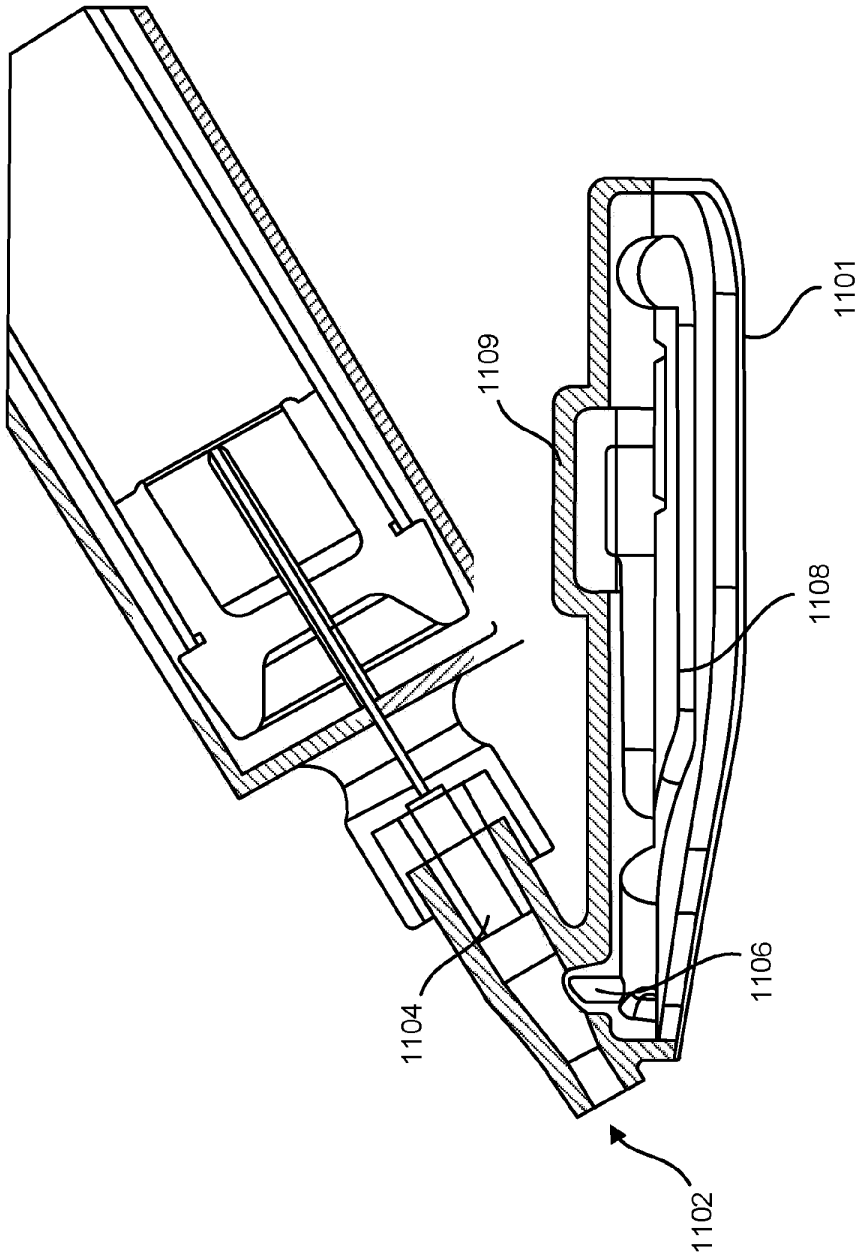


FIG. 11B

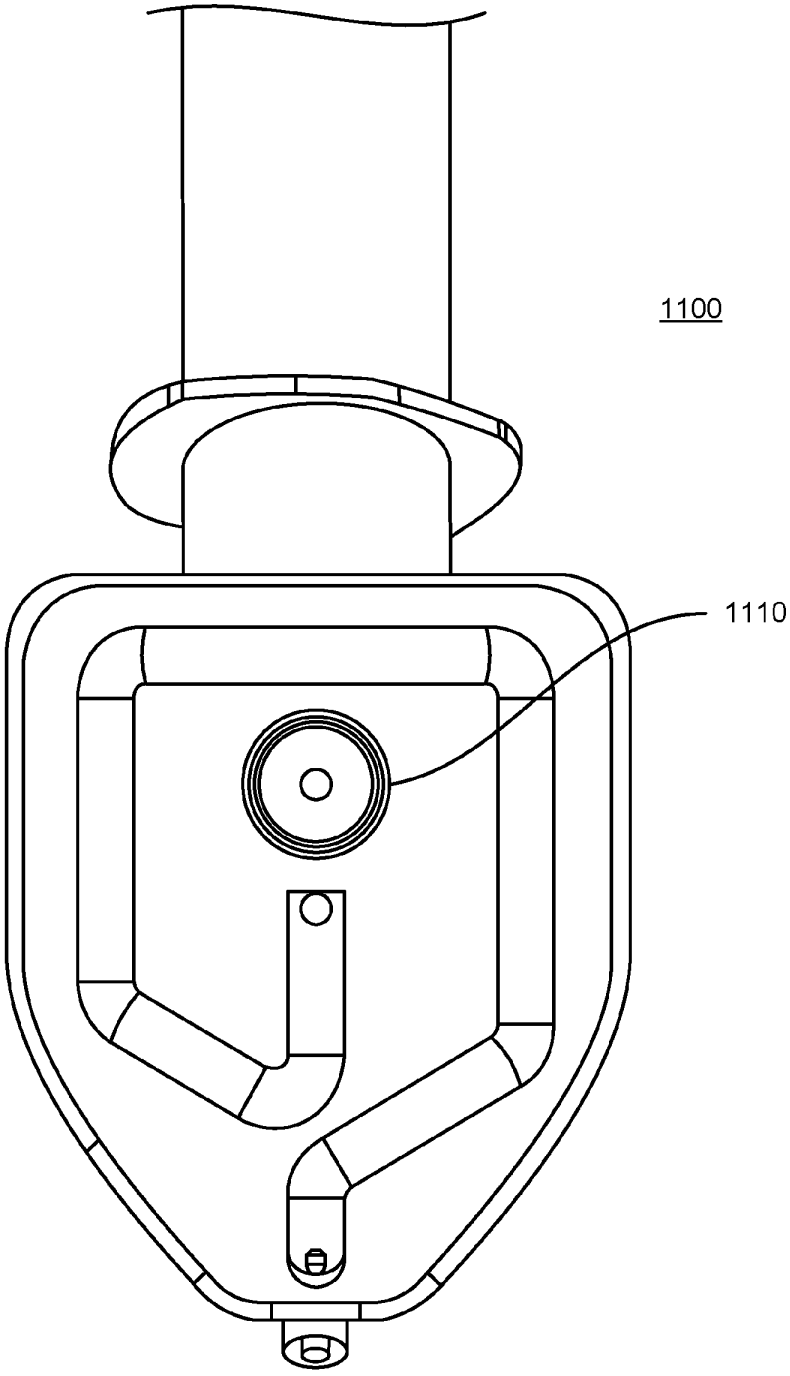


FIG. 11C

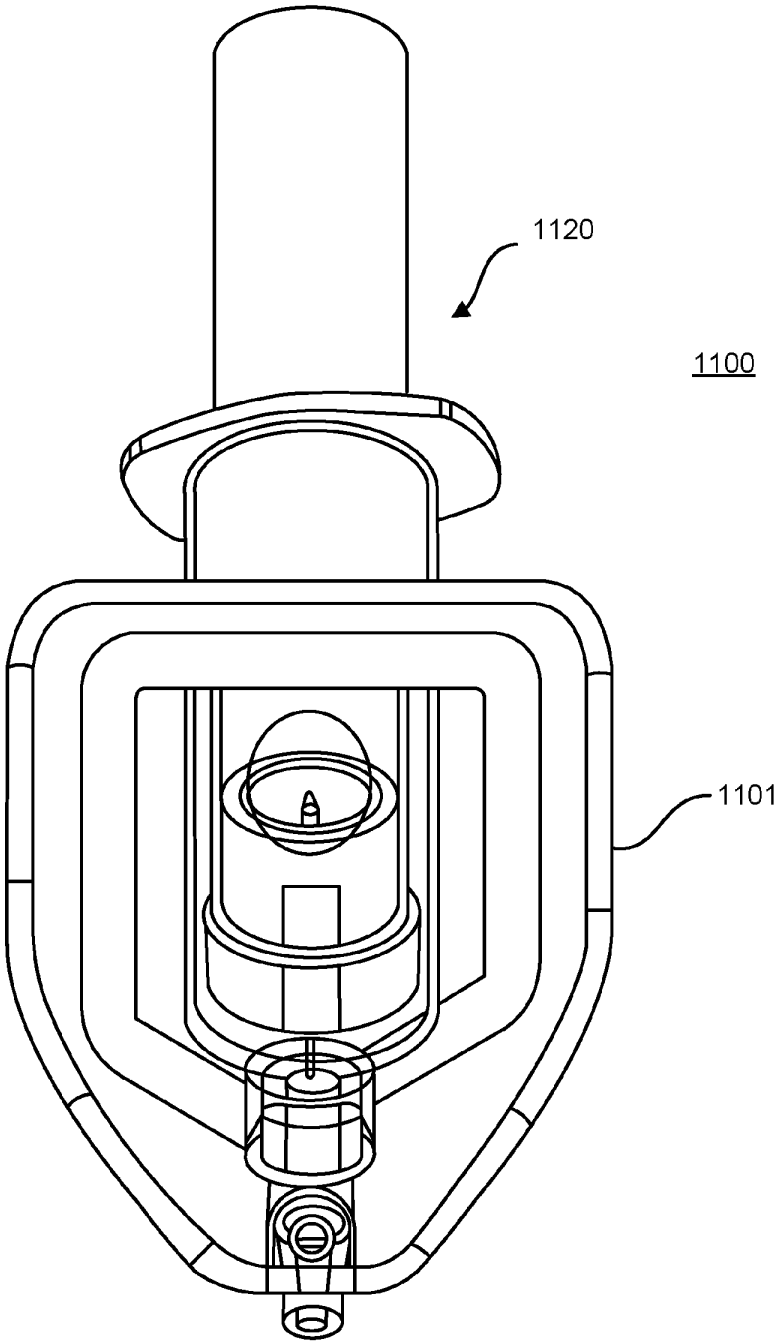


FIG. 11D

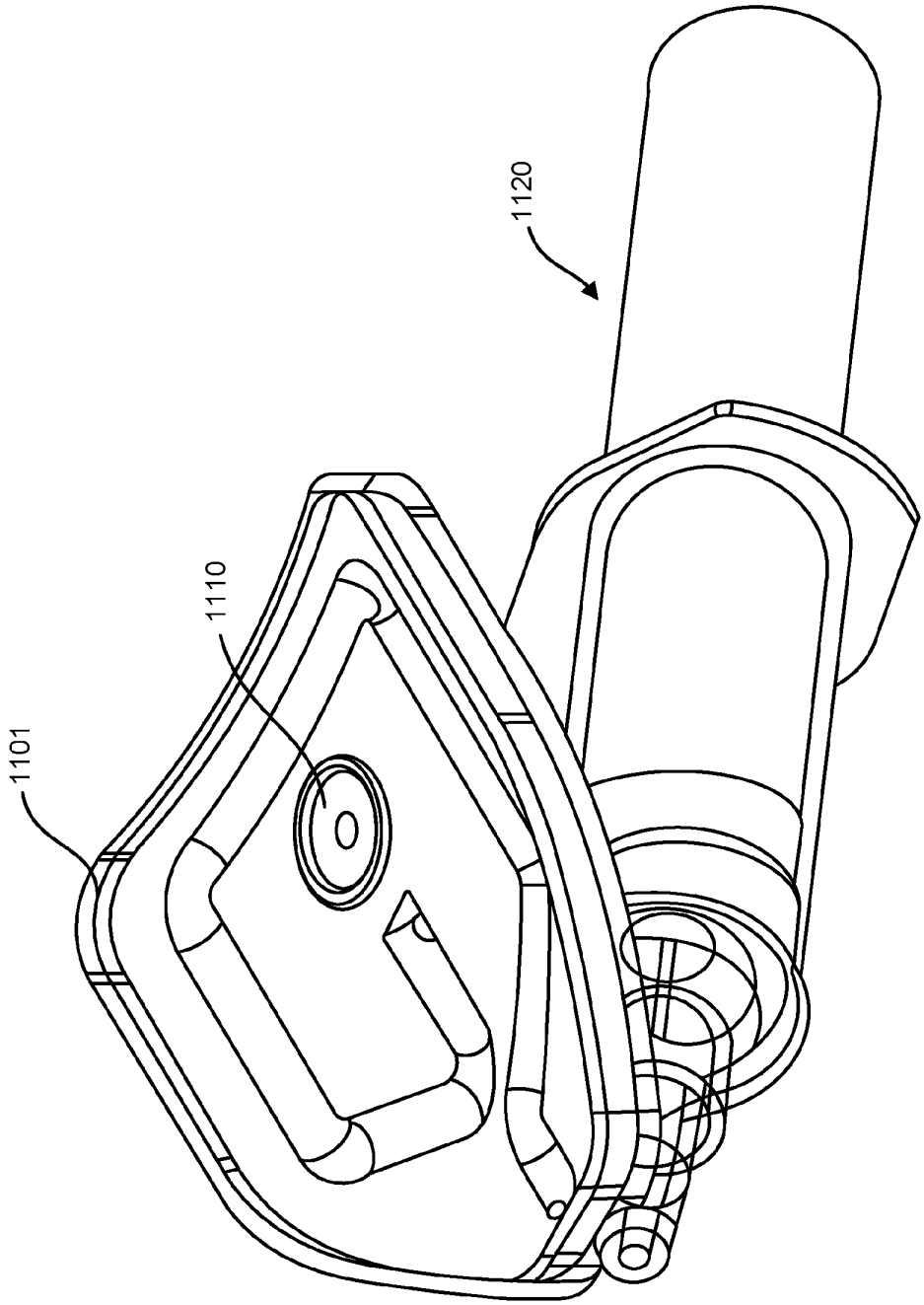


FIG. 11E

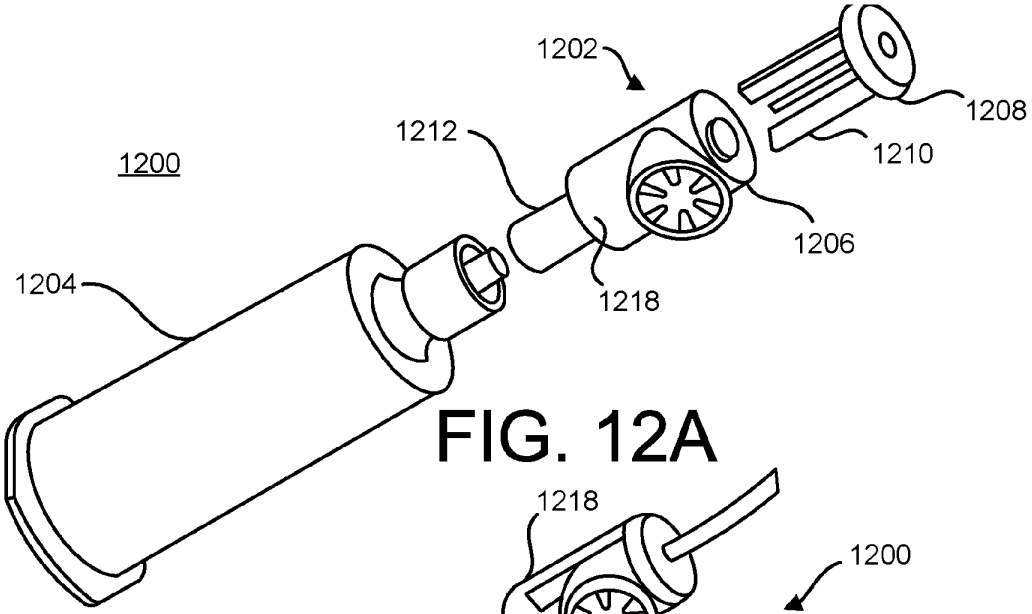


FIG. 12A

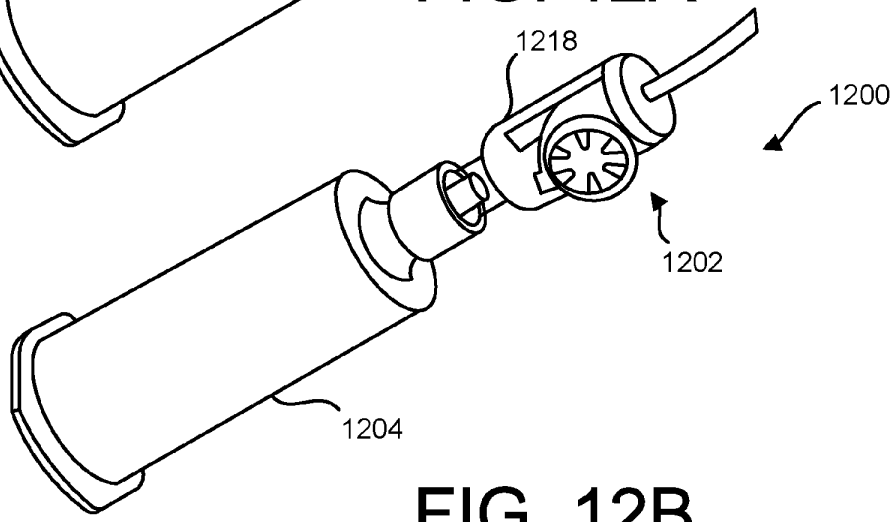


FIG. 12B

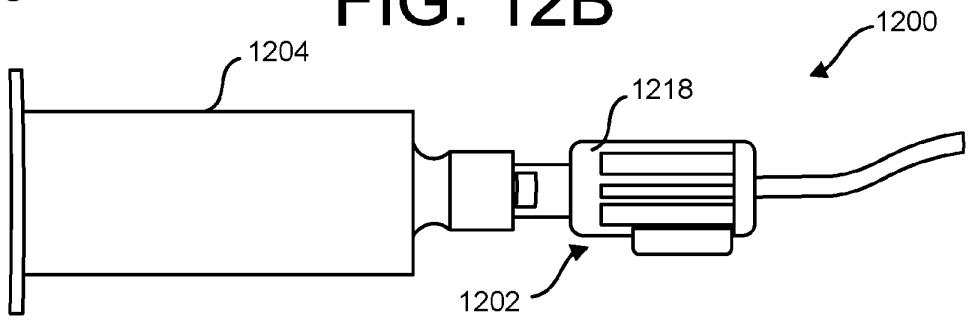


FIG. 12C

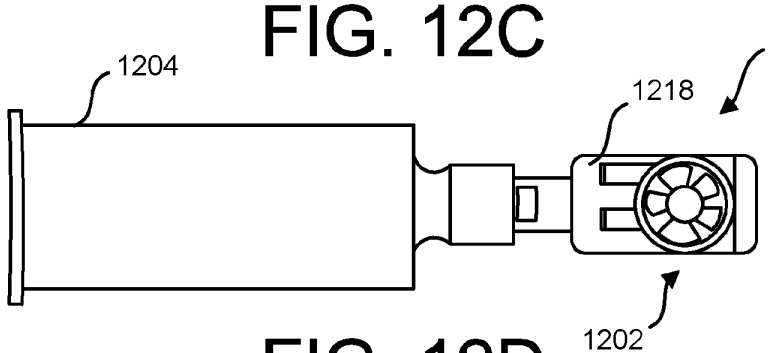


FIG. 12D

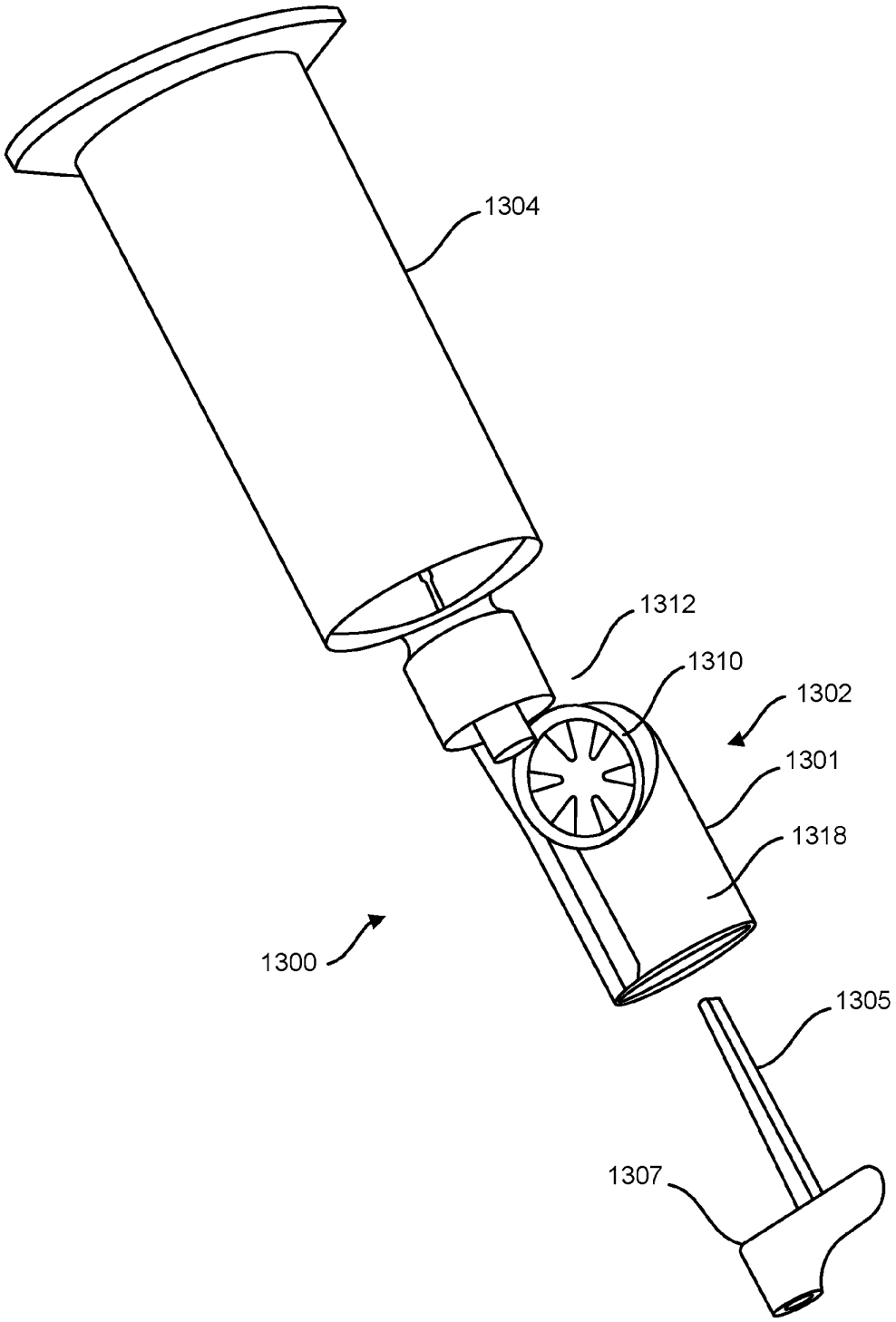


FIG. 13A

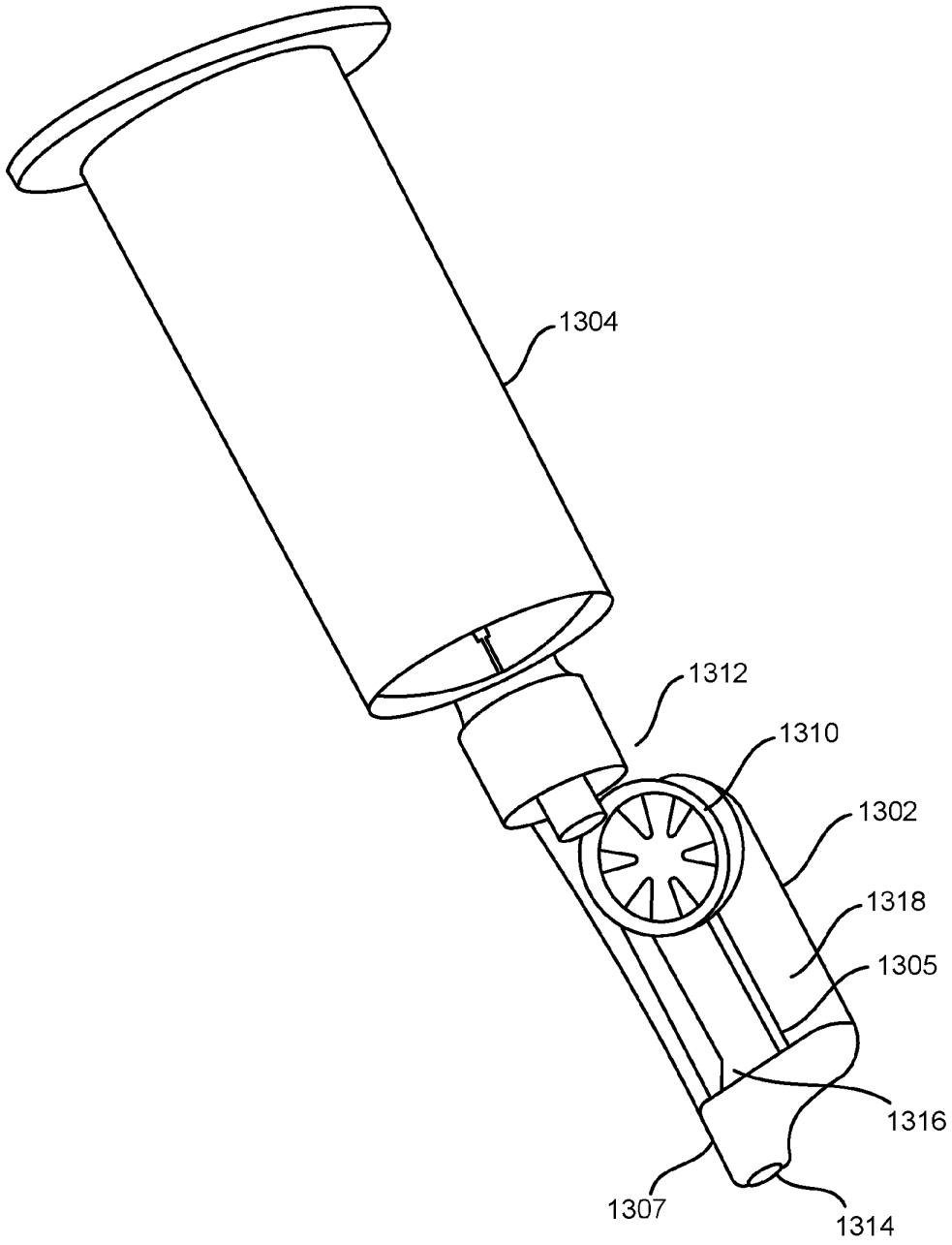


FIG. 13B

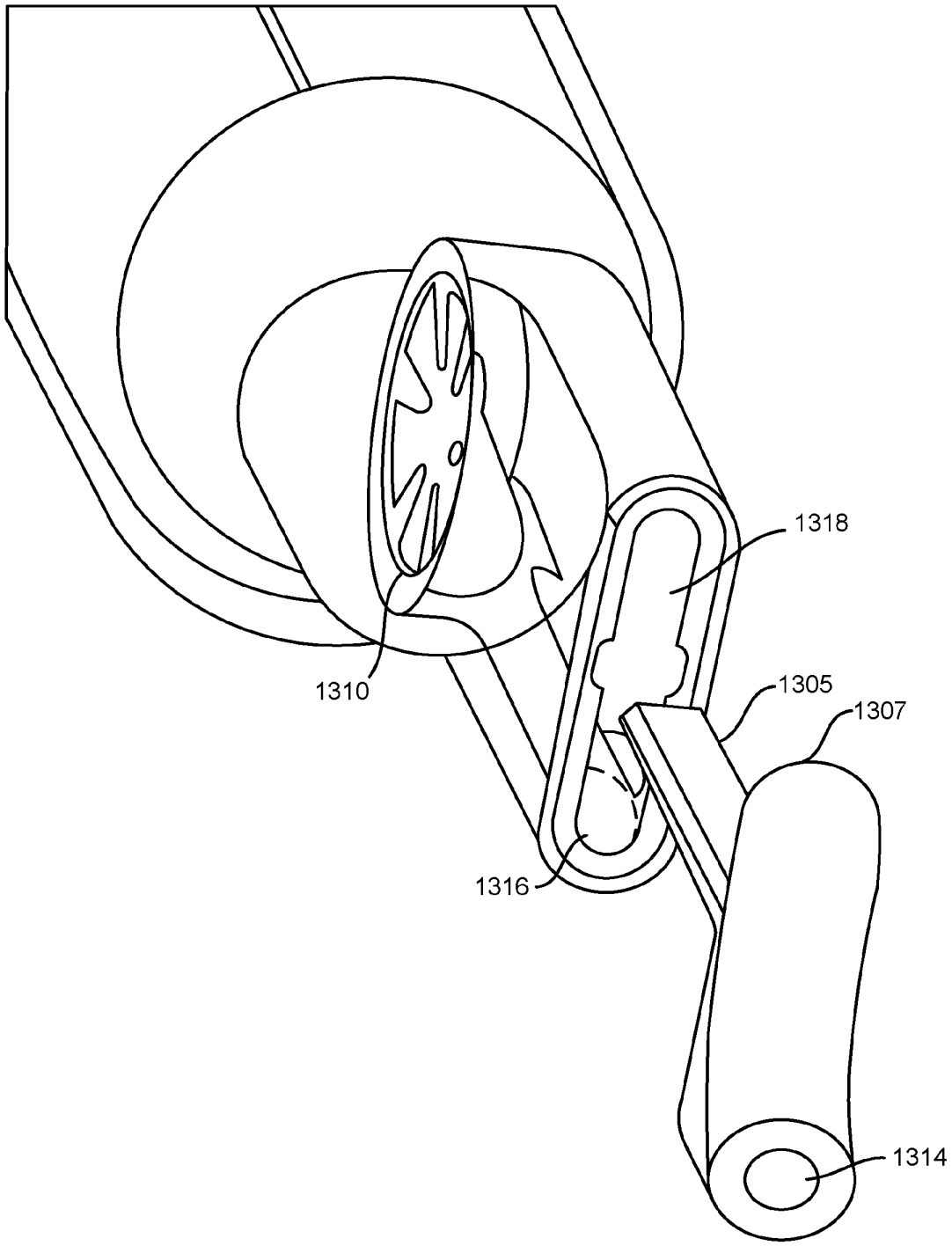


FIG. 13C

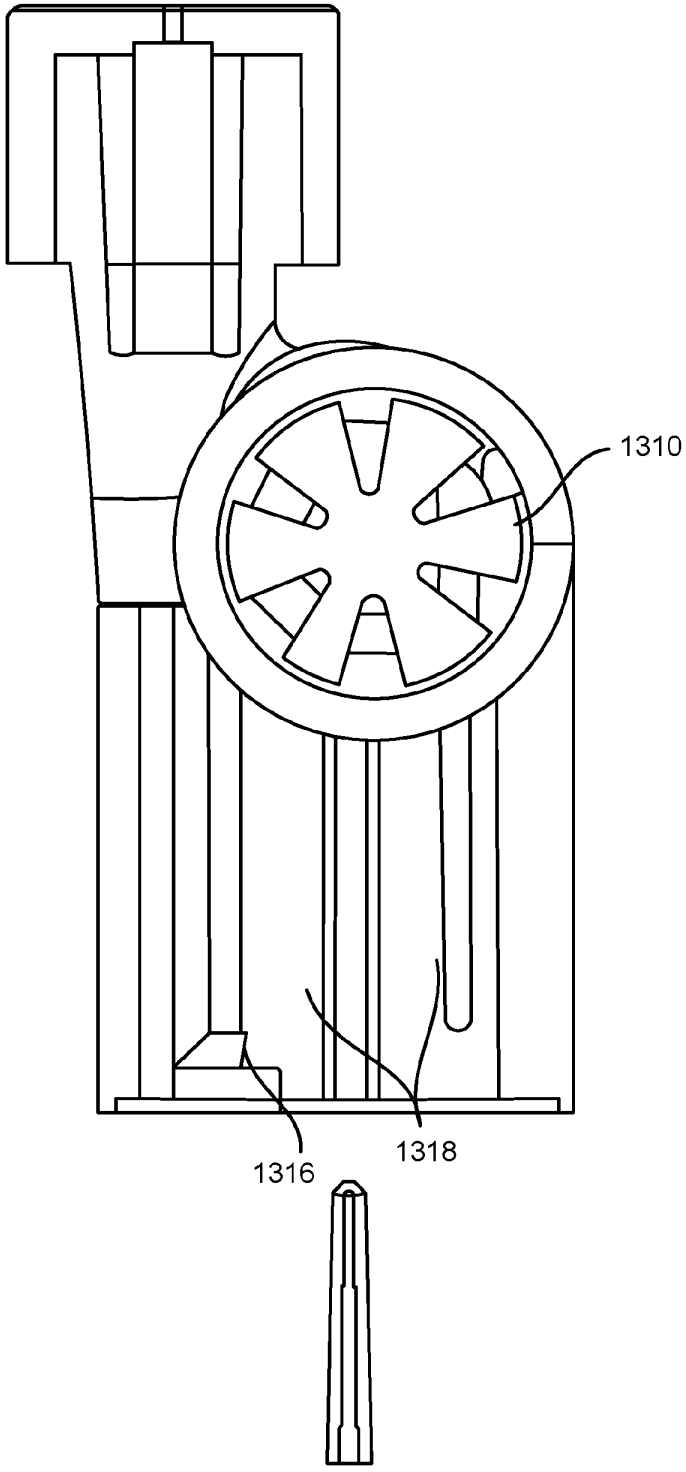


FIG. 13D

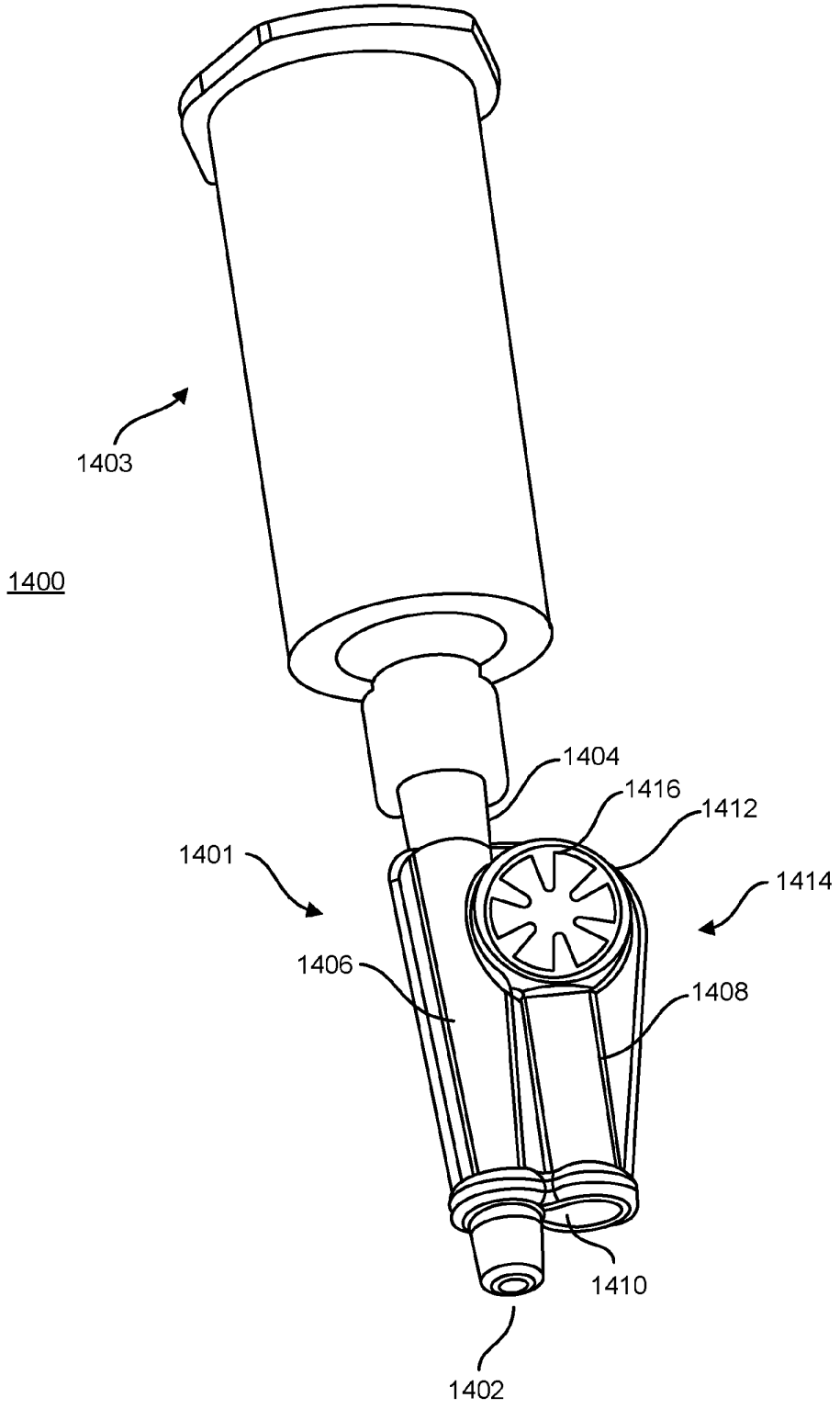


FIG. 14A

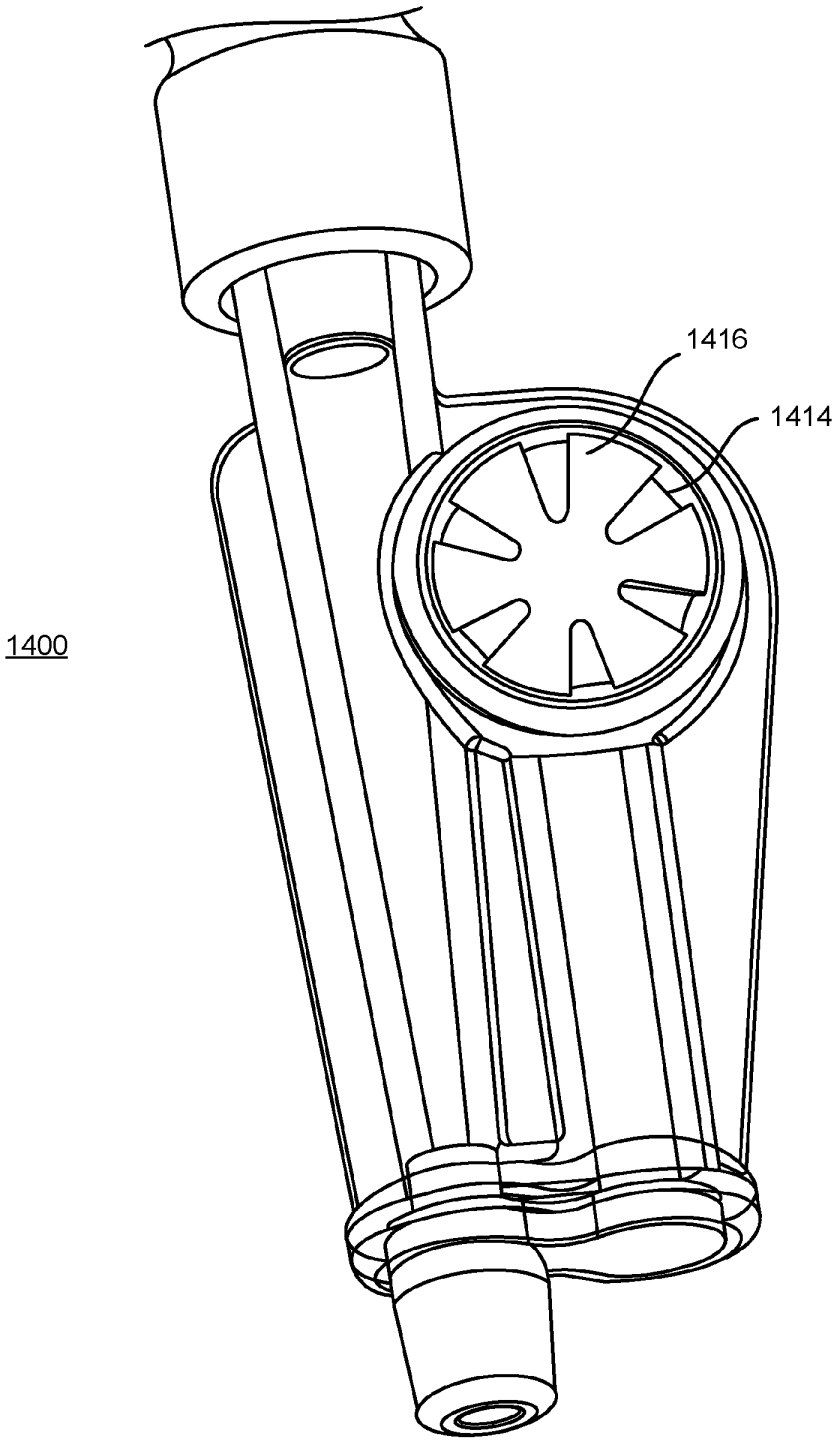


FIG. 14B

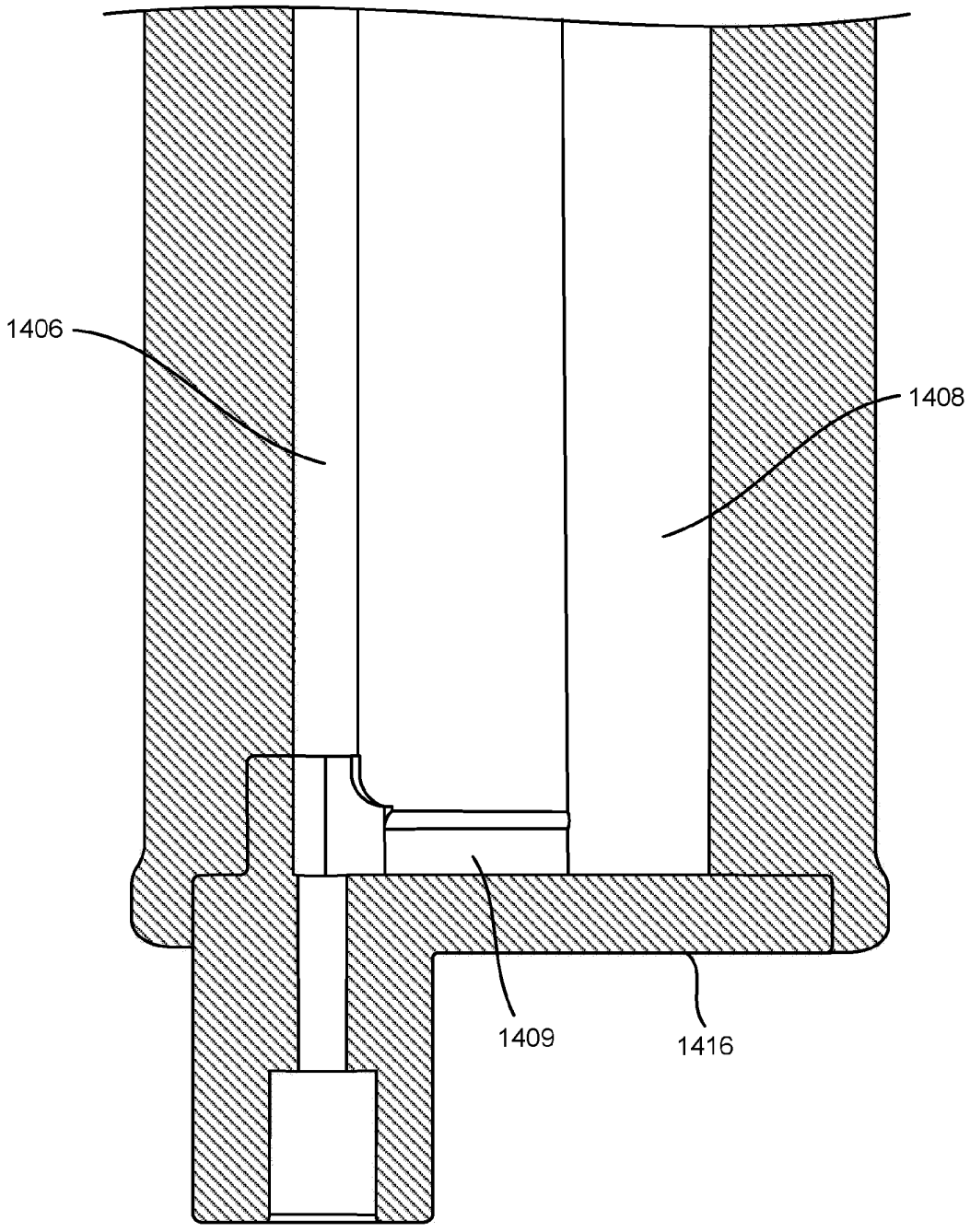


FIG. 14C

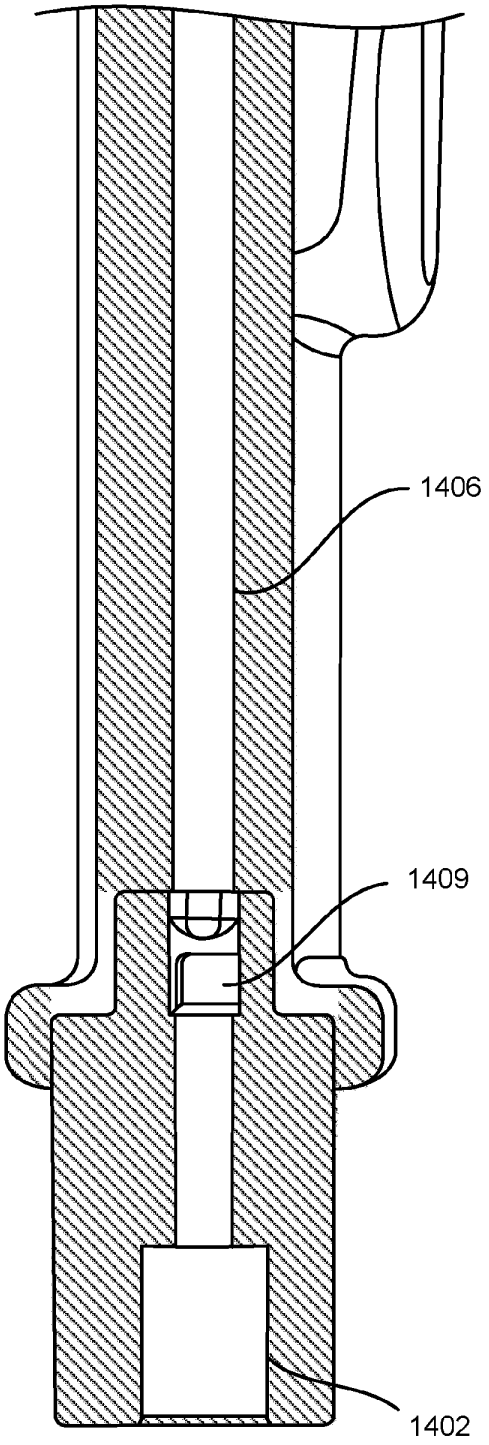


FIG. 14D

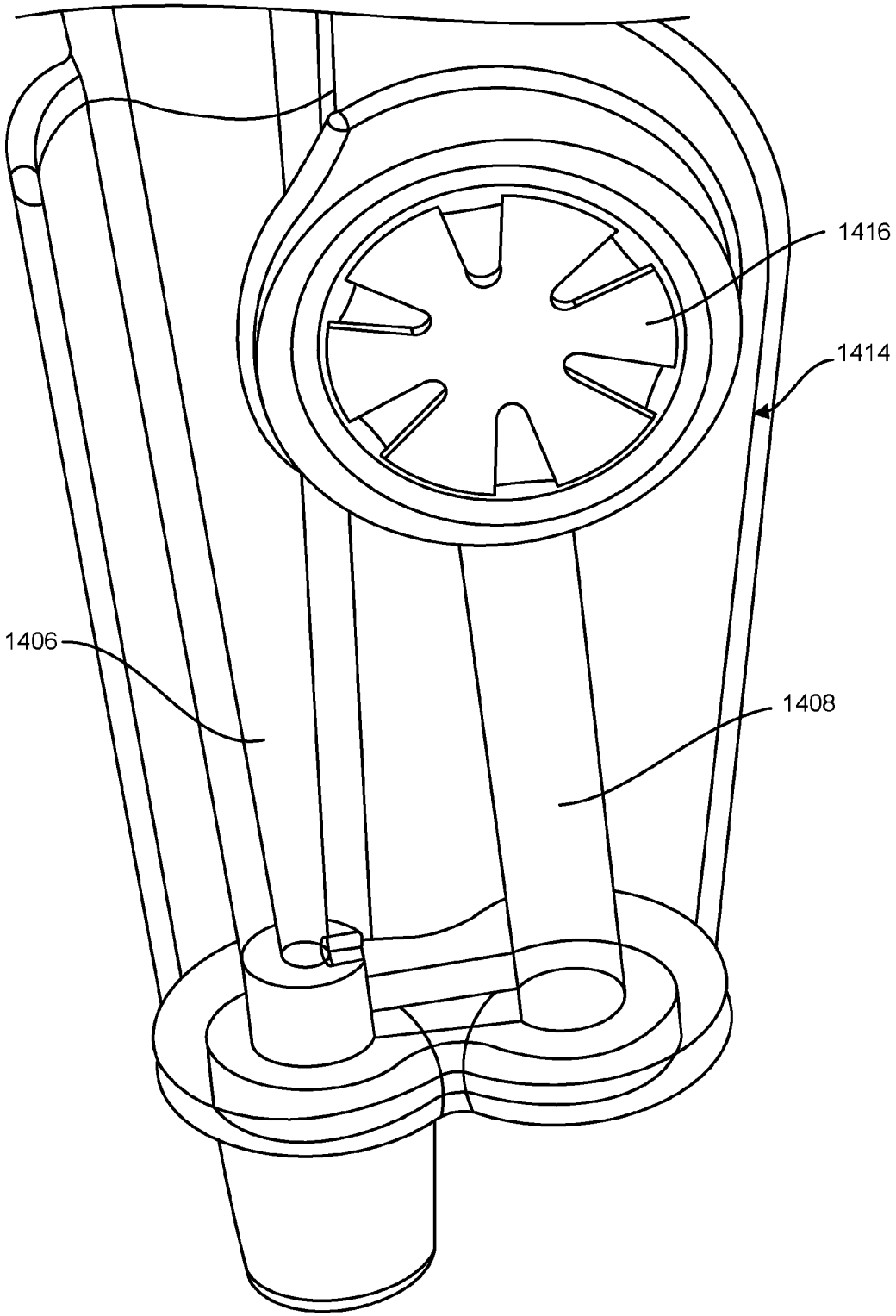


FIG. 14E

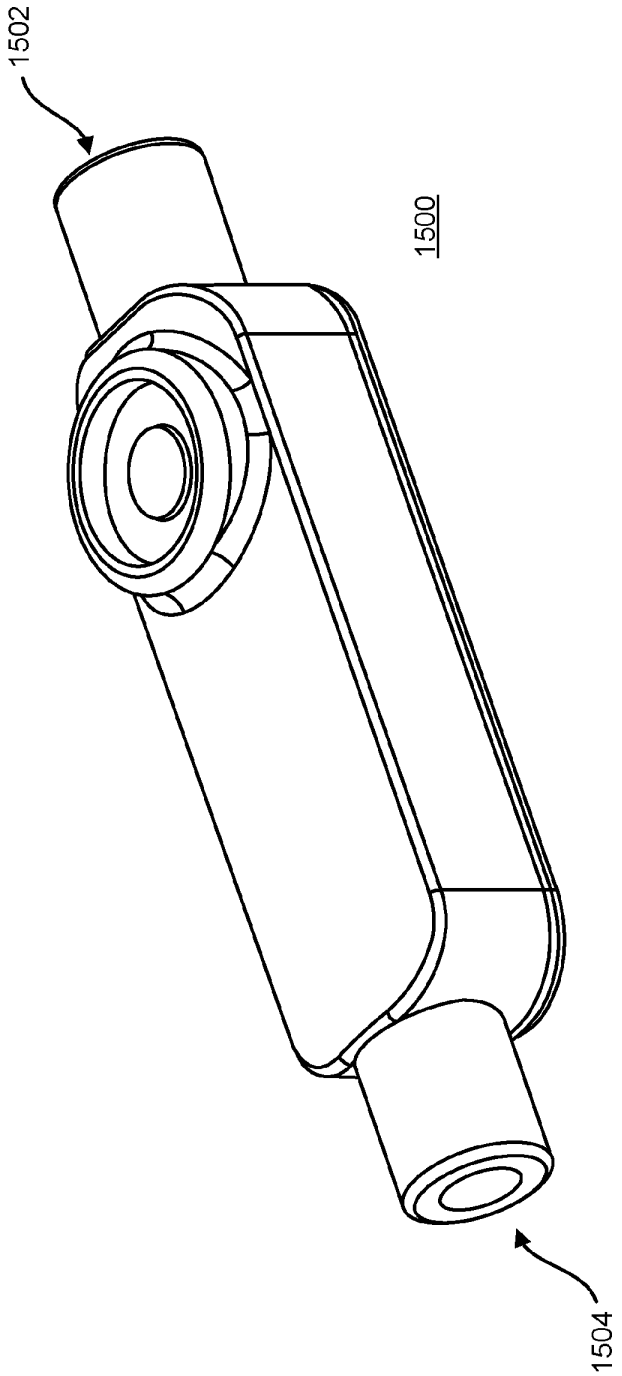


FIG. 15A

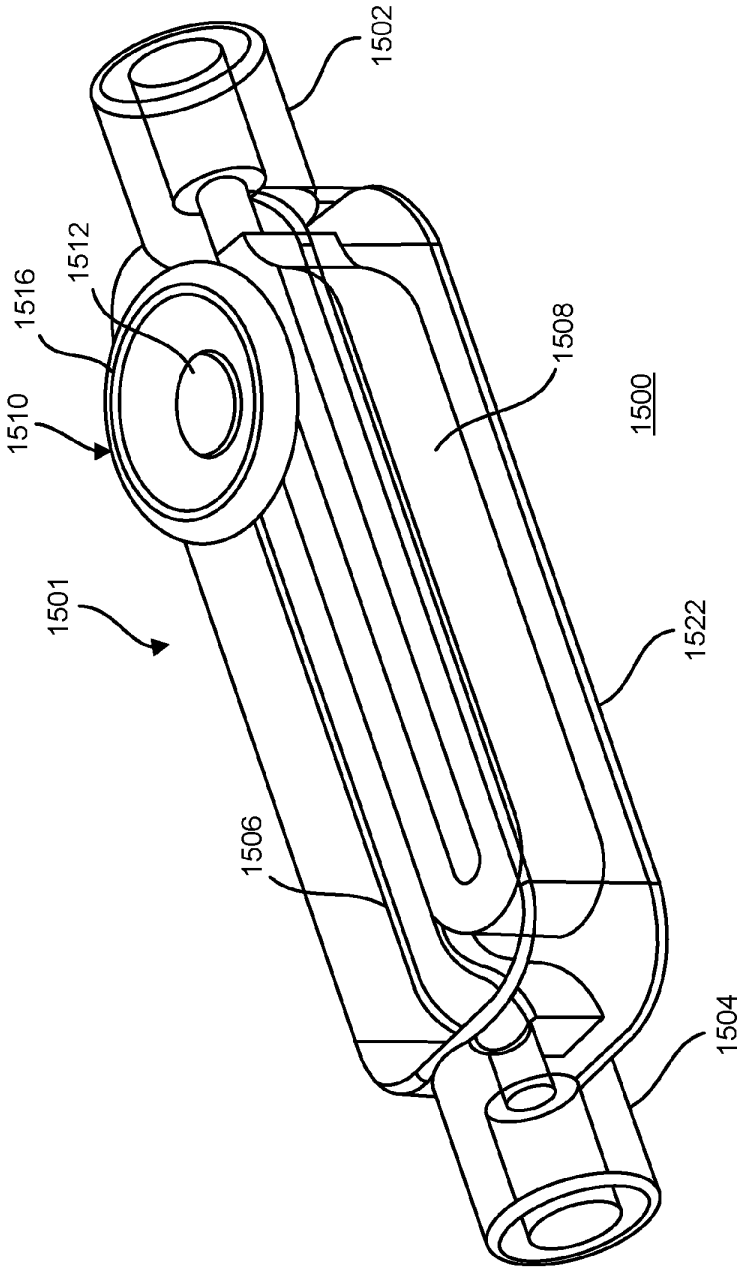


FIG. 15B

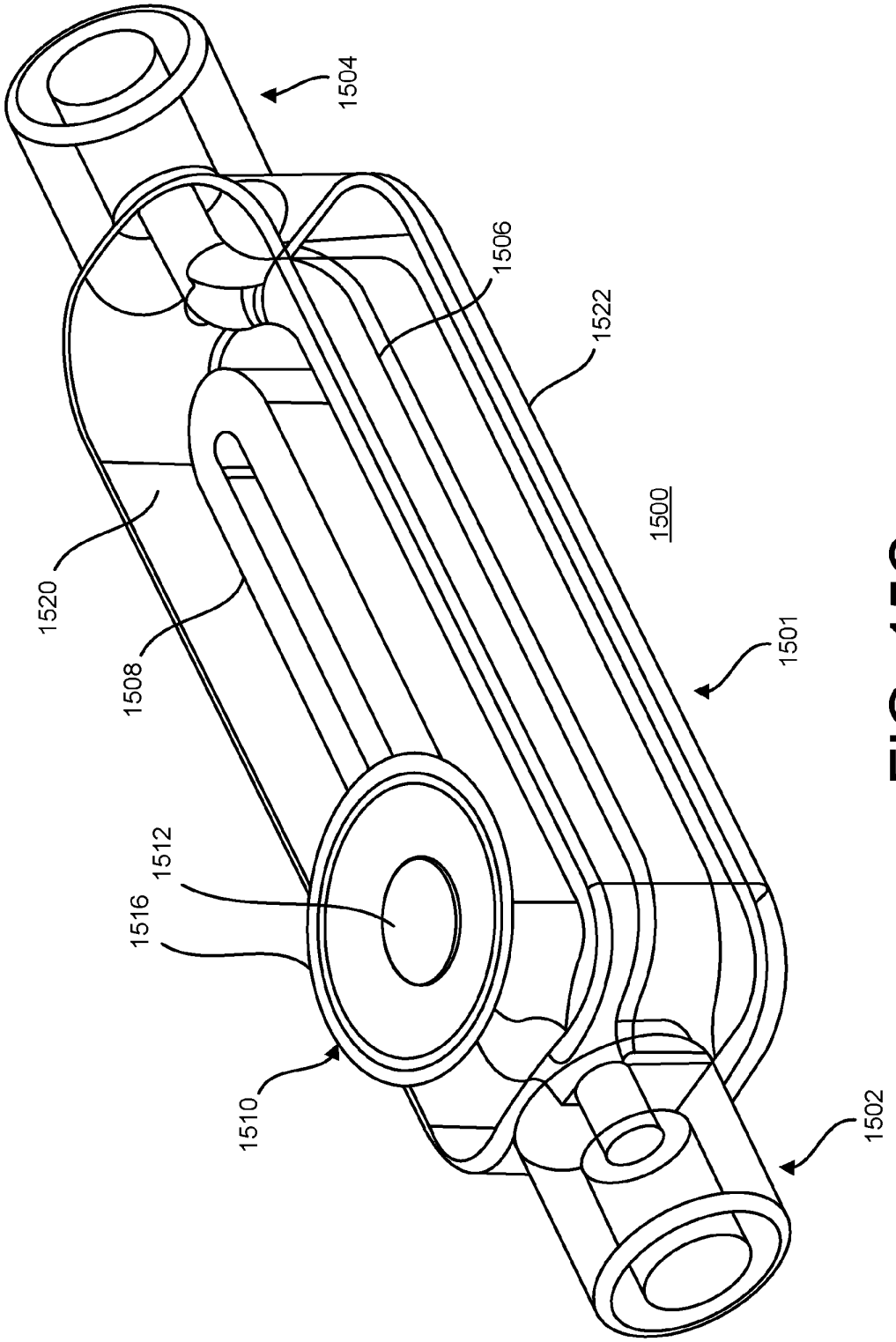


FIG. 15C

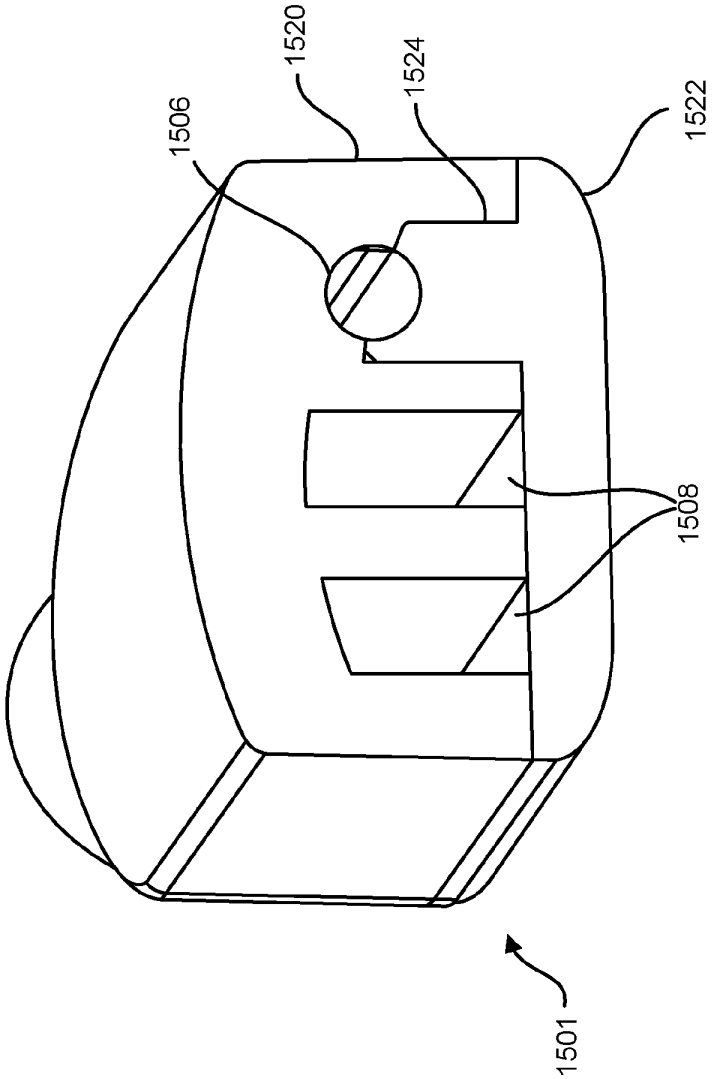


FIG. 15D

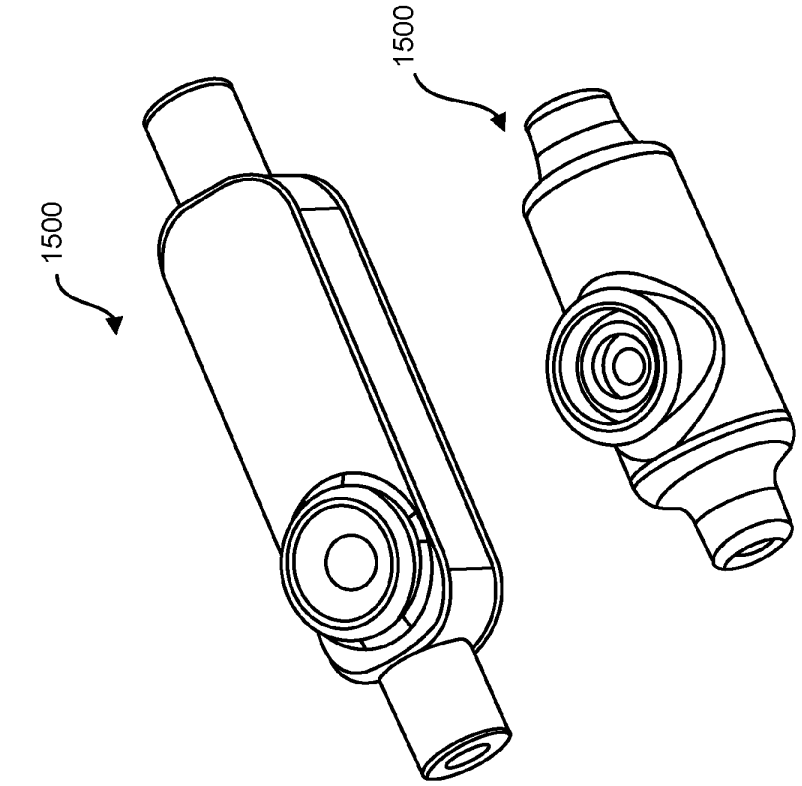


FIG. 15F

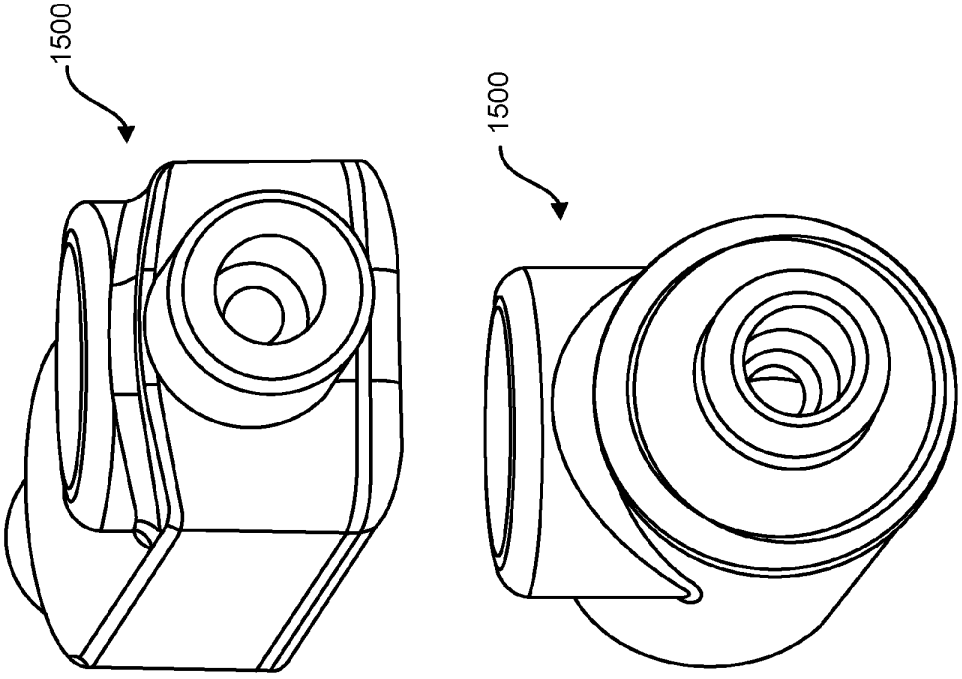


FIG. 15E

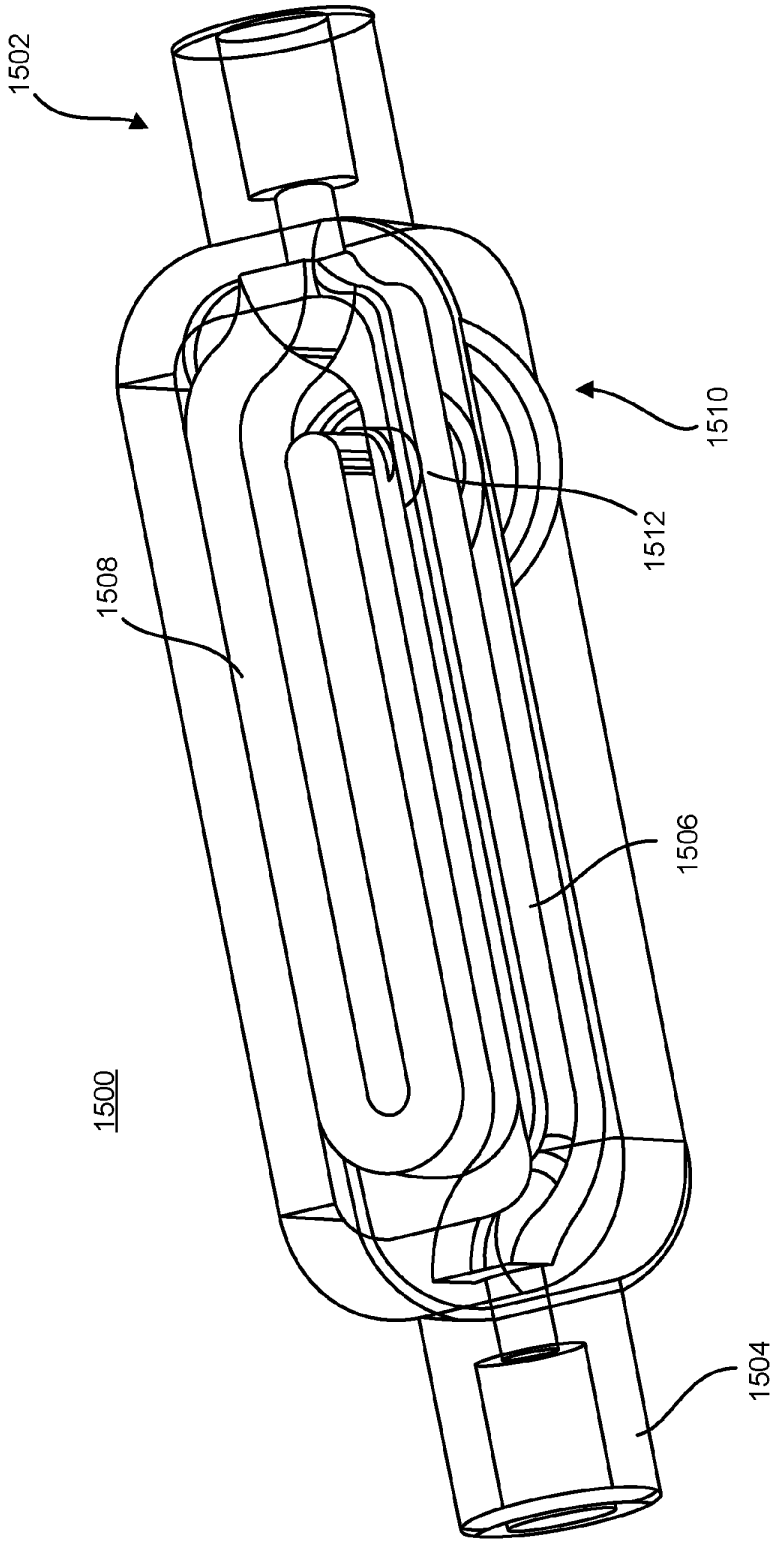


FIG. 15G

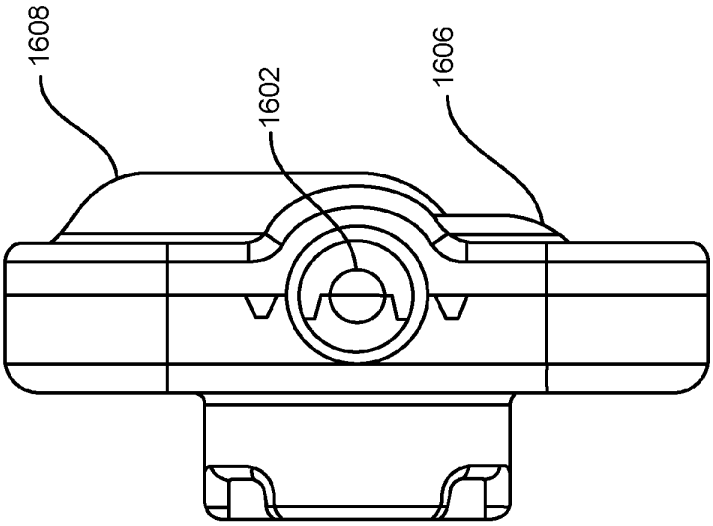


FIG. 16C

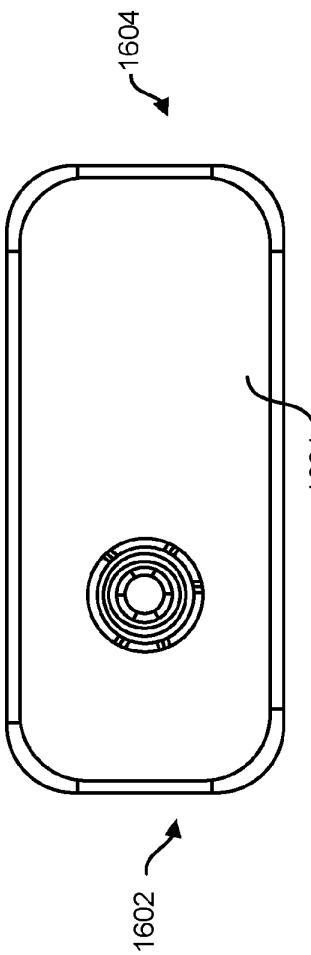


FIG. 16A

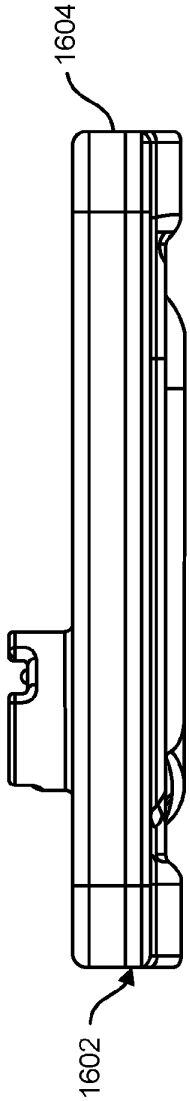


FIG. 16B

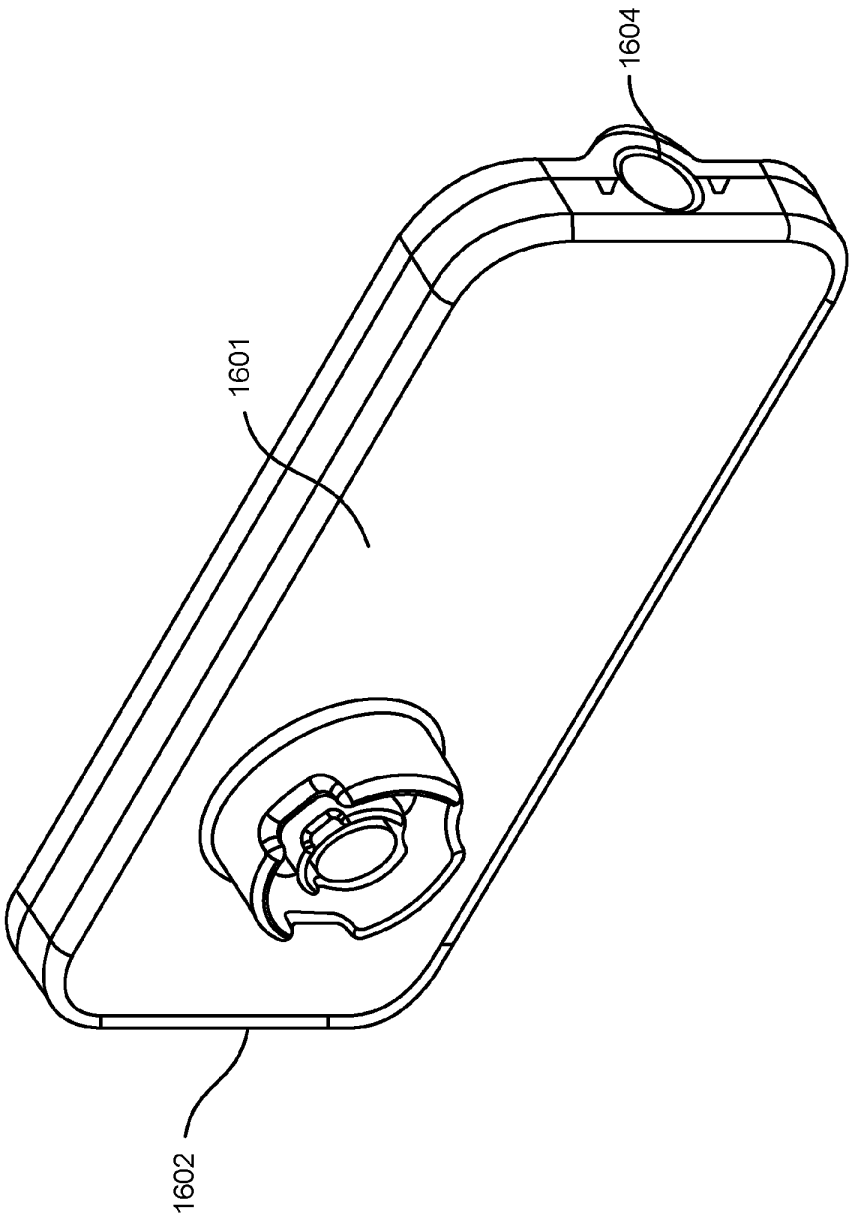


FIG. 16D

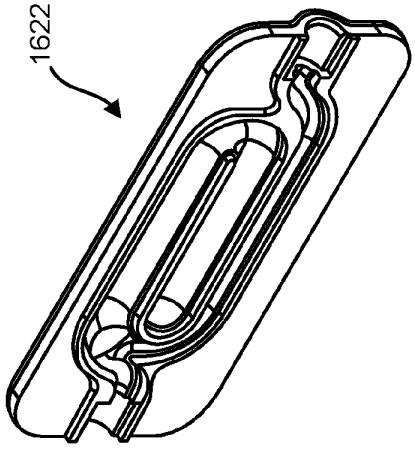


FIG. 17B

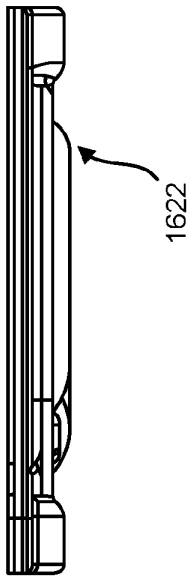


FIG. 17E

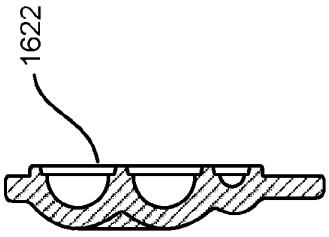


FIG. 17D

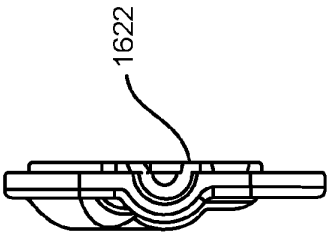


FIG. 17C

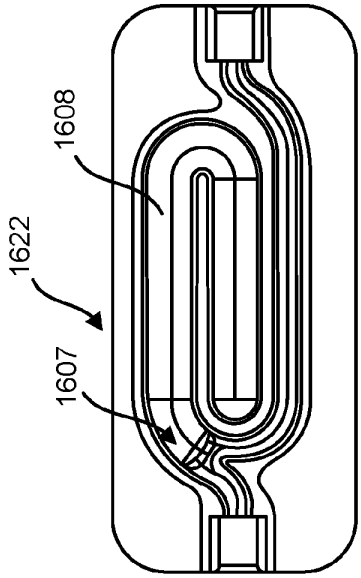


FIG. 17A

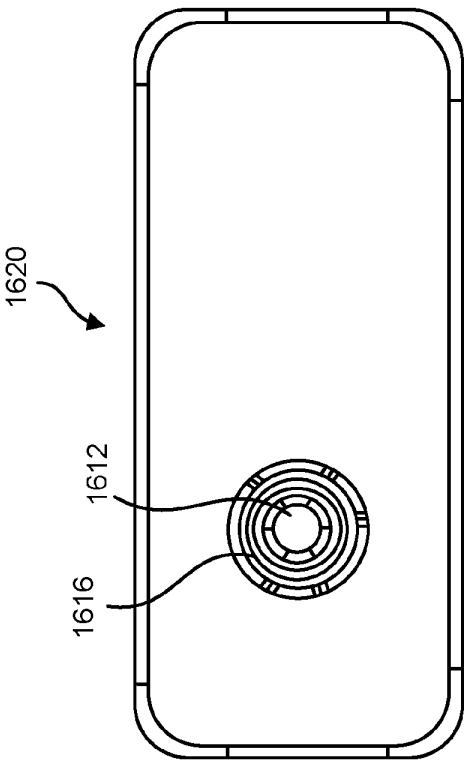


FIG. 18A

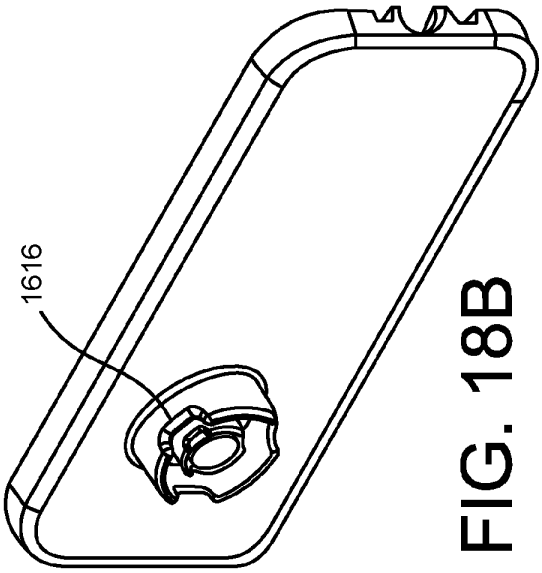


FIG. 18B



FIG. 18C

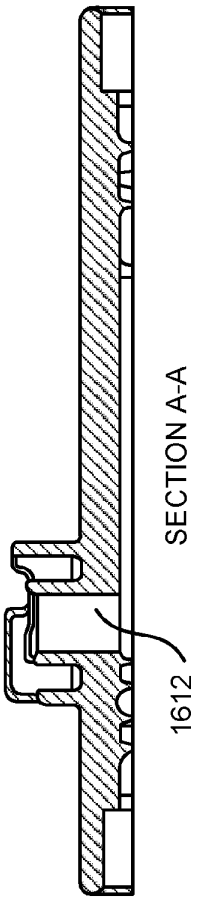


FIG. 18D

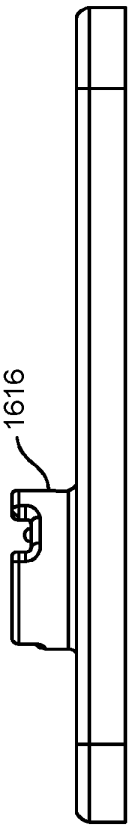


FIG. 18E

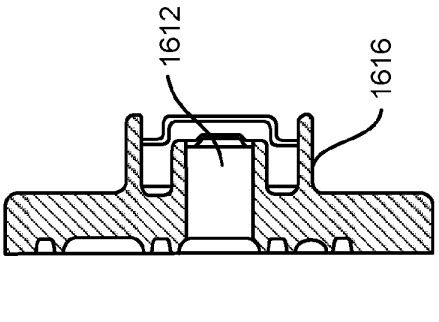


FIG. 18F

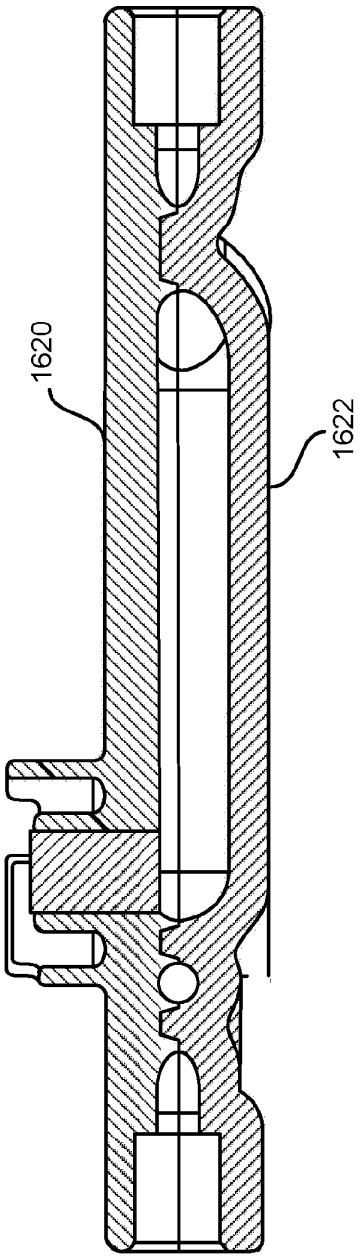


FIG. 19A

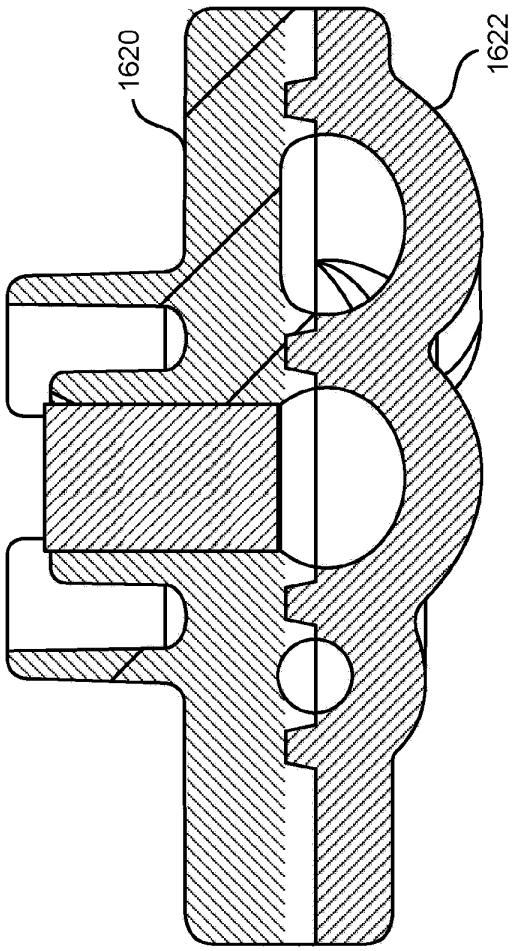


FIG. 19B

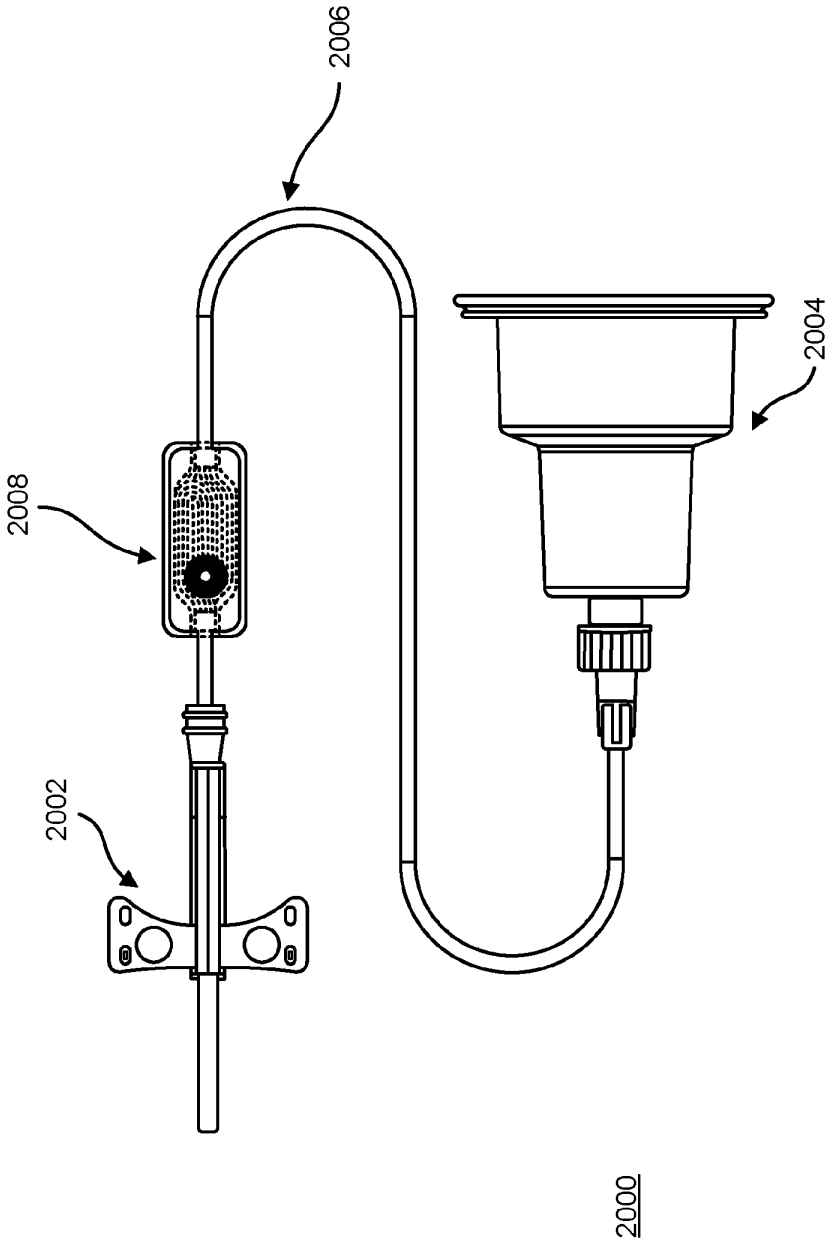


FIG. 20

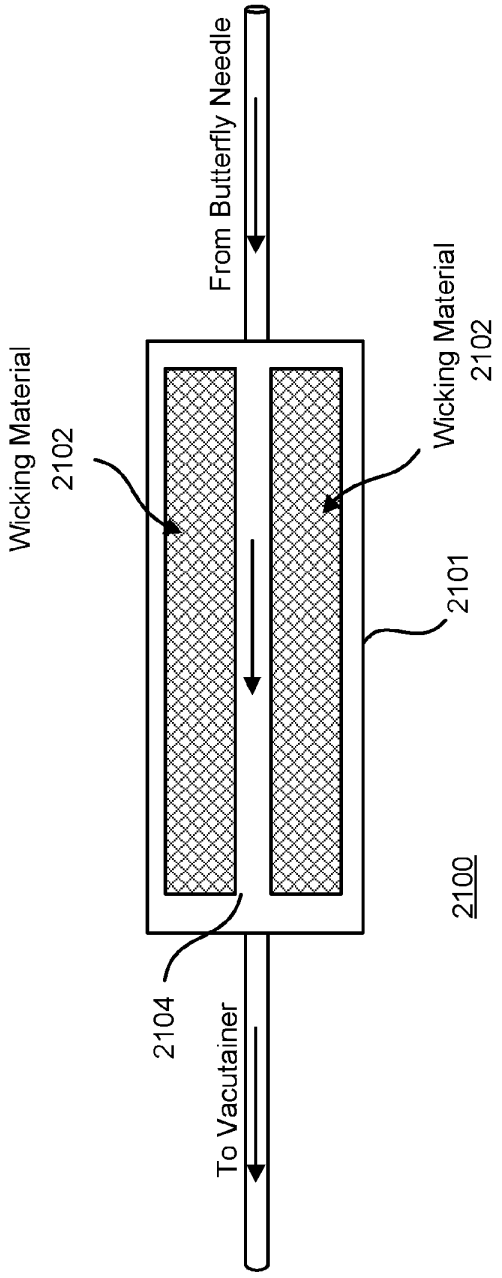

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

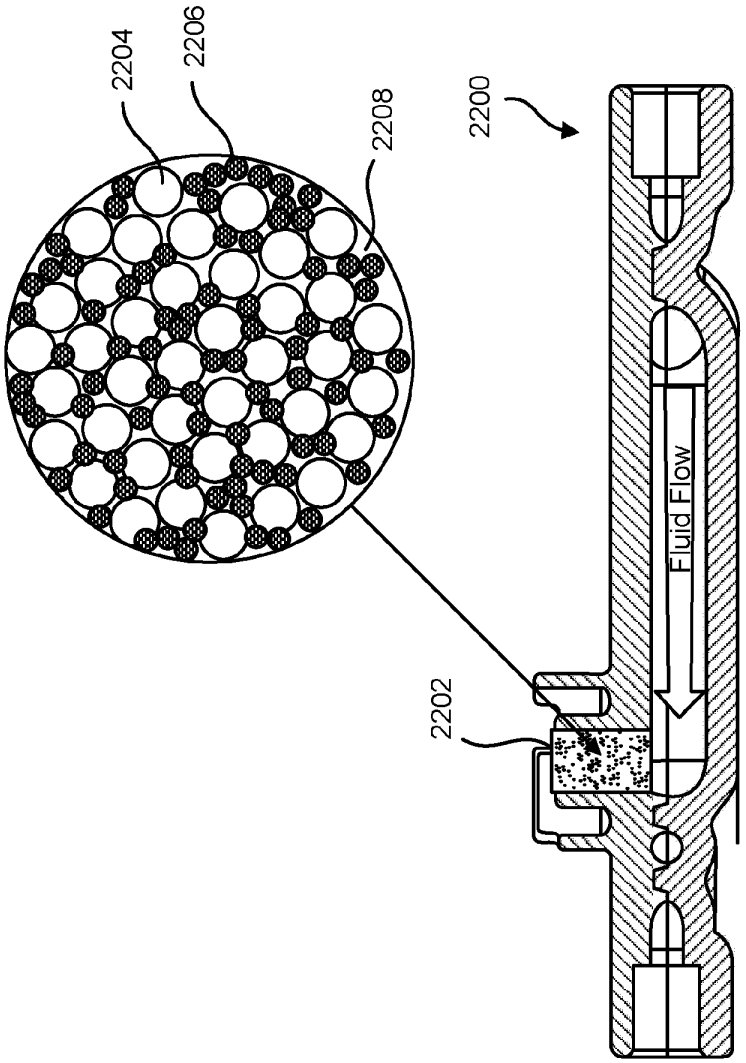


FIG. 22A

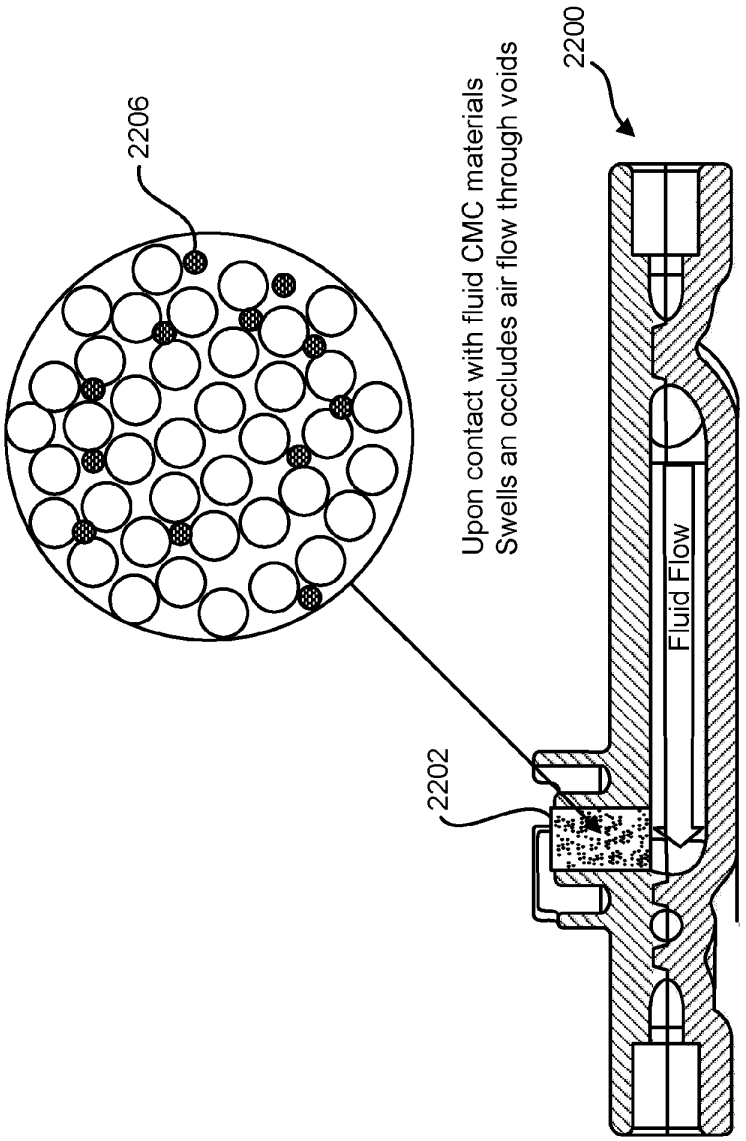

2206
2200
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
Fluid Flow
2202

FIG. 22B

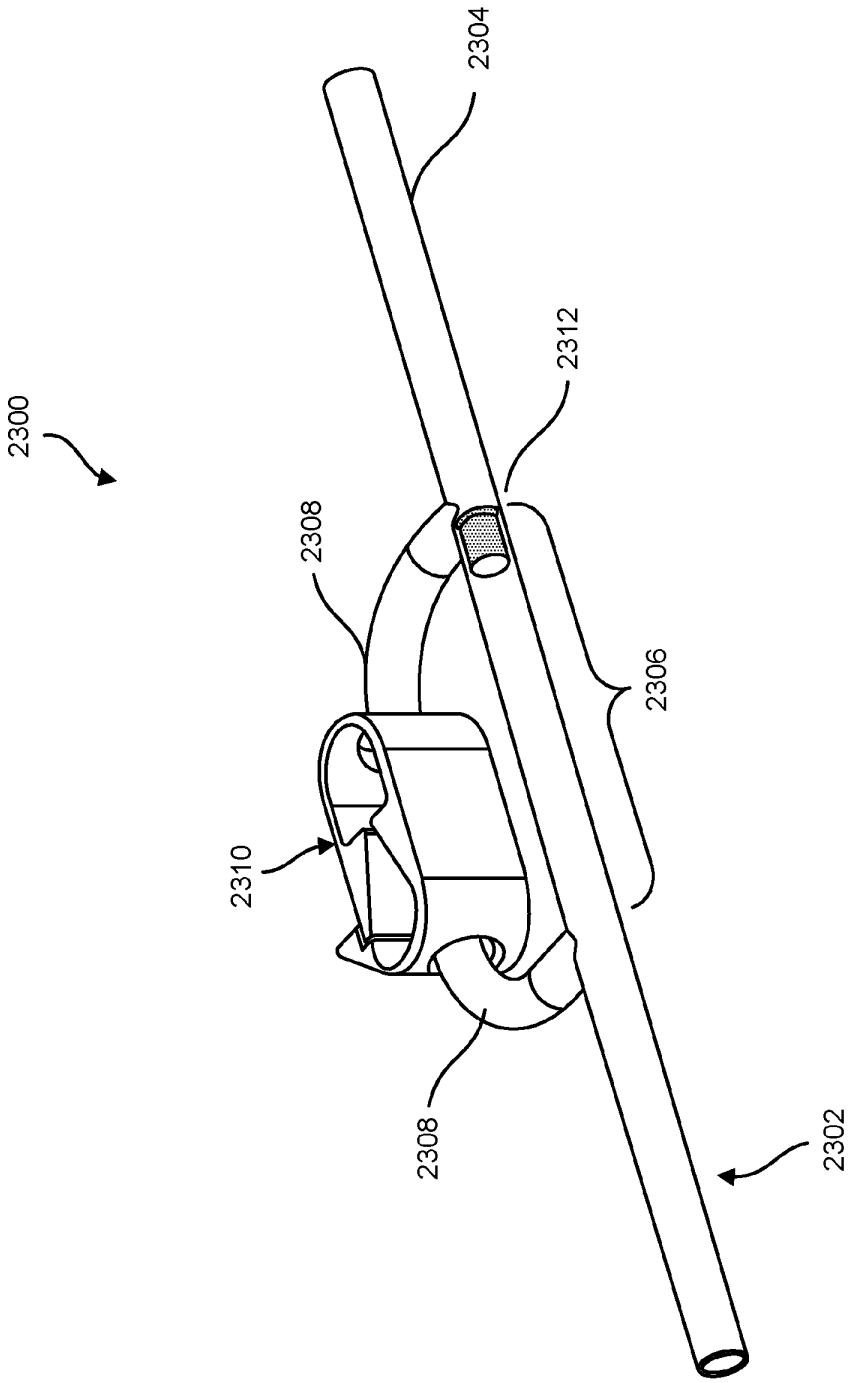


FIG. 23A

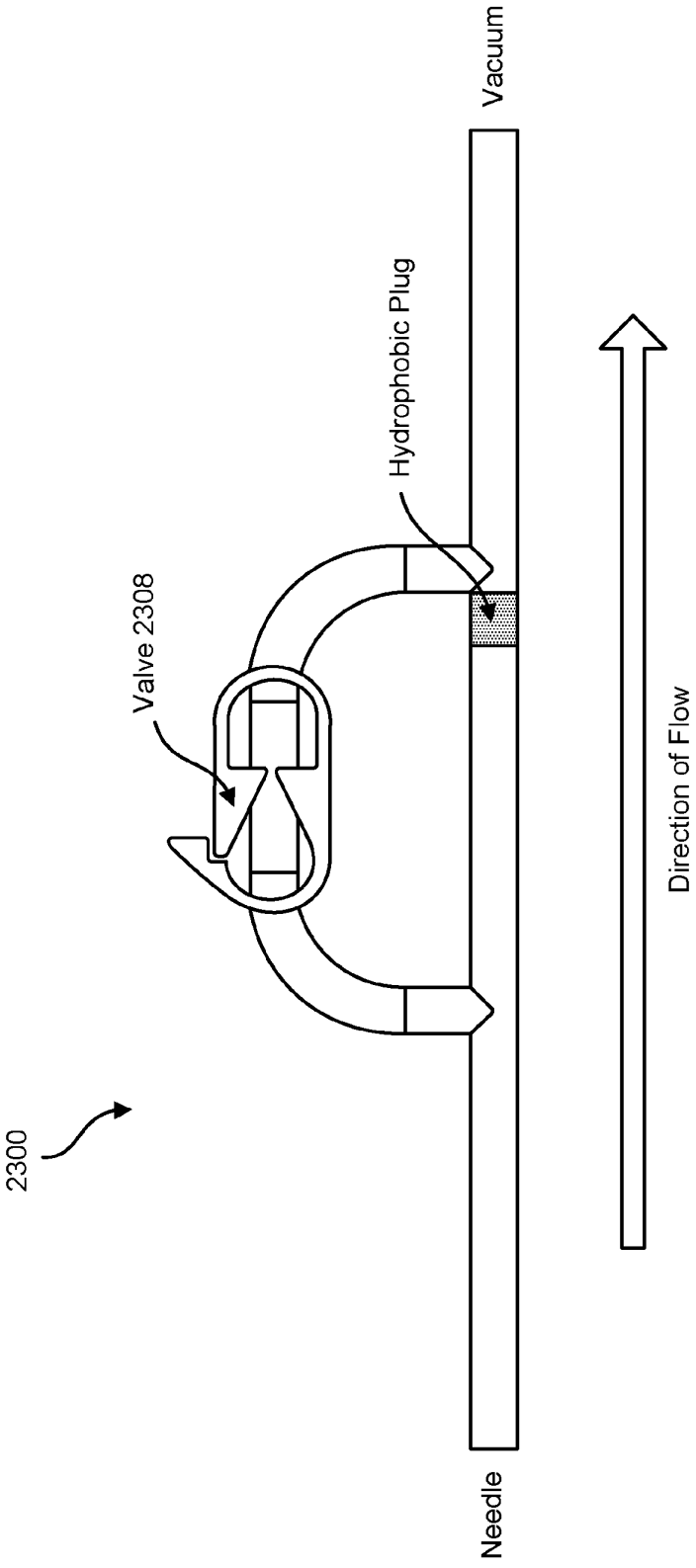

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

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 :

"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

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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

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

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

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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/US2016/043709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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English close

Literature display help

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Japanese Patent Application Laid-Open No. 57-089869

Registration Gazette public notice Document unit PDF progress information OPD search key URLs

Display format of the document display screen:

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primary literature

The scope of the claims

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[Claims]

1. A single sample needle assembly adapted to recognize insertion of the needle into a blood vessel when collecting a blood sample from a patient into the evacuated vessel, the single sa mple needle assembly having at least a forward end, a rearward end and an interior chamber. a housing having a transparent portion surrounding the chamber so that a user can see the ch amber; a first opening formed in a front end of the housing and communicating with the cham ber; and a first opening extending outwardly into the chamber. a first puncture needle that co mmunicates and is inserted into a patient; a second opening that is formed in the rear end of the housing and communicates with the chamber; a second cannula closed and having two sp aced apart transverse holes, and a plug of air permeable blood impermeable material in fluid t ight sliding contact with the housing enclosing the chamber and the second puncture needle. said plug initially in a position covering a first side hole remote from said second opening and not covering the other second side hole from a first puncture needle under constant tournique t pressure; Blood entering the chamber is prevented by the plug from flowing out into the sec ond cannula, allowing only the air in the chamber to flow out so that the user can see through the transparent housing that the first needle has entered the blood vessel. , wherein a negativ e pressure gradient acting on the second opening causes the plug to slide to open the first lat

eral hole, allowing blood to flow from the chamber through the first lateral hole and the secon d cannula to the second opening. A single sample needle assembly, characterized in that it is collected externally.

2. 2. A needle assembly according to claim 1, wherein the distance between said lateral holes is greater than the longitudinal length of said plug so that said plug does not simultaneously c over said lateral holes.

3. 3. The needle assembly of claim 1, wherein only a portion of said plug outer surface is in fl uid tight contact with a housing enclosing a chamber.

4. The plug includes an air and blood impermeable material in combination with the air and bl ood impermeable material, the impermeable material being in fluid tight contact with the hou sing surrounding the chamber and the second cannula. of patent claimsThe needle assembly of claim 1.

5. 5. The needle assembly of claim 4, wherein only a portion of the outer surface of said impe rmeable plug material is in liquid-tight contact with the housing surrounding the chamber.

6. 6. The needle assembly of claim 5, wherein only a portion of the surface of said impermeab le plug material is in fluid tight contact with the second cannula.

7. 7. A needle assembly according to claim 6, wherein said impermeable material is a membe r surrounding the outside of the air permeable material and has at least one opening in which the air permeable material communicates directly with the chamber.

8. 8. The needle assembly of claim 7, wherein said impermeable material includes a plurality of apertures communicating air permeable material with the chamber.

9. 5. The needle assembly of claim 4, wherein said impermeable material is flexible.

10. 10. The needle assembly of claim 9, wherein said impermeable material is elastomeric.

11. 11. The needle assembly of claim 10, wherein said impermeable material is silicone rubbe r.

12. 3. A needle assembly as in claim 1, wherein said plug is in the shape of a hollow cylinder.

13. 3. The needle assembly of claim 1, wherein said plug material is porous.

14. 14. The needle assembly of claim 13, wherein said plug material is sintered polyethylene and the average pore diameter is about 10 microns.

15. 3. The needle assembly of claim 1, wherein the end of the second cannula extending into said chamber is sealed with an adhesive.

16. 3. The needle assembly of claim 1, including an exit needle in communication with said se cond cannula and extending outwardly from a second opening through a blood sample collecti on evacuated vessel.

17. 17. The needle assembly of claim 16, wherein said second cannula and exit needle are joi ned to form a unitary construction.

18. 4. The needle assembly of claim 1, wherein said entire housing is transparent.

19. 3. The needle assembly of claim 1, including a vacuum vessel holder connected to said ho using.

20. A single sample needle assembly adapted to be in fluid communication when collecting a f luid sample from a fluid supply to a vacuum collector, the assembly defining a chamber therei n and first and second openings communicating with the chamber. a housing having solution v iewing means and a second opening in communication with the vacuum collection device; a d evice for placing two openings in a closed relationship with a chamber and slidingly sealing sai d chamber to prevent liquid from flowing into one of the holes and permitting air to flow into o ne of the holes in a first position. a plug device for making the liquid within the chamber visibl e by visual means, said plug device being slidable by a negative pressure gradient acting on t he second opening to force the liquid through one of the holes at the second location within th e chamber. A single sample needle assembly, characterized in that the liquid is allowed to flow into the second opening and collect from the second opening.

21. A needle assembly adapted to be in fluid communication when collecting a fluid sample fr om a fluid supply into a vacuum collection device, the needle assembly defining a chamber th erein and first and second openings communicating with the chamber, the chamber contents. a housing having liquid viewing means and a second opening in communication with a vacuu m collection device; an extension device extending into said chamber for directing gas and liq uid to said second opening; and operatively sealing said chamber. a plug device for preventing liquid from flowing into the extension device and allowing gas to flow into the extension devic e at a first position within the chamber, the liquid within the chamber being visible by visual m eans, the plug device A needle assembly as characterized in that when moved to a second pos ition, fluid is allowed to flow into the extension device to allow fluid to be collected from the se cond opening.

22. A single sample needle assembly adapted to recognize a vascular puncture when collectin g a blood sample from a patient into an evacuated vessel, the assembly comprising a transpar ent housing having a front end, a rear end and an internal chamber; A first needle in commun ication extending outwardly from the front end of the housing for insertion into the patient, an d an outer portion extending outwardly from the rear end of the housing for penetrating the bl ood sample collection evacuated vessel. a second puncture needle with an inner portion exten ding into the chamber and having a closed end and two spaced apart transverse holes;and a plug slidable within the chamber as a composite member of an air permeable blood impermea ble material and an elastic impermeable material, the impermeable material forming an outer member surrounding the air permeable material. a plurality of apertures providing an air per meable material in direct communication with the chamber, said impermeable material being i n fluid tight contact with a housing surrounding the chamber and an inner portion of the seco nd needle; , the plug initially covers the first lateral hole furthest from the trailing end and op ens the other second lateral hole to the chamber, thereby providing a constant tourniquet pre ssure from the first needle. blood flowing into the chamber below is prevented by the plug fro m flowing into the second needle to allow room air flow to allow blood to be visualized throug h the transparent housing to indicate that the first needle has entered the vessel; The plug sli

des due to the negative pressure gradient acting on the second needle from the vacuum vess el to open the first lateral hole, and the blood that has flowed into the chamber is collected in the vacuum vessel through the first lateral hole and the second needle. A single sample needl e assembly, characterized in that:

detailed description open —

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a needle assembly for collecting fluid from a patient, and mor e particularly to a needle assembly having means for collecting a single sample of blood from a patient and recognizing when the needle has entered the patient's blood vessel. Regarding s olids.

In collecting bodily fluids, such as blood, from a patient, a nurse or clinician must locate or ori entate the patient's blood vessels as the fluid is being collected, but even with the application of tourniquet pressure, the vessels are narrow. In some cases, or if the blood vessel is remote from the skin surface, it may not be possible to insert the needle directly into the patient's blo od vessel. In this case, the needle may be punctured at a location other than the location of t he blood vessel, or may penetrate the small vessel completely. As a result, the flow of blood t hrough the needle and into the evacuated blood collection tube is uncomfortable and extremel y slow because it does not flow out of the patient's blood vessel. Nurses have to start over an d often have to use another evacuated blood collection tube in this case, increasing equipmen t, cost and patient anxiety.

To reduce wastage of evacuated blood collection tubes when a nurse needs to locate a vessel, many blood collection devices have been proposed that have an indicator to show when the n eedle has entered the vessel. This visual indicator system usually has an antechamber and is i solated by some valve system from a needle through which blood is collected in an evacuated tube. When the nurse locates the vessel and the needle enters the vessel, it indicates that the blood has entered the antechamber through the needle and into the vessel in the correct posit ion. The blood collection process is now started, the evacuated blood collection tube is plugge d into the blood collection holder, the valve is opened and blood flows into the collection tube. Examples of blood collection devices with visual indicators are U.S. Pat. Nos. 4,166,450 and 3, 585,984.

In theory, antechamber structures for viewing blood flow are operable and sometimes work w ell, but there are inherent problems. That is, the anterior chamber is normally filled with air w hen the front end of the needle is inserted into the patient's blood vessel. Due to the valve clo sure between the second needle passing through the evacuated blood collection tube, the air i

n the antechamber has no escape and forms stagnant air. Thus, even if the nurse knows the l ocation of the vessel and the needle is well within the vessel, the constant tourniquet pressur e will not allow blood flow from the patient through the needle and into the antechamber. That is, the stagnant air in the anterior chamber prevents blood from entering the anterior chambe r through the needle even under constant tourniquet pressure. As a result, the nurse conclude s that the required endovascular insertion was not performed because no blood was visible in the anterior chamber. An unnecessary second vascular puncture is performed, which is not onl y uncomfortable for the patient, but also inefficient and wasteful.

Therefore, there is a need for new visual indicators for users of blood collection devices. Thus, there is a need for an improved blood collection device of the type that will know when the ne edle has been inserted into the patient's blood vessel prior to inserting the evacuated blood co llection tube into the blood collection holder, as per normal blood collection procedures.

A needle assembly capable of recognizing the arrival of liquid when collecting a liquid sample f rom a liquid source into a vacuum collection device in accordance with the present invention c omprises a housing having an interior chamber and a chamber in communication with the cha mber. and a first and second opening device. The housing includes means for viewing the cont ents of the chamber, and the second opening device is communicable with the vacuum collecti on device. Extending into the room with gasand an extension device for directing the liquid to the second opening device. There is a plug device in operative engagement within the chambe r to prevent liquid from flowing into the extension device and permit gas to flow into the exte nsion device at a first position within the chamber. When the plug device is moved to the seco nd position fluid is allowed to flow into the extension device and is collected through the secon d opening device.

In the preferred embodiment of the needle assembly according to the invention described abo ve, the housing is transparent and provides a front end, a rear end and an interior chamber. A first cannula extends forwardly from the front end of the housing and communicates with the chamber. A second cannula has an outer portion extending outwardly from the rearward end o f the housing and an inner portion extending into the chamber having a closed end and first a nd second longitudinally spaced transverse bores. The plug device is a combination plug of an air permeable, blood impermeable material and an elastic impermeable material, slidable with in the chamber, the impermeable material forming an outer member surrounding the air perm eable material. A plurality of openings extend through the impermeable material and commun icate the air permeable material directly to the chamber. The impermeable material is in liquid -tight contact with the inner housing wall surrounding the chamber and the inner portion of th e second sleeve. In the first position, the plug covers the first cross-bore of the second bushin g, remote from the rear end of the housing, and the second cross-bore communicates with th e chamber. Blood flowing through the first cannula into the chamber under constant tournique t pressure is prevented by the plug from flowing into the second cannula and is visible to the user, and air passes through the plug to the second cannula. 2 cannula. A negative pressure g

radient acting on the second cannula causes the plug to slide open the first crossbore and mo ve toward the second crossbore. Blood in the chamber therefore flows from the first lateral ho le through the second cannula and into the blood collection container.

The components and characteristics of the needle assembly according to the invention differ si gnificantly from known ones of this type. For example, the plug material within the housing ch amber acts as a valve to prevent blood from flowing out of the chamber when the needle is in serted into the patient's vessel. At this stage of the blood collection procedure, the evacuated blood collection tube is normally not plugged in. Therefore, it is necessary to prevent blood fro m escaping the needle assembly at this stage. However, when a nurse punctures a patient's bl ood vessel, blood flows through the front needle and into the chamber of the needle assembly housing. The plug material is essentially blood impermeable, thus preventing blood from flowi ng through the chamber. However, because the plug material of the present invention is air pe rmeable, air originally present in the chamber and front needle escapes from the chamber. Th erefore, there is no air stagnation as with known needle assemblies with visual indicators. In addition, the plug is slidable within the chamber, and when a vacuum blood collection tube is attached to the rear of the needle assembly, the negative pressure gradient will cause the plu g to slide within the chamber to bring the front lateral port of the collection cannula into the bl ood flow path. expose. Thus, when a negative pressure blood collection tube is attached, the plug immediately moves to create an opening effect and blood flows through the needle asse mbly and into the blood collection container.

As noted above, the present invention solves the problem of air stagnation in known needle a ssemblies. That is, the needle assembly of the present invention allows the user to see blood entering the housing chamber as soon as the needle assembly is correctly inserted into the bl ood vessel. Since air within the needle assembly is free to escape, blood flows freely into the housing chamber.

Embodiments and drawings illustrating the invention will now be described. The present inven tion can be modified in various ways, and the examples and drawings are examples for facilita ting understanding of the present invention and do not limit the invention.

FIG. 1 shows an embodiment of a single sample needle assembly 10 according to the present invention. The basic components of needle assembly 10 include a housing 12, a first puncture needle 14 for insertion into the patient, and a second puncture needle 15 for puncturing a vac uum vessel 16 on the opposite side of housing 12 from which a blood sample is collected. incl ude. A threaded portion 18 of the housing 12 is adjacent to the second puncture needle 15 an d threads into internal threads 20 at the front end of the container holder 19 . By slidingly eng aging the vacuum container 16 within the holder 19 the second puncture needle 15 penetrate s the pierceable stopper 21 at the front end of the container 16 . Blood sample collection in th e general configuration described above is well known.

Figures 2, 3 and 4 show the detailed construction of the needle assembly 10 according to the present invention. The housing 12 has a forward end 24 and a rearward end 25 which are sep

arated so that a slidable pillar 26 can be placed in place within the housing.make it The front end portion 24 is cylindrical in the illustrated example, and a hole 29 into which the puncture needle 14 is slidably fitted extends from the front end to a partial depth. Hole 29 does not ext end through front end 24, but a small diameter passageway 30 extends from hole 29 to form an opening 31 at the trailing edge of front end 24. As shown in FIG. A shoulder 33 is formed b etween the hole 29 and the passageway 30 . The puncture needle 14 comes into contact with the shoulder 33 and comes to a predetermined position. After the puncture needle 14 is at a p redetermined position, it is fixed with an adhesive or the like.

The front end 24 of the housing 12 is formed with a plurality of longitudinal ribs 28 surroundin g the puncture needle. A needle shield, not shown, covers the outwardly projecting needle an d has internal ribs that match ribs 28 . Inner-outer ribs between the needle shield and the ne edle assembly facilitate attachment and detachment of the needle assembly from the holder 1 9 by the user. An annular flange 32 formed on the front end 24 forms a joining surface for the housing halves. Both parts 24, 25 are secured together using any desired attachment means, such as adhesive.

The rear end 25 is also cylindrical in the illustrated example, with a large hole partially extendi ng from one end in the direction of the second puncture needle. This large hole defines a cha mber 40 within housing 12, described in more detail below. A small hole 41 extending through the rear end portion of rear end 25 is substantially similar to hole 29 in the front end. The hol e 41 is sized to allow the diameter of the second puncture needle 15 to pass through, and the puncture needle 15 is fixed to the hole 41 with an adhesive or the like. External threads 18 ar e formed on the outer surface of the rear end surrounding the bore 41 to provide a connectio n to the holder as previously described. The outer surface 42 of the rear end 25 surrounding t he chamber 40 is smooth and transparent to allow the user to see inside the housing. In man y instances, it is preferred that the entire trailing and leading ends be made of a transparent material for ease of manufacture and to minimize the variety of materials used to manufactur e the needle assembly. A transparent rigid synthetic resin is the preferred material for manufa cturing the needle assembly. However, it could also be constructed with closed windows or por ts where desired. The window or port closure is configured so that blood entering chamber 40 will not leak out when the needle enters the vessel.

The distal end of the second puncture needle 15 extends outwardly from the rear end 25 of th e housing and the inner portion 44 extends through the hole 41 into the chamber 40 to a leng th such that the plug 26 cannot be removed. The inner end 45 of the hollow puncture needle 15 is closed according to the invention, eg, glued, crimped, or the like. Two holes 48, 49 are f ormed in the side of the inner portion 44 of the needle 15 to provide communication between the chamber 40 and the needle lumen. The holes 48 , 49 are axially spaced apart in the inner portion 44 . An annular flange 46 formed at the housing rear end 25 contacts the flange 32 to join the housing halves 24,25. When assembling, the plug 26 is in a predetermined position, t he front end portion 24 and the rear end portion 25 are brought into contact with each other,

and the flanges 32 and 46 are fixed by an adhesive or the like. The plug 26 is within the chamber 40 and contacts the inner wall of the housing portion 42 surrounding the chamber 40 and slides along the outer surface of the inner portion 44 of the second puncture needle 15 . In the example shown, the spacing between the lateral holes 48, 49 is greater than the longitudinal length of the plug 26 so that the sliding plug 26 can cover only one lateral hole. 2 shows the needle assembly 10 in its pre-use condition, with the plug 26 positioned to cover the lateral hole 49 furthest from the hole 41 in the rear end 25. FIG. The plug 26 is in fluid tight sliding contact with the inner wall of the transparent housing portion 42 surrounding the chamber 42 as well as the outer wall of the inner portion 44 of the second needle 15 . A preferred construction for plug 26 is shown in FIGS.

The plug 26 is of composite construction in the illustrated example, and the outer member 51 is made of a gas and liquid impermeable material. In a preferred example, this impermeable material is a flexible elastic material such as natural rubber, silicone rubber or the like. The illustrated example is cylindrical and has an annular flange 52 at one end. The outer diameter of flange 52 is sized to provide a fluid tight fit against the inner housing wall surrounding chamber 40 . Since only the flange 52 contacts the housing inner wall and no other portion of the outer member 51 , friction surfaces are minimized and the plug 26 is easily slid under the vacuum acting within the chamber 40 . In the combined structure of the plug 26 , an outer member 51 made of an impermeable material is combined with an inner space 54 , with openings 55 and 56 at both ends communicating with the space 54 . The inner diameter of opening 55 is fluidly sealed against inner portion 44 of needle 15 .A tight fit is provided and the opening 56 is larger than the outer diameter of the needle to allow air flow from the end of the plug. A chamber 58 is formed to facilitate assembly of the inner and outer members 54, 51 of the plug. A plurality of openings 59 are formed in the outer wall of outer member 51 as longitudinal slots in the illustrated example. Although four openings 59 are shown in the illustrated example, any desired number may be used. Apertures 59 allow air communication between chamber 40 and interior space 54 .

The second member of combination plug 26 is a generally cylindrical member 60 made of a material that is permeable to gases such as air and impermeable to liquids such as blood. A passageway 61 extends longitudinally through the member 60 and passes through the inner portion 44 of the needle. Although the passageway 61 and the inner portion 44 are of non-contact construction, slight contact may be made. The air permeable member 60 is compression-fitted within the inner space 54 of the outer member 61 so that the plug 26 is impermeable to fluids such as blood. The member 60 is pushed into the space 54 through the opening 56 using the elasticity of the outer member 51 . A preferred example of the material from which the air permeable member 60 is made is a porous material such as sintered polyethylene, with pores on the order of 10 microns in diameter.

FIG. 6 shows the needle assembly 10 according to the invention connected to the holder 19. FIG. In the first stage of blood collection, the puncture needle 14 is inserted into the patient P

without the vacuum tube 16 attached. The plug 26 is now in fluid tight contact with the inner housing wall surrounding the chamber 40 and the inner portion 44 of the second needle and i s in the position of FIG. In this position the inner cross-bore 49 is covered by the plug 26 and the lower cross-bore 48 is uncovered. Since the interior of the second needle 15 communicate s with the atmosphere rather than with a vacuum, the lumens of the chamber 40 and the nee dles 14, 15 are at atmospheric pressure and air is present. Once the first needle 14 is in the v essel, blood will flow through the needle 14 and fill the front portion 40a of the chamber 40 u nder normal tourniquet pressure. Air that was present in front portion 40a of chamber 40 esca pes through slots 59 in impermeable member 51 and through air permeable member 60. FIG. Air escapes through the tip of second needle 15 through lateral holes 48 or 49 . As a result, bl ood fills the front chamber 40a and there is no air stagnation as in known devices. Blood cann ot flow into the second needle 15 because the impermeable member 51 is in fluid tight engag ement with the needle 15 and the inner wall of the housing, and the air permeable member 6 0 is fluid impermeable. Blood in the anterior chamber 40a is visible to the user through the tr ansparent material 42, indicating that the first needle 14 has entered the blood vessel. The th rust from blood entering chamber 40 under normal tourniquet pressure is small and the plug will not slide out of its initial position shown in FIG.

When the user visually confirms that the needle has entered the blood vessel, the vacuum tub e 16 is inserted into the holder 19 and the second needle 15 penetrates the stopper 21 . FIG. 7 shows the evacuated blood collection tube 16 inserted. If the second needle 15 communicat es with the vacuum space within the tube 16, a negative pressure gradient will act within the chamber 40 via the lateral hole 48. FIG. This negative pressure acts on the lower surface of th e plug 26 causing it to move within the chamber 40 along the inner portion 44 of the second n eedle 15 towards the tube 16 . Although FIG. 7 shows the cross-bore 48 completely covered b y the sliding of the plug 26, some or all of the cross-bore 48 may be uncovered depending on the vacuum conditions at work. This sliding creates communication between the lateral hole 4 9 and the front portion 40a of the chamber, and blood in the front chamber 40a is free to flow into the second needle 15. As shown in FIG. Blood flows through the second needle into tube 16 and the first needle 14 is withdrawn from the patient when the desired amount of blood sa mple has entered tube 16, completing the blood sample collection procedure.

As demonstrated by the above, the needle assembly according to the present invention has a slidable plug that can be easily installed and entered the vessel upon the first vessel puncture allowing air to escape. I can confirm that. Because this air escape is allowed, blood will immed iately flow into the chamber once the needle punctures the blood vessel, providing a visual in dicator for the user to see that it has entered the blood vessel. Based on this visualization, a b lood collection tube can be attached to facilitate the collection of a blood sample from the pati ent.

Brief description of the drawing open —

BRIEF DESCRIPTION OF THE DRAWINGS FIG.

1 shows a single sample sensor in accordance with a preferred embodiment of the present inv ention.2 is an exploded perspective view showing the pull needle assembly, holder and evacua ted blood collection tube; FIG. 2 is a cross-sectional view taken along line 2--2 of FIG. 1; FIG. 3 is an enlarged view taken along line 3--3 of FIG. 2; 4 is an enlarged cross-sectional view of the plug taken along line 4-4 of FIG. 3, FIG. 5 is an enlarged cross-sectional view of the air pe rmeable member in the plug of FIG. 4, and FIG. 6 is the needle assembly. FIG. 7 is a perspect ive view of puncturing a patient's blood vessel, and FIG. 7 is a cross-sectional view showing th e state of use along line 7--7 of FIG.

10---needle assembly 12---housing

14, 15---needle 16---vacuum container

19---holder 24---front end

25---rear end 26---plug

40- -- Chamber 44 --- Inner portion

48, 49 --- Lateral hole 51 --- Outer member

59 --- Opening 60 --- Air permeable member

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Espacenet

Bibliographic data: JPS5789869 (A) — 1982-06-04

SINGLE SAMPLE NEEDLE ASSEMBLAGE

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Applicant(s): BECTON DICKINSON CO ± (BECTON DICKINSON & CO, ; BECTON DICKINSON CO)

Classification: - international: ***A61B5/15; A61B5/154; A61M5/178; A61M5/32;*** (IPC1-7): A61B5/14; A61M5/18; A61M5/32
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150488 (EP, US); A61B5/150511 (EP, US); A61B5/150519 (EP, US); A61B5/1545 (EP, US);** A61B5/150389 (EP, US); A61B5/150732 (EP, US)

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Priority number(s): US19800193054 19801002

Also published as: AU541390 (B2) AU7555981 (A) BR8106266 (A) DK154536 (B) DK154536 (C) more

Abstract not available for JPS5789869 (A)
Abstract of corresponding document: US4312362 (A)

A needle assembly preferably suitable for single sample blood collection and for determining vein entry when collecting a blood sample from a patient into a vacuum collection device. This assembly includes a housing with an interior chamber with a blood inlet needle on one side of the housing and a blood outlet needle on the other. The outlet needle extends interiorly into the chamber, is closed at the end and includes a pair of holes each spaced preferably along an axial line. A slidable plug is operatively positioned in the chamber to prevent liquid from flowing into the side holes while allowing gas to flow into at least one of the side holes at a first position in the chamber whereby the prevented liquid may be viewed by a user through a transparent portion of the housing. The operative plug is movable to a second position in the chamber to allow liquid to flow into at least one of the side holes whereby liquid may be collected from the outlet needle of the assembly.

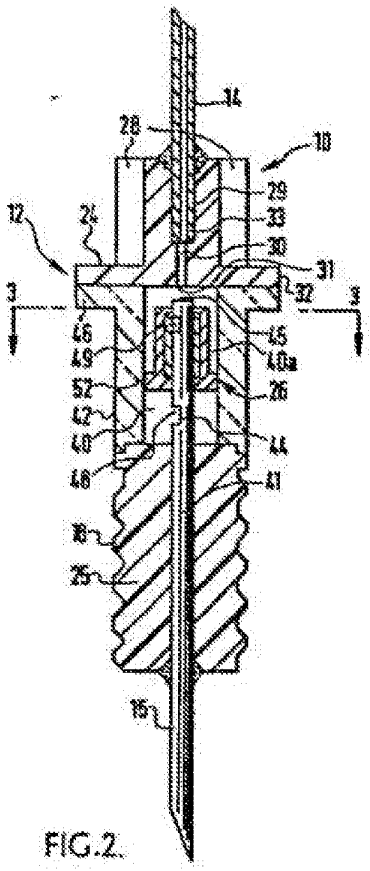

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FIG.2.

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭57—89869

⑤1Int. Cl.³	識別記号	庁内整理番号
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A 61 B 5/14		6530—4C
A 61 M 5/32		6408—4C

⑬公開　昭和57年(1982)6月4日

発明の数　4
審査請求　未請求

（全 8 頁）

⑤4単一サンプル針組立体

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1.〔発明の名称〕

単一サンプル針組立体

2.〔特許請求の範囲〕

1. 患者から血液サンプルを真空容器内に収集する時に針の血管内への挿入を認識するようにした単一サンプル針組立体であつて、前端部と後端部と内部の室とを有し少なくとも室を囲む部分を透明として使用者が室を見得るようにしたハウジングと、ハウジングの前端部に形成し室に連通した第1の開口と、第1の開口から外方に延長して室に連通させ患者内に挿入する第1の穿刺針と、ハウジングの後端部に形成し室に連通した第2の開口と、第2の開口に連通して室内に延長し室内部分の端部を閉鎖し2個の離間した横孔を有する第2の套管と、上記室を囲むハウジングと第2の穿刺針とに液を通さない滑動接触とした空気透過血液不透過性材料のプラグとを備え；上記プラグは最初は上記第2の開口に対して離れた第1の横孔を覆い他方の第2の横孔は覆わない位置とし、定常止血帯圧力の下で第1の穿刺針から上記室に流入する血液は上記プラグによつて第2の套管内に流出することを防止され室内の空気のみを流出させ、使用者が透明ハウジングを通して見て第1の針が血管内に入つたことを示し、第2の開口に作用する負圧勾配によつてプラグが滑動して第1の横孔を開いて血液が室から第1の横孔と第2の套管を通つて流れて第2の開口外で収集されることを特徴とする単一サンプル針組立体。

2. 前記両横孔間の間隔をプラグの長手方向の長さよりも大としてプラグは同時に両横孔を覆わないようになつている特許請求の範囲第1項記載の針組立体。

3. 前記プラグ外面の一部のみが室を囲むハウジングに液を通さない接触となつている特許請求の範囲第1項記載の針組立体。

4. 前記プラグには前記空気透過血液不透過性材料と組合せ構造とした空気血液不透過性材料を含み、上記不透過性材料が室を囲むハウジングと第2の套管とに液を通さない接触となる特許請求の

範囲第1項記載の針組立体。

5. 前記不透過性プラグ材料の外面の一部のみが室を囲むハウジングに液を通さない接触となつている特許請求の範囲第4項記載の針組立体。

6. 前記不透過性プラグ材料の面の一部のみが第2の套管に液を通さない接触となつている特許請求の範囲第5項記載の針組立体。

7. 前記不透過性材料は空気透過性材料の外側を囲む部材として少なくとも1個の開口によつて空気透過性材料を直接室に連通させる特許請求の範囲第6項記載の針組立体。

8. 前記不透過性材料には空気透過性材料を室に連通させる複数の開口を含む特許請求の範囲第7項記載の針組立体。

9. 前記不透過性材料は可撓性である特許請求の範囲第4項記載の針組立体。

10. 前記不透過性材料は弾性体である特許請求の範囲第9項記載の針組立体。

11. 前記不透過性材料はシリコンゴムである特許請求の範囲第10項記載の針組立体。

12. 前記プラグは中空円筒の形状である特許請求の範囲第1項記載の針組立体。

13. 前記プラグ材料は多孔性である特許請求の範囲第1項記載の針組立体。

14. 前記プラグ材料は焼結ポリエチレンであり孔の平均直径は約10ミクロンである特許請求の範囲第13項記載の針組立体。

15. 前記室内に延長する第2の套管の端部は接着剤によつて封鎖されている特許請求の範囲第1項記載の針組立体。

16. 前記第2の套管に連通して第2の開口から外方に延長し血液サンプル収集用真空容器を貫通する出口針を含む特許請求の範囲第1項記載の針組立体。

17. 前記第2の套管と出口針とを接合して一体構造とする特許請求の範囲第16項記載の針組立体。

18. 前記ハウジング全部が透明である特許請求の範囲第1項記載の針組立体。

19. 前記ハウジングに接続された真空容器用ホルダを含む特許請求の範囲第1項記載の針組立体。

20. 液供給源から真空収集装置に液サンプルを集める時に液連通を認識するようにした単一サンプル針組立体であつて、内部に室と室に連通する第1第2の開口とが形成され室内容液目視手段を有し第2の開口は真空収集装置と連通し得るようにしたハウジングと、第2の開口からほぼ軸線方向に沿つて室内に離間して形成した2個の孔を除いて第2の開口と室とを閉鎖関係とする装置と、上記室を滑動封鎖して第1の位置において液が一方の孔に流入するのを防ぎ空気が一方の孔に流入するのを可能にして室内の液を目視手段によつて見得るようにしたプラグ装置とを備え、上記プラグ装置は第2の開口に作用する負圧勾配によつて滑動して室内の第2の位置において液を一方の孔を通つて第2の開口に流入させて第2の開口から液を収集可能とすることを特徴とする単一サンプル針組立体。

21. 液供給源から真空収集装置内に液サンプルを収集する時に液連通を認識するようにした針組立体であつて、内部に室と室に連通する第1第2の開口とが形成され室内容液目視手段を有し第2の開口は真空収集装置に連通し得るようにしたハウジングと、上記室内に延長しガス及び液を第2の開口に導く延長装置と、上記室を作動封鎖して室内の第1の位置において液が延長装置内に流れるのを防ぎガスが延長装置内に流れるのを可能にするプラグ装置とを備え、室内の液を目視手段によつて見得るようにし、プラグ装置が第2の位置に動いた時に液が延長装置内に流入可能として液を第2の開口から収集可能とすることを特徴とする針組立体。

22. 患者から血液サンプルを真空容器内に収集する時に血管穿刺を認識するようにした単一サンプル針組立体であつて、前端部と後端部と内部の室とを有する透明のハウジングと、室に連通してハウジングの前端部から外方に延長し患者内に挿入する第1の穿刺針と、外方部分がハウジングの後端部から外方に延長して血液サンプル収集真空容器を貫通可能とし内方部分が室内に延長して閉鎖端と2個の離間した横孔とを有する第2の穿刺針

と、空気透過血液不透過性材料と弾性不透過性材料との複合部材として上記室内を滑動可能としたプラグとを備え、上記不透過性材料は空気透過性材料を囲む外側部材を形成して複数の開口によつて空気透過性材料を室に直接連通させ、上記不透過性材料は室を囲むハウジング及び第2の針の内方部分に液を通さない接触とし、上記プラグの上記横孔の間隔に対する寸法関係は上記プラグが最初は上記後端部から最も離れた第1の横孔を覆い他方の第2の横孔を室内に対して開放し、これによつて第1の針から定常止血帯圧力の下で室内に流入する血液はプラグによつて第2の針内に流れるのを防ぎ室内空気の流れを可能にし透明ハウジングを通して血液を目視可能として第1の針が血管内に入つたことを示し、真空容器から第2の針に作用する負圧勾配によつてプラグが滑動して第1の横孔を開き室内に流入した血液は第1の横孔から第2の針を経て真空容器内に収集されることを特徴とする単一サンプル針組立体。

3.〔発明の詳細な説明〕

本発明は患者から液を収集する針組立体に関し、特に患者から血液の単一サンプルを収集し針が患者の血管内に入つたことを認識する手段を有する針組立体に関する。

体内液例えば血液を患者から収集する際に、看護婦又は臨床医は、液を集める時に患者の血管の位置を探し又は見当をつける必要があるが、止血帯圧力を作用しても血管が細い場合又は血管が皮膚面から離れている場合には針を直に患者の血管内に挿入し得ないことがある。この場合には針が血管の位置以外の位置に穿刺されるか、細い血管を完全に貫通することがある。その結果、針を通つて真空の血液収集管に流れる血液流は患者の血管から流れないため、不快であり著しく遅い。看護婦は始めからやり直し、この場合に多くは別の真空血液収集管を使用する必要があるため、器材、費用が多くなり、患者に不安を与える。

看護婦が血管の位置を探す必要のある場合に真空血液収集管の浪費を少なくするために、針が血管内に入つたことを示すインジケータを有する多くの血液収集装置が提案されている。この目視インジケータ装置では通常前室を設け、真空の管内に集める血液を通す針との間を何らかの弁装置によつて遮断する。看護婦が血管を探しあてて血管内に針が入つた時は、血液が針を通つて前室に入り、血管の正しい位置に入つたことを示す。ここで血液収集過程が開始され、真空血液収集管を血液収集ホルダに差込み、弁を開いて血液は収集管に流入する。この目視インジケータ付血液収集装置の例として米国特許第4166450号、3585984号がある。

理論上は血液流を見るための前室構造は作動が可能であり、時には十分に作用するが、本質的な問題点が存在する。すなわち患者の血管内に針の前端を挿入した時に通常は前室内に空気が充満する。真空血液収集管を貫通する第2の針との間は弁によつて閉鎖されるため、前室内の空気は逃げ場がなく、停留空気を形成する。このため、看護婦は血管の位置を知り十分に血管内に針が入つても、定常止血帯圧力では患者からの血液流は針を通つて前室内に入ることはない。即ち、定常止血帯圧力が作用しても前室内停留空気は血液が針を通つて前室に流入するのを防ぐ。この結果、看護婦は目視で前室内血液が見えないため、所要の血管内挿入が行なわれなかつたと結論する。不必要な第2の血管穿刺が行なわれ、患者に不快であるばかりでなく効率が悪く無駄が多い。

それ故、血液収集装置の使用者にとつて、新らしい目視インジケータの開発が要望されている。即ち、通常の血液収集手順の通り、真空血液収集管を血液収集ホルダに差込む前に患者の血管に針が挿入されたことを知り得る型式の血液収集装置の改良が必要となつている。

本発明による液供給源から真空収集装置内に液サンプルを収集する時に液に到達したことを認識することが可能な針組立体は、ハウジングを備え、ハウジングには内部の室と、室に連通した第1第2の開口装置とを有する。ハウジングには室内の内容物目視手段を含み、第2の開口装置は真空収集装置に連通可能とする。室内に延長してガスと

液とを第２の開口装置に導く延長装置を有する。室内に作動係合して室内の第１の位置において液が延長装置内に流れるのを防ぎ、ガスが延長装置内に流れるのを可能にするプラグ装置を有する。プラグ装置が第２の位置に動いた時に液が延長装置に流れるのを可能にし液は第２の開口装置を通つて収集される。

上述の本発明による針組立体の好適な実施例において、ハウジングを透明として前端部と後端部と内部の室とを設ける。第１の套管はハウジングの前端部から前方に延長し室に連通させる。第２の套管の外方部分はハウジングの後端部から外方に延長し、内方部分は室内に延長して閉鎖端と第１第２の長手方向に離間した横孔とを有する。プラグ装置は空気透過性で血液不透過性の材料と弾性不透過性材料との組合せプラグとし、室内を滑動可能とし、不透過性材料が空気透過性材料を囲む外側部材を形成する。複数の開口が不透過性材料を貫通し、空気透過性材料を直接室に連通させる。不透過性材料は室を囲むハウジング内壁及びのハウジングの室内に流入する。プラグ材料は本質的に血液不透過性であるため、血液が室を通つて流れるのを防ぐ。しかし、本発明プラグ材料は空気透過性であるため、室及び前部針内に最初に存在した空気は室から逃れる。このため、既知の目視インジケータ付きの針組立体のように空気の停留を生ずることがない。更に、プラグは室内を滑動可能とし、真空血液収集管を針組立体の後部に取付けた時は、負圧勾配によつてプラグは室内を滑動して収集套管の前方の横孔を血流経路に露出する。かくして、負圧血液収集管を取付ければプラグは直ちに動いて開弁効果を生じ、血液は針組立体内を流れて血液収集容器に入る。

上述した通り、本発明によつて既知の針組立体に生じた空気の停留による問題点を解決した。即ち、本発明の針組立体は血管内に正しく穿刺すれば直ちにハウジング室内に入つた血液を使用者が見ることができる。針組立体内の空気は自由に逃れることが可能であるため、血液はハウジング室内に自由に流入する。第２の套管の内方部分に液を通さない接触となる。最初の位置では、ハウジング後端部から離れた第２の套管の第１の横孔をプラグが覆い第２の横孔は室に連通させる。第１の套管を通つて定常止血帯圧力の下で室内に流れる血液はプラグによつて第２の套管に流れるのを防がれ、使用者が目視可能であり、空気はプラグを通つて第２の套管に流れる。第２の套管に作用する負圧勾配によつてプラグは滑動して第１の横孔を開き第２の横孔の方に動く。それ故、室内の血液は第１の横孔から第２の套管を通つて流れ、血液収集容器に入る。

本発明による針組立体の構成素子及び特性はこの型式の既知のものとは著しく異なつている。例えば、ハウジング室内のプラグ材料は患者の血管内に針が挿入された時に室外に血液が流出するのを防ぐ弁の役割をする。血液収集手順のこの段階では、真空血液採取管は通常は差込まれない。それ故、この段階で血液は針組立体から逃れるのを防ぐ必要がある。しかし、看護婦が患者の血管を穿刺した時は、血液は前部の針を通つて針組立体

本発明を例示とした実施例並びに図面について説明する。本発明は種々の変型が可能であり、実施例並びに図面は本発明の理解を容易にするための例示であつて発明を限定するものではない。

第１図には本発明による単一サンプル針組立体１０の実施例を示す。針組立体１０の基本構成部品にはハウジング１２、患者内に挿入する第１の穿刺針１４、ハウジング１２の反対側で血液サンプルを集める真空容器１６を穿刺するための第２の穿刺針１５を含む。ハウジング１２のねじ部１８は第２の穿刺針１５に近接し、容器ホルダ１９の前端の内ねじ２０にねじこむ。真空容器１６をホルダ１９内に滑動係合させることによつて第２の穿刺針１５は容器１６の前端の穿刺可能のストッパ２１を貫通する。上述の一般形状とした構造の血液サンプル収集は周知である。

第２、３、４図は本発明による針組立体１０の詳細な構造を示す。ハウジング１２は前端２４と後端２５とを有し、両端部を分離して滑動可能ピラグ２６をハウジング内の所定位置に置き得るよ

うにする。前端部２４は図示の例では円筒形として穿刺針１４を滑動嵌合させる孔２９は前端から一部の深さに延長する。孔２９は前端部２４を貫通しないが小直径の通路３０が孔２９から延長して前端部２４の後縁に開口３１を形成する。孔２９と通路３０との間に肩部３３を形成する。穿刺針１４は肩部３３に接触して所定位置となる。穿刺針１４が所定位置となつた後に接着剤等によつて固定する。

ハウジング１２の前端部２４に穿刺針を囲む複数の長手方向リブ２８を形成する。図示しない針シールドは外方に突出した穿刺針を覆い、リブ２８に適合する内側リブを有する。針シールドと針組立体との間の内側外側リブによつて、使用者が針組立体をホルダ１９に取付取外しを行なうのを容易にする。前端部２４に形成した環状フランジ３２はハウジング両部を接合する面を形成する。所要の取付手段例えば接着剤を使用して両部２４、２５を互に固着する。

後端部２５も図示の例では円筒形とし、大きな孔が一端から第２の穿刺針の方向に部分的に延長する。この大きな孔はハウジング１２内に室４０を形成し、詳細は後述する。後端部２５の後端部分内を貫通した小さな孔４１は前端部の孔２９とほぼ同様とする。孔４１は第２の穿刺針１５の直径を通す寸法とし、穿刺針１５は例えば接着剤等によつて孔４１に固着する。孔４１を囲む後端部外面に外ねじ１８を形成して、前述した通りにホルダに対する連結装置となる。室４０を囲む後端部２５の外面４２は平滑透明とし、使用者がハウジング内を見得るようにする。多くの例では、全体の後端部及び前端部を透明材料製として製造を容易にし、針組立体の製造材料の種類を最小にするのが好適である。透明剛性合成樹脂が針組立体製造用材料として好適である。しかし、所要場所に封鎖した窓又はポートを有する構造とすることもできる。窓又はポートの封鎖は、針が血管に入つた時に室４０に入つた血液が漏出しない構成とする。

第２の穿刺針１５の先端部はハウジング後端部２５から外方に延長し、内方部分４４は孔４１を通つて室４０内に延長し、プラグ２６が外れない長さとする。中空穿刺針１５の内方端４５は本発明によつて閉鎖し、例えば接着剤、かしめ等で封鎖する。針１５の内方部分４４の側面に２個の孔４８、４９を形成して室４０と針内腔とを連通させる。孔４８、４９は内方部分４４の軸線方向に離間させる。ハウジング後端部２５に形成した環状フランジ４６は、フランジ３２に接触してハウジング両部２４、２５を接合する。組立に際してプラグ２６を所定位置として前端部２４、後端部２５を接触させ、接着剤等によつてフランジ３２、４６を固着する。プラグ２６は室４０内にあり、室４０を囲むハウジング部４２の内壁に接触し、第２の穿刺針１５の内方部分４４の外面に沿つて滑動する。図示の例では横孔４８、４９の間隔はプラグ２６の長手方向の長さよりも大とし、滑動プラグ２６によつて一方のみの横孔を覆い得るようにする。第２図には針組立体１０の使用前の状態を示し、プラグ２６は後端部２５の孔４１から最も離れた横孔４９を覆う位置にある。プラグ２６は室４２を囲む透明ハウジング部４２の内壁、並びに第２の針１５の内方部分４４の外壁に対して液を通さない滑動接触とする。プラグ２６の好適な構造は第２、３、４、５図に示す。

プラグ２６は図示の例では組合せ構造であり、外側部材５１はガス、液を通さない材料製とする。好適な例では、この不透過性材料は可撓性弾性材料例えば天然ゴム、シリコンゴム等とする。図示の例では円筒形で一端に環状フランジ５２を有する。フランジ５２の外径は、室４０を囲むハウジング内壁に対して液を通さない嵌合となるように定める。フランジ５２のみがハウジング内壁に接触し、外側部材５１の他の部分は接触しないため、摩擦面は最小となり、プラグ２６は室４０内に作用する負圧によつて容易に滑動する。プラグ２６の組合せ構造において、不透過性材料で形成する外側部材５１に内側スペース５４を組合せ、両端の開口５５、５６がスペース５４に連通する。開口５５の内径は針１５の内方部分４４に対して液

を通さない嵌合とし、開口５６は針外径よりも大きくしてプラグ端からの空気の流通を可能にする。室５８を形成してプラグの内側外側部材５４、５１の組合せを容易にする。複数の開口５９を図示の例では長手方向のスロットとして外側部材５１の外壁に形成する。図示の例では４個の開口５９としたが所要の数とすることができる。開口５９は室４０と内側スペース５４間の空気の流通を可能にする。

組合せプラグ２６の第２の部材はほぼ円筒形部材６０であり、空気等のガスを通し、血液等の液を通さない材料製とする。部材６０の長手方向に通路６１を貫通させ、針の内方部分４４を通す。通路６１と内方部分４４との間は接触しない構造であるが僅かな接触はさせてもよい。外側部材６１の内側スペース５４内に空気透過部材６０を圧縮嵌合とし、プラグ２６を血液等の液が透過しないようにする。部材６０は開口５６からスペース５４に外側部材５１の弾性を利用して押込む。空気透過部材６０を形成する材料の好適な例は焼結ポリエチレン等の多孔性材料とし、孔の直径はほぼ１０ミクロン程度とする。

第６図は本発明による針組立体１０をホルダ１９に連結した状態を示す。血液採集操業の第１段階では、真空の管１６は取付けないで穿刺針１４を患者Ｐ内に穿刺する。ここでプラグ２６は室４０内で室を囲むハウジング内壁と第２の針の内方部分４４とに液を通さない接触であり、第２図の位置にある。この位置では内方の横孔４９はプラグ２６によつて覆われ、下方の横孔４８は覆われない。第２の針１５内は真空でなく大気に連通するため、室４０、針１４、１５の内腔は大気圧であり、空気が存在する。第１の針１４が血管内に入れば、血液は通常の止血帯圧力によつて針１４内を通り室４０の前部部分４０ａに充満する。室４０の前部部分４０ａ内に存在した空気は、不透過性部材５１のスロット５９から空気透過部材６０を透過して逃げる。空気は横孔４８又は４９を通つて第２の針１５の先端部を通つて逃げる。その結果、血液は前部室４０ａに充満し、既知の装置のように空気の停留は生じない。不透過性部材５１が針１５及びハウジング内壁に対して液を通さない係合であり、空気透過部材６０は液を透過させないため、血液が第２の針１５内に流入することはない。前部室４０ａ内の血液は透明材料４２を通して使用者が見ることができ、第１の針１４が血管内に入つたことを示す。通常の止血帯圧力によつて室４０内に流入する血液による推力は小さく、プラグは第２図に示す最初の位置から滑動することはない。

使用者が目視で血管内に針が入つたことを確認すれば、真空管１６をホルダ１９に挿入し、第２の針１５はストッパ２１を貫通する。第７図は真空の血液採集管１６を挿入した状態を示す。第２の針１５が管１６内の真空スペースに連通すれば、横孔４８を経て負圧勾配が室４０内に作用する。この負圧はプラグ２６の下面に作用してプラグ２６は室４０内を第２の針１５の内方部分４４に沿つて管１６の方向に動く。第７図はプラグ２６の滑動によつて横孔４８を完全に覆つた状態を示したが、作用する真空条件に応じて横孔４８の一部又は全部が覆われないこともある。この滑動によつて横孔４９と室の前部部分４０ａとの間が連通し、前部室４０ａ内の血液は第２の針１５内に自由に流入する。血液は第２の針を通つて管１６内に流れ、所要量の血液サンプルが管１６に入つた時に第１の針１４を患者から抜き、血液サンプル収集手順は終了する。

上述によつて明らかにされた通り、本発明による針組立体は滑動可能のプラグを有し、プラグは容易に組込むことができ、最初の血管穿刺に際して空気が逃げるのを可能にして血管内に入つたことを確認できる。この空気の逃げを可能にしたため、血管を針が穿刺すれば血液は直ちに室内に流入し、使用者が血管に入つたことを視認する目視インジケータの特性を有する。この視認に基いて血液収集管を取付けて患者から血液サンプルを容易に採取できる。

4.〔図面の簡単な説明〕

第１図は本発明の好適な実施例による単一サン

プル針組立体とホルダと真空血液収集管とを示す分解斜視図、第2図は第1図の2-2線に沿う断面図、第3図は第2図の3-3線に沿う拡大断面図、第4図は第3図の4-4線に沿うプラグの拡大断面図、第5図は第4図のプラグ内の空気透過部材の拡大断面図、第6図は針組立体を患者の血管に穿刺した斜視図、第7図は第1図の7-7線に沿う使用状態を示す断面図である。

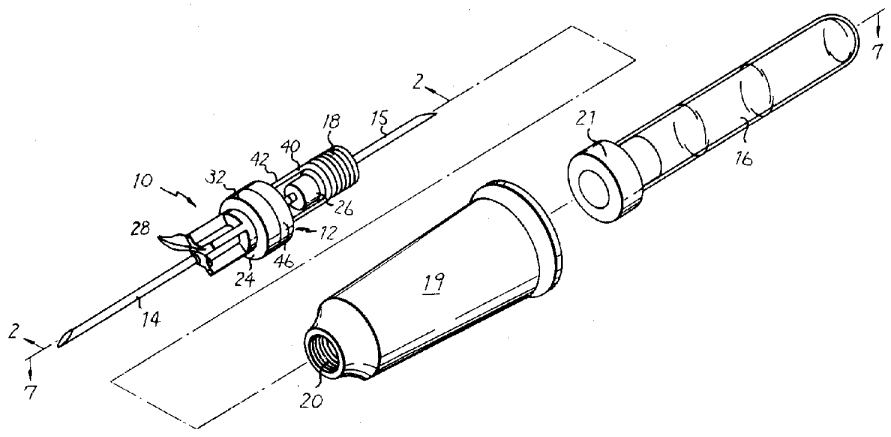
10---針組立体	12---ハウジング
14、15---針	16---真空容器
19---ホルダ	24---前端部
25---後端部	26---プラグ
40---室	44---内方部分
48、49---横孔	51---外側部材
59---開口	60---空気透過部材

特許出願人　ベクトン・デイツキンソン・アンド・カンパニー

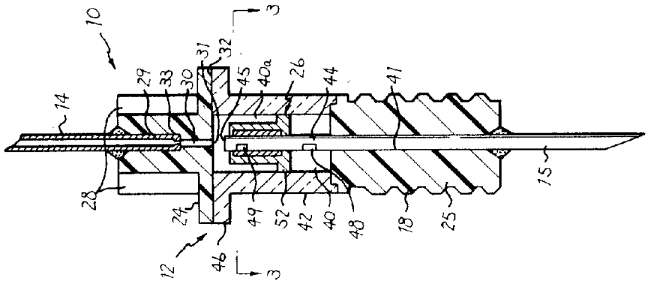
代理人　弁理士　湯浅恭三

(外2名)

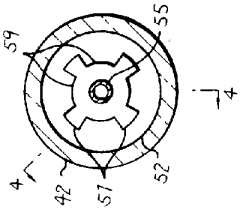
第1図



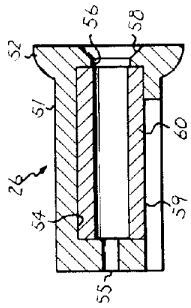
第2図



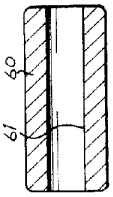
第3図



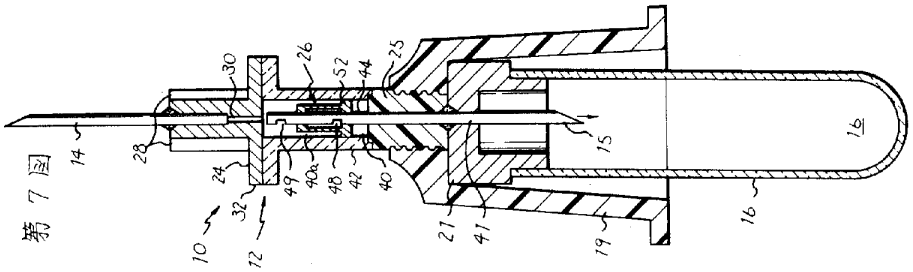
第4図



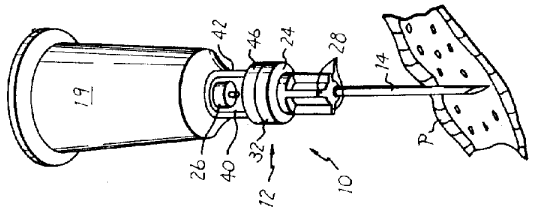
第5図



第7図



第6図



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.
KURIN3PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2017/068569	27 December 2017 (27-12-2017)	27 December 2016 (27-12-2016)
Applicant		
KURIN, 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 4 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,**

[X] the text is approved as submitted by the applicant

[ ] 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. 30B

[ ] as suggested by the applicant

[ ] as selected by this Authority, because the applicant failed to suggest a figure

[X] as selected by this Authority, because this figure better characterizes the invention

b. [ ] none of the figures is to be published with the abstract

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/US2017/068569	27.12.2017	27.12.2016

International Patent Classification (IPC) or both national classification and IPC
INV. A61B5/15 A61B5/153 A61B5/154 A61B5/157

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 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	Nielsen, Michael 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	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20
	No:	Claims	
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

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

In light of the documents cited in the international search report, it is considered that the invention as claimed in the independent claims meets the criteria mentioned in Article 33 (1) PCT, i.e. it appears to be novel, to involve an inventive step and to be industrially applicable.

Prior art: Blood drawing devices capable of isolating a pre-sample in order to minimize the risk of contamination of the main sample. Well known concept, see any of the documents cited in the search report.

Problem: As in the prior art to minimize the risk of contamination of blood drawn from a patient.

Solution: The pre-sample chamber (sequestration chamber) having **the specific vent** as defined in the independent claims 1, 8 and 15.

None of the cited documents hint to said specific solution in order to solve said problem. Contribution to the art.

Claims 2-7, 9-14 and 16 to 20 are dependent on one or more independent claims whose subject-matter is considered as being new and inventive, as discussed above, and as such said dependent claims also meet the requirements of the PCT with respect to novelty and inventive step.

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.

2). The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art (see search report) is not mentioned in the description, nor are these documents identified therein.

4). Upon entering the regional phase via the European Patent Office, the requirements of Rule 43(2) EPC should be observed.

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
PCT/US2017/068569

TITLE: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

APPLICANT: KURIN, INC

IPC CLASSIFICATION: A61B5/15, A61B5/153, A61B5/154, A61B5/157

EXAMINER: Nielsen, Michael

CONSULTED DATABASES: WPI

CLASSIFICATION SYMBOLS DEFINING EXTENT OF THE SEARCH:

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International application No
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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)
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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)
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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/039348 A1 (BULLINGTON GREGORY J [US] ET AL) 6 February 2014 (2014-02-06) the whole document	1-20
A	US 2014/107564 A1 (BULLINGTON GREGORY J [US] ET AL) 17 April 2014 (2014-04-17) the whole document	1-20
A	US 4 813 433 A (DOWNEY JOHN M [US]) 21 March 1989 (1989-03-21) the whole document	1-20
A	US 2013/317391 A1 (BULLINGTON GREGORY J [US] ET AL) 28 November 2013 (2013-11-28) abstract paragraph [0048] - paragraph [0075]; figures 2-12	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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Date of the actual completion of the international search	Date of mailing of the international search report
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/181352 A1 (MAGNOLIA MEDICAL TECHNOLOGIES INC [US]; BULLINGTON GREGORY J [US]; PAT) 5 December 2013 (2013-12-05) abstract paragraph [1090]; figures 11,12	1-20

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2017/068569

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		WO 2013181352 A1	05-12-2013

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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.

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

This study was conducted with review and approval from the Quality Standards Committee at Northwest Hospital and Medical Center/UW Medicine.

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FOOTNOTES

▽Published ahead of print on 13 October 2010.

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Controlled Clinical Laboratory Comparison of Two Supplemented Aerobic and Anaerobic Media Used in Automated Blood Culture Systems To Detect Bloodstream Infections

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A 20-ml blood sample was collected from adult patients with suspected bloodstream infections and distributed equally into the four volume-controlled bottles of a blood culture set consisting of aerobic and anaerobic BACTEC Plus/F bottles and aerobic and anaerobic BacT/Alert FAN bottles. All bottles were incubated in their respective instruments for a standard 5-day protocol or until the instruments signalled positivity. Samples in all bottles with negative results by these instruments were terminally subcultured. A total of 8,390 blood culture sets were obtained during the study period, of which 4,402 (52.5%) met the study criteria. Of these, 946 (21.5%) were positive either by instrument signal or by additional terminal subculture of all negative bottles and yielded growth of microorganisms. Five hundred eighty-nine (13.4%) blood culture sets were considered to have recovered 663 clinically significant organisms. When both the BACTEC and the BacT/Alert systems were used, 465 positive sets were detected; BACTEC alone detected 52 positive sets and BacT/Alert alone detected 72 ($P = 0.09$). No differences were found between the two systems in microbial recovery rate from blood cultures obtained from patients on antibiotic therapy. Significantly more members of the family *Enterobacteriaceae* ($P < 0.01$) were detected from patients without antimicrobial therapy by BacT/Alert than by BACTEC. The false-negative rates were 0.20% for BACTEC and 0.32% for BacT/Alert. A significantly higher false-positive rate was found for BACTEC ($P < 0.0001$). Both systems were comparable for the time to detection of microorganisms. However, gram-positive bacteria were detected faster by BACTEC and *Enterobacteriaceae* were detected faster on average by BacT/Alert. We concluded that both systems are comparable in their abilities to recover aerobic and anaerobic organisms from blood cultures and a terminal subculture might not be necessary for either of the two systems. The increased positivity rate when using an anaerobic bottle in a two-bottle blood culture set is due to the additional blood volume rather than to the use of an anaerobic medium.

Due to the high morbidity and mortality associated with bacteremia (7), the rapid detection and subsequent identification of microorganisms from blood remain critical services of the clinical microbiology laboratory. Numerous blood culture methods are available, and selecting the optimal system for the diagnostic laboratory is an important and often difficult task (15). Many remarkable improvements have been made in an attempt to reduce the time to isolate pathogens from blood. Advancements in the use of liquid media linked with automation technology have enhanced the ability of laboratories to provide faster blood culture results. Two continuously monitored noninvasive blood culture systems, the BACTEC 9240 (Becton Dickinson, Heidelberg, Germany) and the BacT/Alert (Organon Teknika, Eppelheim, Germany), are in widespread use. The main advantages of the two systems over previous generations of blood culture instruments include full automation once the bottles are loaded, a shorter time to detection of blood pathogens, considerable labor savings, and improved laboratory workflow. The BacT/Alert and the BACTEC 9240 systems monitor the growth of organisms by checking for elaboration of CO_2 with a colorimetric and a fluorescent sensor, respectively.

New aerobic and anaerobic media were developed by the manufacturers to remove a variety of growth inhibitors from patients' blood, to enhance the recovery of fastidious organisms, and to improve the detection of bacteremia and fungemia in patients receiving antimicrobial therapy. BACTEC Plus/F medium consists of soybean-casein digest broth, primary supplements, and two types of resin, a nonionic absorbing resin and a cation-exchange resin. FAN medium (BacT/Alert) is a brain heart infusion broth base containing Ecosorb, a proprietary substance that contains adsorbent charcoal, Fuller's earth, and other components.

A number of studies comparing the two systems have been carried out, but to our knowledge, none of them compared the supplemented aerobic and anaerobic BACTEC Plus/F media with the supplemented aerobic and anaerobic BacT/Alert FAN media in one controlled clinical trial.

This study was conducted to compare the performances of the two blood culture systems, BACTEC 9240 and BacT/Alert, in terms of microbial recovery, time to detection, and false-positive and false-negative rates, thereby indicating the performance of the aerobic and anaerobic BACTEC Plus/F resin media and the aerobic and anaerobic BacT/Alert FAN media.

MATERIALS AND METHODS

Patient population. This monocenter study was conducted from August 1995 through February 1997 in a 2,500-bed acute-care community hospital which provides a full range of medical and surgical care. The hospital cares for an appreciable number of transplant, immunosuppressed patients, as well as patients presenting common community-acquired infections. Blood cultures were obtained from all adult patients with suspected bacteremia during the study

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period and processed in the hospital-related Institute of Microbiology and Hygiene.

Study design. Blood culture sets were prepared for the purposes of the study; each set contained four volume-controlled and randomized bottles, one each containing aerobic and anaerobic BACTEC Plus/F media and aerobic and anaerobic BacT/Alert FAN media. Written instructions for obtaining a blood culture, the required amount of blood, and the order of inoculation of the bottles for clinicians were included. In respect of the patient and with the agreement of the ethical commission of our hospital, a 20-ml amount of blood for one blood culture set was considered the maximum to obtain from a single venipuncture. This amount was distributed equally into each of the four bottles. The inoculum volume was determined in the microbiology laboratory by weight. Sets in which any one of the bottles did not contain a minimum of 3 ml of blood or in which the volume difference between two bottles was more than 3 ml were considered noncompliant and excluded from the study but processed for the bene@ of the patient.

On arrival in the laboratory, all bottles were placed in their respective instruments for a 5-day incubation time at 35°C and monitored in accordance with the manufacturers' recommendations. FAN aerobic bottles were vented before incubation.

Bottles indicated as positive by the instrument as well as bottles positive on arrival were Gram stained. Based on the Gram stain result, aliquots of the bottles were subcultured onto adequate media (chocolate agar incubated at 35°C in a 5% CO_2-enriched atmosphere or blood agar with aerobic and anaerobic incubation at 35°C). All microorganisms were identi@ed by standard microbiologic procedures. All false-positive bottles (i.e., bottles that were smear and subculture negative after instrument signal) were replaced into the instrument during the 5 days of protocol. A terminal blind subculture onto chocolate agar and blood agar (aerobic and anaerobic incubation as described above) was performed for all negative bottles. False-negative bottles had no positive signal by the instrument, but growth occurred on the terminal subculture.

Statistical methods. The following data of all blood cultures were entered in a computer database: collection time, loading time, blood volume of each bottle, detection of growth by each bottle, growth on subculture and identity of microorganisms recovered, antimicrobic therapy, and the detection time for each positive bottle. Detection time of a microorganism was de@ed as the time between loading a blood culture bottle into the instrument and the time when a positive signal occurred followed by growth on subculture. For comparison of detection times, only clinically signi@ant isolates recovered in both systems were taken into account. If both bottles of one system recovered the same organisms, the shorter time to detection was taken into account for comparison. The clinical importance of isolated microorganisms was determined after consultation with the patient's physician in accordance with published criteria (6, 10, 16, 18). Statistical analysis was done for blood cultures meeting the study criteria. Only isolates classi@d as being clinically signi@ant were taken into account. Sensitivities were calculated in two manners. For comparison of the two systems, the common denominator of positive cultures was determined by all four terminal blind subcultures. For evaluating the usefulness of terminal subcultures in clinical routines, the detection rate of each system was determined with reference only to the related terminal subculture. The common denominator for the determination of both the false-positive and the false-negative rates for each system was the total of 4,402 compliant sets of the study. The main scienti@ goal of the study was the comparison of the sensitivities and speci@cities of both systems. For these two analyses, the Bonferroni correction was used. All other analysis on subgroups of patients or isolates must be considered explorative without protection against the error of multiple testing. All comparisons were evaluated by McNemar's test ($\alpha = 0.05$, two-sided) by using the statistical package SPSSWIN.

RESULTS

A total of 8,390 blood culture sets were obtained during the study period. Of these, 4,402 (52.5%) met the study criteria; of these, 946 (21.5%) yielded growth of 1,083 bacteria or fungi. Five hundred eighty-nine (13.4%) compliant sets, positive by either instrument signal or terminal subculture only, detected 663 bacteria or fungi that were considered clinically signi@ant. Three hundred @fty-seven (8.1%) sets recovered only organisms classi@ed as contaminants.

Of the 589 positive blood culture sets with signi@ant isolates, 508 (86.3%) were positive by BACTEC 9240 and 523 (88.8%) sets were positive by BacT/Alert. BACTEC alone detected 52 (8.8%) positive sets, and BacT/Alert alone detected 72 (12.2%). With reference to the terminal blind subcultures of both systems, BACTEC and BacT/Alert showed sensitivity rates of 86.3 and 88.8% respectively. With reference to the system-related terminal subculture, the BACTEC instrument demonstrated a detection rate of 98.3% and the BacT/Alert instrument gave one of 97.4%.

TABLE 1. Comparative yields of clinically important bacteria and fungi in BACTEC Plus/F and FAN aerobic and anaerobic culture sets

Microorganism	No. of organisms detected by:			P
	BACTEC only	BacT/Alert only	Both systems	
Gram-positive bacteria	30	34	228	NS[a]
Staphylococcus aureus	11	14	124	
Staphylococcus epidermidis	2	2	9	
Viridans group streptococcus	2	5	18	
Enterococcus spp.	6	7	32	
Streptococcus pneumoniae	6	4	33	
Beta-hemolytic streptococci	3	1	9	
Listeria monocytogenes		1	3	
Enterobacteriaceae	21	45	187	<0.01
Escherichia coli	14	25	101	
Klebsiella spp.	3	12	27	
Enterobacter/Citrobacter spp.	2	5	31	
Salmonella spp.			6	
Proteus/Providencia/Morganella	1	1	11	
Serratia/Hafnia spp.	1	2	11	
Non-*Enterobacteriaceae*	18	13	36	NS
Haemophilus spp.		2	1	
Pseudomonas aeruginosa	7	7	8	
Stenotrophomonas maltophilia	3		6	
Neisseria meningitidis		1	1	
Acinetobacter spp.	8	3	18	
Other			2	
Anaerobic bacteria	6	3	4	NS
Clostridium perfringens	1	1	1	
Bacteroides spp.	3	2	2	
Candida spp.	5	6	14	NS
All microorganisms	80	101	482[b]	

[a] NS, not signi@ant.
[b] For some species with a single isolate, data were not depicted separately but were included in the total

Nine false-negative blood cultures occurred with the BACTEC instrument (three *Candida* species and single isolates of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Enterobacter agglomerans*, *Pseudomonas aeruginosa*, and *Pseudomonas stutzeri*) and 14 false negatives occurred with the BacT/Alert instrument (four *P. aeruginosa*, three *Acinetobacter* species, two *Stenotrophomonas maltophilia*, two *Candida* species, and single isolates of *Streptococcus sanguis*, *Escherichia coli*, and *Proteus mirabilis*).

The false-negative rates for the systems were 0.20% for BACTEC and 0.32% for BacT/Alert.

A signi@antly higher false-positive rate was found for BACTEC, 6.2%, than for BacT/Alert, 1.4% ($P < 0.0001$).

The comparative yields of bacteria and fungi from the two systems are indicated in Table 1. Of the 663 clinically signi@cant organisms from compliant sets, 482 (72.7%) were recovered from both systems, 80 (12%) were recovered by BACTEC only, and 101 (15.2%) were recovered by BacT/Alert only. The differences observed in the recovery of bacteria reached statistical signi@cance only for the *Enterobacteriaceae* group. The BacT/Alert system detected signi@antly more *Enterobacteriaceae* than the BACTEC system did ($P < 0.01$). A similar trend

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TABLE 2. Comparative speed of detection of clinically signi@cant organisms when both systems were positive and detection time was provided for both systems ($n = 421$)

Microorganism	Time to detection (h)		n	P
	BACTEC	BacT/Alert		
Staphylococcus aureus	8.4	11.2	124	<0.001
Viridans group streptococcus	4.0	6.6	18	<0.01
Enterococci	5.1	19.5	32	<0.05
Streptococcus pneumoniae	5.1	6.2	33	<0.05
Escherichia coli	7.6	6.9	101	<0.05
Klebsiella spp.	8.9	5.8	27	NS[a]
Enterobacter spp.	7.8	7.5	31	<0.05
Pseudomonas aeruginosa	15.4	20.7	8	NS
Acinetobacter spp.	6.9	10.2	18	<0.01
Mean values	9.0	10.4	482[b]	<0.05

[a] NS, not signi@cant.
[b] For some species with fewer than 10 isolates, data were not depicted separately but were included in the mean time to detection.

was seen in the recovery of yeasts from blood cultures obtained from patients without antibiotic therapy. For all other organisms, there were no signi@cant differences in the number of positive cultures between systems, neither by organism group nor by species.

Of all compliant blood culture sets, 41.9% (1,807 sets) were obtained from patients receiving antimicrobial therapy. Of the 589 positive compliant sets with signi@cant isolates, 35.5% (208) were obtained from patients receiving antibiotics. There were no signi@cant differences in isolation rates between the two systems for patients receiving antibiotics. The BacT/Alert system detected signi@cantly more *Enterobacteriaceae* than the BACTEC system did ($P < 0.01$) from patients without antibiotic therapy.

The times to detection of several bacterial groups were compared for the two systems (Table 2). Gram-positive bacteria were detected signi@cantly faster by the BACTEC system, whereas *Enterobacteriaceae* on average were recovered faster by the BacT/Alert system. There was no difference between the two systems in the cumulative percentage of positive cultures after 24, 48, and 72 h of incubation. Within the @rst 24 h, BACTEC detected 89.8% and BacT/Alert detected 89.6% of the positive cultures; after 48 h, 95.7 and 96.9% were detected by BACTEC and BacT/Alert, respectively; and after 72 h, 99.0 and 99.4% were detected by the two systems, respectively. The average times to detection were 9.0 h for the BACTEC system and 10.4 h for the BacT/Alert system ($P < 0.05$). The signi@cant difference in average time to detection between both systems was caused by the higher detection rate within the @rst 6 h of the BACTEC instrument (50.7% detected by BACTEC and 45.8% by BacT/Alert).

Delayed entry was de@ned as a time difference of >12 h between blood sample collection and placement of a blood culture bottle into the respective instrument. More than half of the compliant positive blood cultures had a transportation time of >12 h due to the fact that our new hospital building is separated from the laboratory. Delayed entry had no effect on the sensitivity of the BacT/Alert instrument, but for the BACTEC system, the detection rate was signi@cantly lower for blood cultures with delayed entry than for those with no delay ($P = 0.0097$). Differences also occurred in detection of the *Enterobacteriaceae* group: BacT/Alert recovered signi@cantly more *Enterobacteriaceae* from blood cultures with delayed entry than BACTEC did ($P = 0.0062$) when the subgroup of patients not receiving antibiotic therapy was considered.

The data of the two systems allow not only a system-versus-system comparison but also a comparison of the two media, i.e., resin aerobic versus FAN aerobic media and resin anaerobic versus FAN anaerobic media (Table 3). No signi@cant differences were seen between the aerobic media nor between the anaerobic media of the two systems in terms of detection rate. A comparison of the aerobic and anaerobic media of each system showed signi@cant differences. The false-positive rate was signi@cantly higher for both resin media than for the FAN media. The false-negative rates for both anaerobic media (4.7% for resin and 3.9% for FAN) were higher than those for the aerobic media (1.7% for resin and 2.2% for FAN).

Anaerobic bacteria causing septicemia were recovered from 13 compliant blood culture sets. Both systems detected four, the BACTEC system alone detected six, and the BacT/Alert system alone detected three anaerobic bacteria.

DISCUSSION

This monocenter-controlled evaluation compared the performances of the supplemented aerobic and anaerobic BACTEC resin media, under identical conditions of observation against the supplemented aerobic and anaerobic BacT/Alert FAN media in a clinical trial. Simultaneous inoculation of all four bottles from a single blood culture also enabled a system-versus-system comparison of the BACTEC 9240 and the BacT/Alert instruments. To our knowledge, no data have been published yet on this subject. In the past, several studies have evaluated the performance of the BACTEC (20) and BacT/Alert (2, 11) instruments, comparing either the two nonsupplemented media (19), the resin medium and the standard BacT/Alert medium (1, 9, 13), or the aerobic resin medium and the aerobic FAN medium (4, 8, 14). Outcomes have been quite different: the BACTEC system detected signi@cantly more gram-positive cocci and the BacT/Alert system recovered signi@cantly more *Enterobacteriaceae* in a @rst comparison (19) of the two nonsupplemented media.

Auckenthaler et al. (1) as well as Smith et al. (13) compared BACTEC resin medium to standard BacT/Alert medium, and both groups reported a better performance in terms of microbial recovery, false-positive rate, and detection time for the resin medium. A comparison of aerobic resin medium with aerobic FAN medium in a recent multicenter (4) study has demonstrated equal results. The previous single-center study by Pohlman et al. (8) showed a better recovery rate for *Entero-*

TABLE 3. Detection of positive cultures and false-positive signals by aerobic and anaerobic media

Medium	No. of positive cultures			No. of false-positive signals[b]
	Total	Detected by instrument[a]	Detected by terminal subculture	
Aerobic resin	466	456	10	185
Aerobic FAN	489	476	13	54
Anaerobic resin	448	420	28	116
Anaerobic FAN	429	406	23	11

[a] Values for aerobic resin versus aerobic FAN media and for anaerobic resin versus anaerobic FAN media are not signi@cantly different. Values for aerobic resin versus anaerobic resin media and aerobic FAN versus anaerobic FAN media are signi@cantly different ($P < 0.05$ and $P < 0.001$, respectively).
[b] Values for aerobic resin versus aerobic FAN media, anaerobic resin versus anaerobic FAN media, aerobic resin versus anaerobic resin media, and aerobic FAN versus anaerobic FAN media are signi@cantly different ($P < 0.001$).

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bacteriaceae and *Pseudomonas* by use of the BacT/Alert system with fewer false-positive results. In comparison with the results of other studies (4, 11, 12, 17), the positivity rate of blood cultures in our study was high (21.5% positive sets), with 13.4% sets recovering clinically signi@cant organisms. With the exception of members of the *Enterobacteriaceae* group, which were recovered signi@cantly ($P < 0.01$) more often by the BacT/Alert system alone, there were no signi@cant differences in terms of microbial recovery between the two systems. The *Enterobacteriaceae* that were detected signi@cantly more frequently by the BacT/Alert system resulted from blood cultures from patients without antimicrobial therapy. There was also a tendency towards a similar result for the fungi group: BacT/Alert detected slightly more *Candida* sp. isolates from patients without antibiotics than from patients with antimicrobial therapy. However, these are results of an explorative analysis in which, due to the small numbers of cases, a high beta error and the problems of multiple testing must be taken into account.

Reports of high false-negative rates, up to 6% (12, 13), suggest that terminal subculturing of negative BACTEC cultures after 5 days of incubation may be necessary, whereas others have suggested that this is not needed in the BacT/Alert system (3). In our trial, the false-negative rates were similarly low for both systems (0.20% for BACTEC and 0.32% for BacT/Alert) and the sensitivities for the BACTEC and BacT/Alert instruments with reference to the related terminal subcultures were 98.3 and 97.4%, respectively; therefore, we have concluded that a blind terminal subculture may not be necessary for either of the two systems.

The introduction of automated blood culture systems also serves the purpose of reducing the routine workload for laboratory personnel. A low false-positive rate is one important factor here. Our results showed a signi@cantly ($P < 0.0001$) higher false-positive rate for the aerobic and anaerobic resin media (6.2%) than for the FAN media (1.4%). During the study period, both instruments were used in accordance with the recommendations and speci@cations of each manufacturer. Laboratory facilities were equal for both systems. All false-positive blood cultures were replaced into the instrument, incubated for the rest of the 5-day incubation period, and terminally subcultured. A small percentage of the false-positive signals by the BACTEC instrument occurred after an electricity breakdown, which did not affect the BacT/Alert instrument.

Due to the need to reduce laboratory costs, many microbiology laboratories do not have 24-h coverage by technical personnel. Especially in smaller hospitals, there is no microbiology laboratory available, so that blood cultures must be sent to external laboratories. Therefore, a delay may occur from the time blood is drawn until the bottle is placed into a blood culture instrument. Our hospital consists of an original building complex with 1,500 beds and a new building with 1,000 beds which is situated 10 km away. All blood specimens from the new building must be transferred to the laboratory in the original building, so that a delay of >12 h may occur.

Those blood cultures that were obtained after the microbiology laboratory was closed for the day were collected in a central laboratory that is open 24 h per day and were incubated at 35°C, so that almost all blood cultures with delayed entry were preincubated at 35°C. Delayed entry did affect the sensitivity of the BACTEC instrument in that the detection rate was signi@cantly lower for blood cultures with delayed entry than for those with no delay ($P = 0.0097$).

The numbers of false-negative sets with delayed entry and of false negative sets with a transport time of <12 h were too small for valid comparison. For the BACTEC system, 6 of 9 false-negative sets were sets with delayed entry; for BacT/Alert, 8 of 14 false negatives were sets with delayed entry. In spite of the small number, there seems to be no need for blind terminal subculture either for sets with overnight preincubation at 35°C or for sets processed within the @rst 12 h after collection. Both systems detected organisms faster from culture sets with delayed entry since these sets were preincubated. With regards to the handling of preincubated blood culture bottles, the BacT/Alert system offers the advantage of a visible change on the bottom of a positive bottle so that the bottle can be processed onto subcultures before incubation into the instrument. The interpretation of Gram stain results for positive bottles was more dif@cult for FAN media than for resin media due to the charcoal particles in the media.

Staphylococcus epidermidis, which is considered a contaminant, was recovered more frequently from the FAN aerobic bottle ($n = 424$) than from the resin aerobic bottle ($n = 349$); this more frequent recovery may be due to the fact that the FAN aerobic bottle must be vented before incubation in the instrument. The use of needles to manually vent the aerobic FAN bottles may increase the probability of contaminating the bottle.

The question whether there is any advantage to using both aerobic and anaerobic blood culture media routinely (5) or whether anaerobic media should be used for the detection of bacteremia only in patients at risk of having an anaerobic infection is often raised. Only 13 positive blood cultures out of 589 sets with clinically signi@cant organisms recovered anaerobic bacteria, 11 being isolated from the anaerobic medium only and 2 being isolated from both the aerobic and anaerobic media. Four of the 11 blood culture sets with obligate anaerobic bacteria represented polymicrobial septicemia; in addition to the anaerobic bacteria, *Enterobacteriaceae*, *Staphylococcus aureus*, and *Candida* spp. were isolated from the corresponding aerobic bottle as well. De@nitively, seven (1.2%) blood cultures with monomicrobic obligate anaerobic pathogens would not have been detected by using only an aerobic bottle. By using the anaerobic resin bottle in addition to the aerobic one, the detection rate increased by 10.2%, with facultative anaerobic bacteria contributing 8.7% and obligate anaerobic bacteria contributing 1.6%. Analogously, the anaerobic FAN bottle increased the positivity by 9%, of which 8% was due to facultative anaerobic bacteria and 1% was due to strict anaerobic ones. Diagnoses of patients with septicemia due to obligate anaerobic bacteria included colitis ulcerosa, pancreatitis, diabetes mellitus with erysipelas, cholangitis, leukemia, and pneumonia, so that anaerobic infections could have been expected. According to Weinstein et al. (17), an increase in the volume of blood inoculated into BacT/Alert aerobic bottles (from 5 to 10 ml) increased the overall yield (7.2%) of clinically important organisms. From our results and those reported by Weinstein et al. (15, 17), we conclude that the higher recovery rate achieved when the anaerobic bottle is included is due to the inoculation of a larger blood volume rather than to the use of an additional anaerobic medium.

In summary, both systems are comparable for recovering clinically signi@cant microorganisms from adult patients with bacteremia and fungemia receiving antibiotic therapy at the time of blood culture collection. With blood from patients without antibiotic therapy, the BacT/Alert system detected signi@cantly more *Enterobacteriaceae*. The high false-positive rate of the BACTEC system caused additional work and material costs in our laboratory. With the BacT/Alert instrument, the software capabilities were more convenient for the user, and failure rarely occurred.

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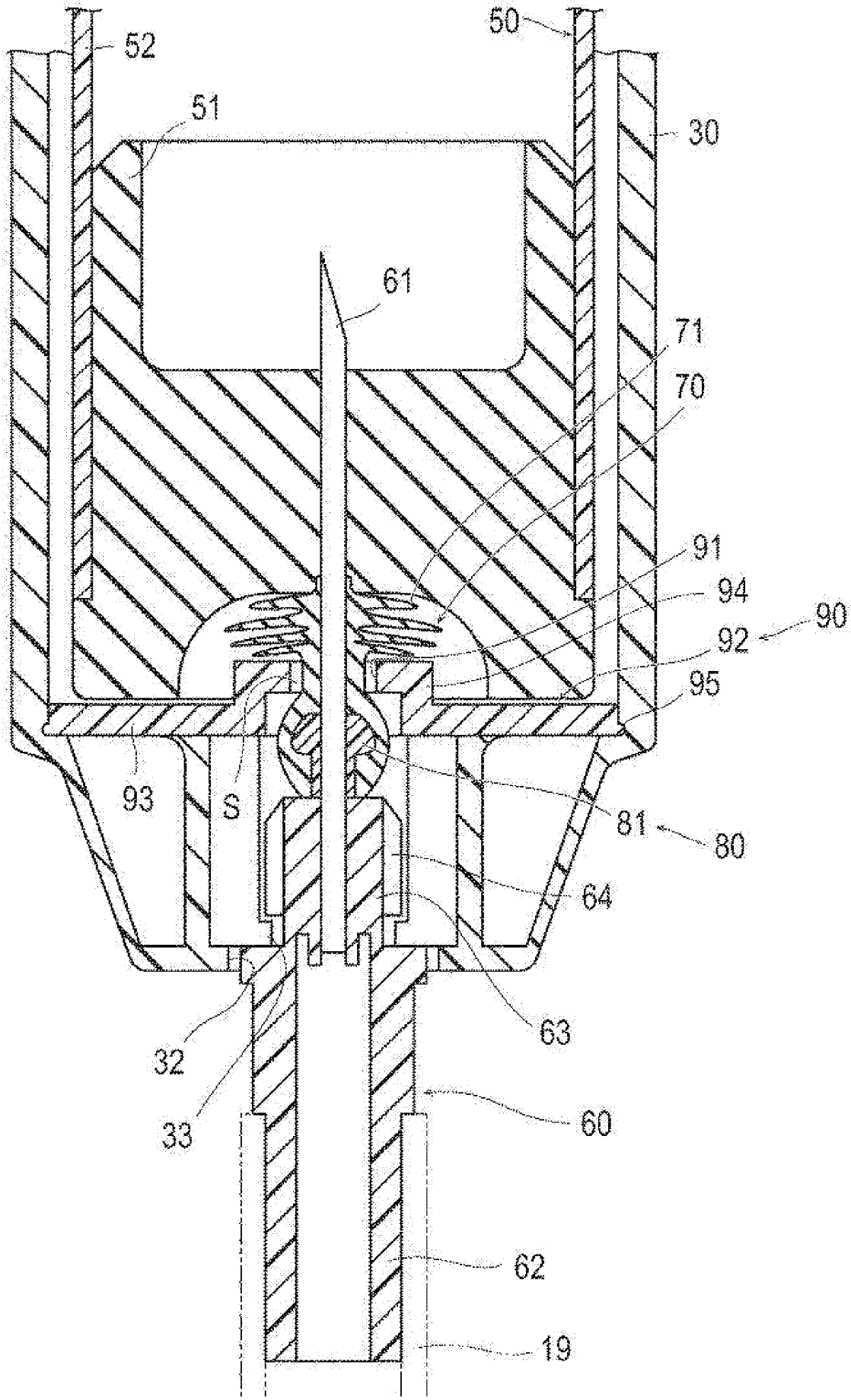
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(57) [Summary]
[Problem] To hold a rubber cap on a needle assembly even when the rubber cap is elastically contracted and wrinkled as a hollow needle is passed through a rubber plug of a blood collecti on tube. To provide a sampling port capable of maintaining force and sufficiently preventing le akage of blood.

A sampling port (20) includes a main body (30) formed with an opening (31) for inserting a bl ood collection tube (50) having a rubber plug (51), a hollow needle (61) that can be freely ins erted into the rubber plug of the blood collection tube, and a hollow needle. a needle assembl y 60 attached to the main body, comprising a hub 64 supporting the proximal end of the need le, an elastic rubber cap 70 covering the hollow needle, and a holding portion 80 holding the r ubber cap; A through hole 91 through which a hollow needle covered with a rubber cap penetr ates is provided, and wrinkles 71 generated by elastic contraction of the rubber cap accompan ying insertion of the hollow needle into the rubber stopper are suppressed from reaching the holding portion. and a plate 92 as a suppressing member 90 .

[Selection drawing] Fig. 4


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The scope of the claims open

What is claimed is

: 1.

A main body having an opening for inserting a blood collection tube having a rubber stopper, a hollow

needle that can be inserted through the rubber stopper of the blood collection tube, and the hollow needle. a hub for supporting the proximal end of the hollow needle; an elastic rubber c ap placed on the hollow needle; and a holding portion for holding the rubber cap

. A through hole is provided through which the hollow needle covered with a rubber cap pen etrates, and wrinkles generated by elastic contraction of the rubber cap as the hollow needle i s inserted into the rubber plug reach the holding portion. and a suppression member that sup presses the sampling port.

2.

The main body is rotatably attached to the needle assembly,

the suppressing member is fixed to the main body, and between the through hole and the ru bber cap, 2. The sampling port of claim 1, having clearance to allow rotation of said body porti on.

3.

The main body has a cylindrical shape, and

the suppressing member has a disk shape and includes a projection projecting toward the op ening of the main body. 3. The sampling port of claim 2.

4.

The sampling port according to any one of claims 1 to 3, wherein a ring-shaped projection pr otruding radially outward is provided on the outer peripheral edge of said suppressing membe r.

[Claim 5]

The main body portion is made of a resin material that shrinks more than the resin material forming the suppressing member when heat is applied, and the suppressing member is shrun k to the main body portion by applying heat for sterilization. A sampling port according to any one of claims 1 to 4, fixed with respect to

detailed description open

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to sampling ports for holding blood collec tion tubes. 2. Description of the Related Art When blood is collected using a blood collection tube with a rubber stopper, a sampling port for holding the blood collection tube is used (see Patent Document 1). The sampling port has a main body with an opening for inserting a blood collection tube, and a needle assembly having a hollow needle that can be freely inserted into the rubber stopper of the blood collection tube is attached to the main body. there is The hollo w needle is covered with an elastic rubber cap to prevent leakage of blood. [0003] As the bl ood collection tube is inserted into the body of the sampling port and the hollow needle is pas sed through the rubber plug, the rubber cap is elastically contracted and wrinkled to expose t he hollow needle. The exposed hollow needle is used to collect blood into a collection tube. W hen the blood collection tube is pulled out after blood collection, the rubber cap elastically stre tches from the contracted state as if smoothing the wrinkles, and restores to the state where i t covers the hollow needle again. This prevents leakage of blood from the hollow needle. The r ubber cap is held on the needle assembly by, for example, fitting the root portion to the needl e assembly. [Prior Art Document] [Patent Document] [Patent Document 1] Japanese Patent A pplication Laid-Open No. 2002-291724 [Summary of the Invention]

[0005] However, when the hollow needle is passed

through the rubber plug of the blood collection tube, the wrinkles caused by the elastic contr action of the rubber cap may reach the base of the rubber cap. There is In such a case, the ro ot portion of the rubber cap swells, weakening the holding force for holding the rubber cap to the needle assembly. For this reason, if the tip of the rubber cap is biting into the small inserti on hole of the rubber stopper of the blood collection tube, the rubber cap will be pulled togeth er when the blood collection tube is pulled out, and the position of the rubber cap will be affec ted. There is a risk that the blood will not be sufficiently prevented from leaking.

[0006]

The present invention was made in order to solve the above-mentioned problems associated with the prior art. When a hollow needle is passed through a rubber plug of a blood collection tube, the rubber cap is elastically contracted and wrinkled. It is an object of the present inven tion to provide a sampling port capable of maintaining a holding force for holding a rubber cap to a needle assembly even when the needle assembly is closed, thereby sufficiently preventin g leakage of blood. [0007] A sampling port of the present
invention for achieving the above objects comprises a main body having an opening for inser ting a blood collection tube having a rubber stopper, and the blood collection tube . a hollow needle that can be freely inserted into the rubber plug of the above, a hub that supports the b ase end of the hollow needle, an elastic rubber cap that covers the hollow needle, and a holdi ng portion that holds the rubber cap a needle assembly attached to the main body, and a thro ugh hole through which the hollow needle covered with the rubber cap passes, wherein the r ubber cap is elastic as the hollow needle is inserted into the rubber plug and a suppressing m ember that suppresses wrinkles generated by the contraction from reaching the holding portio n.

[0008] The suppressing

member suppresses wrinkles generated by elastic contraction of the rubber cap as the hollo w needle is passed through the rubber stopper of the blood collection tube from reaching the holding portion. , the rubber cap does not swell at the holding part, and the holding force for holding the rubber cap to the needle assembly does not weaken. Therefore, even if the rubber cap is pulled together when the blood collection tube is pulled out after blood collection, the p osition of the rubber cap will not be displaced, and blood leakage can be sufficiently prevente d. Thus, even if the rubber cap is elastically contracted and wrinkled as the hollow needle is p assed through the rubber plug of the blood collection tube, the holding force for holding the ru bber cap to the needle assembly can be maintained, Thus, a sampling port that can sufficientl y prevent blood leakage can be provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

FIG. 1 is a block diagram showing a blood bag system incorporating a sampling port;
2 is a perspective view showing the initial blood bag shown in FIG. 1 and a sampling port; FI G.
FIG. 3 is a cross-sectional view showing essential parts of a sampling port before a blood colle ction tube is inserted;

FIG. 4 is a cross-sectional view showing the essential parts of the sampling port after the bloo d collection tube has been inserted;

5(A) is a perspective view showing a plate as a suppressing member, FIG. 5(B) is a cross-sect ional view along line 5B-5B in FIG. 5(A), and FIG. It is sectional drawing which expands and s hows 5C part of FIG.5(B).

6A and 6B are cross-sectional views showing how a plate as a suppressing member is fixed to the main body; FIG.

FIG. 7A is a conceptual diagram for explaining the action of the present embodiment, and FI G. 7B is a conceptual diagram for explaining the action in the case of contrast without a plate;

8A to 8D are cross-sectional views showing modified examples of the plate; FIG.

9A and 9B are plan views showing further modifications of the plate; FIG.

DETAILED DESCRIPTION OF THE INVENTION Embodiments of the present invention will now

be described with reference to the accompanying drawings. In the description of the drawing s, the same elements are denoted by the same reference numerals, and overlapping descripti ons are omitted. Also, the dimensional ratios in the drawings are exaggerated for convenience of explanation, and may differ from the actual ratios.

Referring to FIG .

1, the illustrated blood bag system 10 removes the initial flow (initial blood flow) of the colle cted blood when collecting blood, and uses the initial blood flow as test blood. It is a blood coll ection device. Bacteria present on and under the skin enter along with the skin fragments at t he time of puncture, so the initial blood flow is removed. A blood bag system 10 includes a b lood collecting needle 11, a blood bag 12 containing blood collected through the blood collecti ng needle 11, a blood collecting tube 13 connecting the blood collecting needle 11 and the blo od bag 12, and a blood collecting tube

.

13, an initial blood flow bag 16 communicating with the blood collection tube 13 via a branch t ube 15 connected to the branch connector 14, and a sampling port 20 connected to the end of the initial blood flow bag 16. ,have. The branch connector 14 is provided with a sealing memb er 17 that seals communication with the blood bag 12 . The sealing member 17 seals the com munication with the blood bag 12 until the collection of the initial blood flow into the initial blo od bag 16 is completed. The branch tube 15 is provided with a clamp member 18 that blocks blood flow to the initial blood bag 16 . After collecting the initial blood flow, the clamp membe r 18 clamps the branch tube 15 to block the blood flow to the initial blood bag 16 . After that, the sealing member 17 is opened to start collecting blood into the blood bag 12 .

[0013]

FIG. 2 shows a state in which the initial blood contained in the initial blood bag 16 is collecte d as test blood. A sampling port 20 is connected to a blood extraction tube 19 connected to a n initial blood bag 16 . A lid member 40 that opens and closes the opening 31 is rotatably con

nected to the sampling port 20 via a hinge 41 . When collecting the initial blood contained in t he initial blood bag 16 as test blood, a reduced-pressure blood collection tube 50 (correspondi ng to a blood collection tube) having a rubber plug 51 is inserted into the sampling port 20 thr ough the opening 31 .

A reduced

-pressure blood collection tube 50 is an instrument for collecting the initial blood that is stor ed in the initial blood bag 16 . The vacuum blood collection tube 50 has a blood collection tub e body 52 and a rubber plug 51 fitted into the opening of the blood collection tube body 52 . T he vacuum blood collection tube 50 is in a vacuum or a reduced pressure state. When the vac uum blood collection tube 50 is connected to the sampling port 20 , the rubber stopper 51 is p ierced by the hollow needle 61 . As a result, the inside of the vacuum blood collection tube 50 and the blood extraction tube 19 are communicated, and the initial blood flow from the blood extraction tube 19 is collected in the vacuum blood collection tube 50 .

[0015]

With reference to FIGS. 3 and 4, the sampling port 20 according to the embodiment is gener ally composed of a body portion 30 formed with an opening 31 for inserting a blood collection tube 50 having a rubber stopper 51, a blood collection tube A hollow needle 61 that can be fre ely inserted into the rubber plug 51 of 50, a hub 64 that supports the base end of the hollow needle 61, an elastic rubber cap 70 that covers the hollow needle 61, and a holder that holds the rubber cap 70. and a needle assembly 60 attached to the body portion 30 with a portion 8 0 . The sampling port 20 further suppresses wrinkles 71 (see FIG. 4) caused by elastic contra ction of the rubber cap 70 as the hollow needle 61 is inserted into the rubber plug 51 from rea ching the holding portion 80. It has a member 90 . The suppressing member 90 has a throug h hole 91 through which the hollow needle 61 covered with the rubber cap 70 passes. 3 and 4, the upper side in the drawings is defined as the "upper side" of each member, and the lowe r side in the drawings is defined as the "lower side" of each member. Details are given below.

The body portion 30 has a cylindrical shape and has a tapered shape on the lower side

.

The main body 30 has

, an insertion port 32 for inserting the needle assembly 60, and an engaging portion 33 for pr eventing the inserted needle assembly 60 from coming off.

Body

portion 30 is rotatably attached to needle assembly 60 . By making it rotatable, the body po rtion 30 can be rotated with respect to the needle assembly 60 to easily finely adjust the posit ion of the lid member 40 with respect to the initial blood flow bag 16 . A needle assembly 60 includes a hollow needle 61 having a sharp tip at its tip, a connecting portion 62 connected to the blood extraction tube 19, a boss portion 63 holding the proximal end portion of the hollow needle 61

,

have. The hub 64 is provided so as to protrude radially outward from the boss portion 63 . Th e needle assembly 60 is attached to the body portion 30 with the hub 64 overcoming the locki ng portion 33 when it is inserted into the insertion port 32 of the body portion 30 . The upper end of the hub 64 in the figure is formed into an inclined surface so that it can easily get over the engaging portion 33 when it is inserted. In order to pivotally attach the body portion 30 t o the needle assembly 60, the clearance between the connecting portion 62 of the needle ass embly 60 and the receptacle 32 of the body portion 30 and the outer circumference of the hu b 64

are

and the body portion 30 are adjusted. As the blood collection tube 50 is inserted into the ma in body 30 and the hollow needle 61 is passed through the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrinkles 71, thereby exposing the hollow needle 61

.

Let When the blood collection tube 50 is pulled out, the rubber cap 70 is elastically stretched f rom the shrunk state so as to smooth out the wrinkles 71, and restores to the state where it c overs the hollow needle 61 again. This prevents blood from leaking from the hollow needle 61

.

[0021]

The holding portion 80 includes a lock member 81 through which the hollow needle 61 is ins erted and which is attached to the boss portion 63 of the needle assembly 60 . The locking m ember 81 has an undercut shape in which the base end side of the hollow needle 61 has a sm aller diameter than the tip end side. The undercut shape of the locking member 81 holds the r ubber cap 70 .

5(A) and 5(B), restraining member 90 includes a disk -

shaped flat plate portion 93 fitted in main body portion 30 and a center portion of flat plate portion 93 protruding upward. It consists of a plate 92 with a projection 94 . A through-hole 9 1 through which the hollow needle 61 with the rubber cap 70 is attached is formed in the conv ex portion 94 . As shown in FIG. 5C , a ring-shaped projection 95 projecting radially outward i s provided integrally with the flat plate portion 93 on the outer peripheral edge of the flat plat e portion 93 . 3 and 4, the plate 92 is mounted inside the main body 30 at a position above t he lock member 81 forming the holding portion 80. As shown in FIG

.

As the blood collection tube 50 is inserted into the main body 30 and the hollow needle 61 is passed through the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrin kles 71, thereby exposing the hollow needle 61. . A clearance S between the through hole 91 of the plate 92 and the rubber cap 70 is relatively small. Therefore, the plate 92 prevents the wrinkles 71 generated by the elastic contraction of the rubber cap 70 from reaching the holdin g portion 80 (FIG. 4).

[0024]

As described above, the body portion 30 is rotatably attached to the needle assembly 60 . A clearance S is provided between the through hole 91 of the plate 92 fixed to the main body 30 and the rubber cap 70 to allow the main body 30 to rotate. By setting the clearance S to a di mension that does not hinder the rotation of the main body 30, the rotational position of the main body 30 with respect to the needle assembly 60, the position of the lid member 40 with respect to the initial blood bag 16, and the like can be easily finely adjusted. becomes possibl e.

By providing the plate 92 with the protrusions 94, it is possible to increase the area of the ru bber cap 70 in the longitudinal direction that is not affected by the wrinkles 71. As shown in F IG . As a result, a decrease in holding force for holding the rubber cap 70 to the needle assem bly 60 can be further suppressed. Even if the arrangement position of the plate 92 is shifted u pward from the position shown in FIG. 4, the area in the longitudinal direction of the rubber c ap 70 that is not affected by the wrinkles 71 can be increased. However, in this case, since th e position of the blood collection tube 50 is also shifted upward, it may be necessary to slightl y increase the longitudinal dimension of the main body 30 . Therefore, by providing the plate 92 with the convex portion 94 projecting toward the opening 31 side of the body portion 30, while maintaining the length of the body portion 30 in the longitudinal direction, It is possible to secure a sufficient holding force for holding the rubber cap 70 to the needle assembly 60 b y increasing the area not affected by the wrinkles 71 .

[0026]

The material of the main body 30, the cover member 40, the needle assembly 60 excluding t he hollow needle 61, the holding part 80, and the plate 92 is not particularly limited, but exa mples thereof include polycarbonate, polyethylene, polypropylene, ethylene- Examples include polyolefins such as vinyl acetate copolymers and modified polyolefins. The material of the ho llow needle 61 is not particularly limited, but examples include various metal materials such a s stainless steel, aluminum or aluminum alloys, titanium or titanium alloys, superelastic alloys such as Ni--Ti alloys, polyphenylene sulfide, and the like

.

and various hard resin materials.

[0028]

The material constituting the rubber cap 70 is not particularly limited, but examples include natural rubber, isoprene rubber, butadiene rubber, styrene-butadiene rubber, nitrile rubber, chl oroprene rubber, butyl rubber, acrylic rubber, ethylene-propylene rubber, hydrin rubber, Variou s rubber materials such as urethane rubber, silicone rubber, and fluororubber can be used.

FIGS.

6A and 6B show how the plate 92 is fixed to the body portion 30. FIG. In this embodiment, t he body portion 30 is made of a resin material that shrinks more than the resin material formi ng the plate 92 when heat is applied. This is because the plate 92 can be fixed to the body po

rtion 30 by applying heat for sterilization. More specifically, as shown in FIG. 6A, before heat is applied, the inner diameter of the main body 30 is relatively large, and the ring-shaped proj ection 95 of the plate 92 bites into the main body 30 by a small amount

.

I'm in. Since the plate 92 can be inserted into the main body 30 relatively easily, the assembl y work of the plate 92 can be easily performed.

Then ,

as shown in FIG. 6(B), when heat is applied for sterilization, for example, in a high-pressure steam sterilization method (autoclave), the main body 30 shrinks more than the plate 92 doe s. As a result, the ring-shaped protrusion 95 of the plate 92 further bites into the body portion 30 , and the plate 92 can be easily fixed to the body portion 30 . As an example of a combin ation of resin materials as described above, for example, polypropylene can be used as the m olding material for the main body 30 and polycarbonate can be used as the molding material f or the plate 92

. [0033]

The operation of this embodiment will be described. When collecting blood, the blood collec tion tube 50 is inserted into the body portion 30 of the sampling port 20, and is hollow

.

A needle 61 is passed through the rubber stopper 51 . As the hollow needle 61 is inserted thr ough the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrinkles 71, th ereby exposing the hollow needle 61. As shown in FIG. Referring to FIG. 7B, in the case of c ontrast without plate 92, rubber cap 170 is elastically closed as hollow needle 161 is inserted i nto rubber plug 51 of blood collection tube 50

.

Wrinkles 171 caused by shrinking may reach the base of the rubber cap 170 . In such a case, the base portion of rubber cap 170 swells, and the holding force for holding rubber cap 170 to needle assembly 160 is weakened. Therefore, when the blood collection tube 50 is pulled out, the rubber cap 170 may be pulled together, and the position of the rubber cap 170 may be dis placed, resulting in insufficient prevention of blood leakage. On the other hand, referring to FIGS. 4 and 7A, in the present embodiment, the plate 92 is positioned above the locking mem ber 81 forming the holding portion 80, and the main

body

It is installed inside the part 30 . This plate 92 prevents wrinkles 71 generated by elastic contr action of the rubber cap 70 as the hollow needle 61 is inserted into the rubber plug 51 of the blood collection tube 50 from reaching the locking member 81 . Since the rubber cap 70 does not swell at the portion of the lock member 81, the holding force for holding the rubber cap 7

0 to the needle assembly 60 is not weakened.

[0037]

The exposed hollow needle 61 is inserted through the rubber stopper 51 and blood is collected into the blood collection tube 50 . When the blood collection tube 50 is pulled out after blood collection, the rubber cap 70 elastically expands from the shrunk state so as to smooth out the wrinkles 71 and restores to the state where it covers the hollow needle 61 again. This prevents blood from leaking from the hollow needle 61 . The rubber cap 70 is held by the needle assembly 60 at the locking member 81 .

When the tip of the rubber cap 70 bites into the

minute insertion hole of the rubber stopper 51 of the blood collection tube 50 and the blood collection tube 50 is pulled out, the rubber cap 70 is pulled together. However, since the portion of the locking member 81 is not affected by the wrinkles 71, the holding force remains set at the initial stage. Therefore, the rubber cap 70 does not come off from the hollow needle 61 and the blood collection tube 50 is released from biting into the rubber plug 51 . As a result, the position of the rubber cap 70 is not displaced, and blood leakage can be sufficiently prevented.

As described

above, even if the rubber cap 70 is elastically contracted as the hollow needle 61 is inserted into the rubber stopper 51 of the blood collection tube 50 and wrinkles 71 are generated, the rubber cap 70 is attached to the needle assembly 60. It is possible to provide the sampling port 20 which can maintain a holding force for holding and thereby sufficiently prevent leakage of blood. Main body 30 is rotatably attached to needle assembly 60 , plate 92 is fixed to main body 30 , and main body 30 is positioned between through hole 91 and rubber cap 70

.

Since there is a clearance S that allows rotation, it is possible to easily finely adjust the rotation position of the main body 30 with respect to the needle assembly 60 .

[0041]

In addition, since the plate 92 has a convex portion 94 that protrudes toward the opening 31 side of the body portion 30, the longitudinal length of the rubber cap 70 is increased while maintaining the length of the body portion 30 in the longitudinal direction. It is possible to secure a sufficient holding force for holding the rubber cap 70 to the needle assembly 60 by enlarging the area that is not affected by the wrinkles 71 . In addition, since the ring-shaped projection 95 projecting radially outward is provided on the outer peripheral edge of the plate 92, the plate 92 is attached to the body portion 30 so that the ring-shaped projection 95 bites into the body portion 30 by a small amount

.

It can be inserted into the plate 30, and the assembly work of the plate 92 can be easily performed.

becomes possible. The main body 30 is made of a resin material that shrinks more than the

resin material forming the plate 92 when heat is applied

.

Since it is fixed to the body portion 30, the plate 92 can be relatively easily inserted into the b ody portion 30 before heat is applied, and the plate 92 can be easily assembled. On the other hand, when heat is applied for sterilization, the body portion 30 contracts more than the plate 92 . This makes it possible to easily fix the plate 92 to the body portion 30 .

(

Modified Example of Plate)

The plate has a through hole 91 through which the hollow needle 61 with the rubber cap 70 attached passes. As long as wrinkles 71 generated by elastic contraction of 70 are prevented f rom reaching holding portion 80, the shape can be modified as appropriate.

For example, referring to FIG. 8, a plate 92a (FIG. 8A) in which

a projection 94 smoothly protrudes from a flat plate portion 93, a plate 92b with a thicker ov erall thickness and a flat upper surface, 92c (FIGS. 8B and 8C), and a cap-shaped plate 92d (FIG. 8D) that covers the holding portion 80 without covering the entire bottom surface of the main body portion 30 can be exemplified. Further, referring to FIG. 9, a plate 92e (FIG. 9A) i n which the flat plate portion 93 is not formed with the through portion, and a plate 92f (FIG. 9A) in which the flat plate portion 93 is formed with the through portion 96 are provided

.

(B)).

(

Other modifications)

Although the lock member 81 having an undercut shape has been exemplified as the holding portion 80 that holds the rubber cap 70, the holding portion 80 is not limited to this case. The holding part 80 can be appropriately modified as long as it has a function of preventing the ru bber cap 70 from coming off and holding it in the needle assembly 60 . For example, the holdi ng part 80 uses a form in which the rubber cap 70 is adhered to the hollow needle 61 with an adhesive to hold it, a form in which the rubber cap 70 is held by being fused to the hollow nee dle 61 by ultrasonic fusion, or a clip. For example, a configuration in which the rubber cap 70 i s held on the hollow needle 61 by fitting is exemplified. These holding portions 80 may be use d alone, or may be a holding portion 80 in which two or more types are combined.

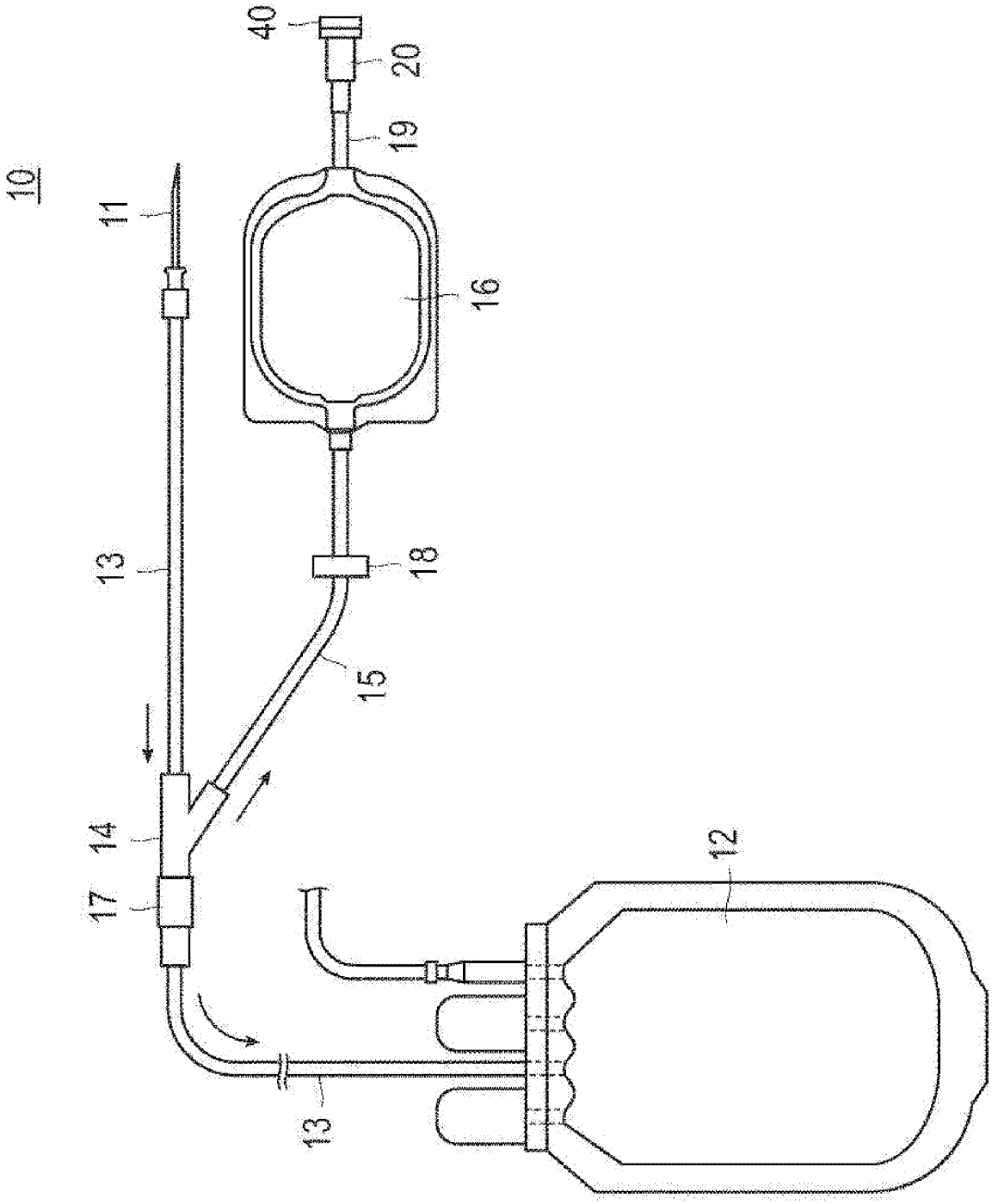
20 sampling port 30 main body 31 opening 50 vacuum

blood collection tube (collection tube) 51 rubber plug 60 needle assembly 61 hollow needle 64 hub 70 rubber cap 71 wrinkles 80 holding part 81 locking member 90 suppressing member 91 through hole 92 plate (suppressing member);

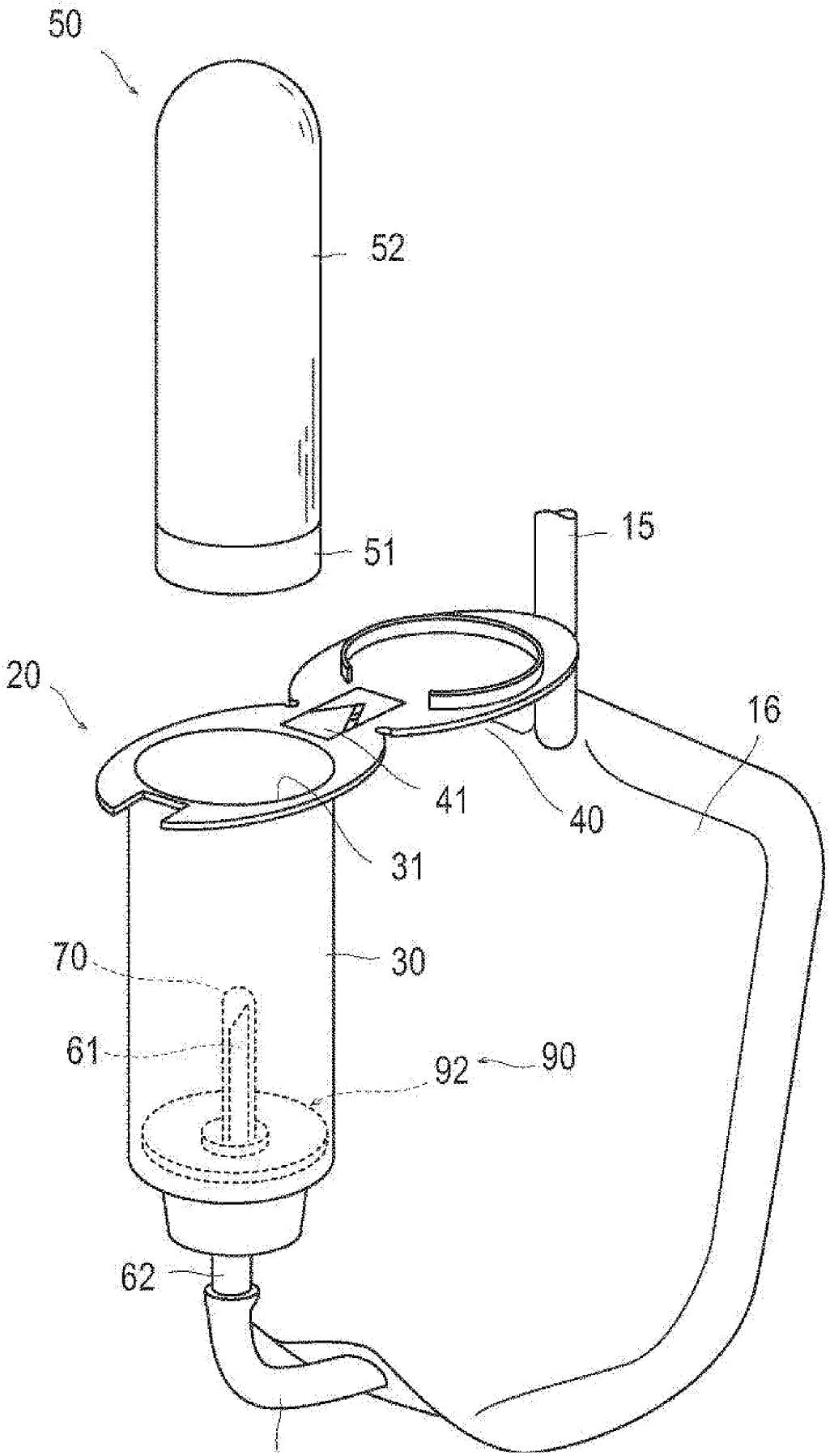
93 flat plate portion,
94 convex portion,
95 ring-shaped projection,
S clearance.

drawing open —

[Fig. 1]

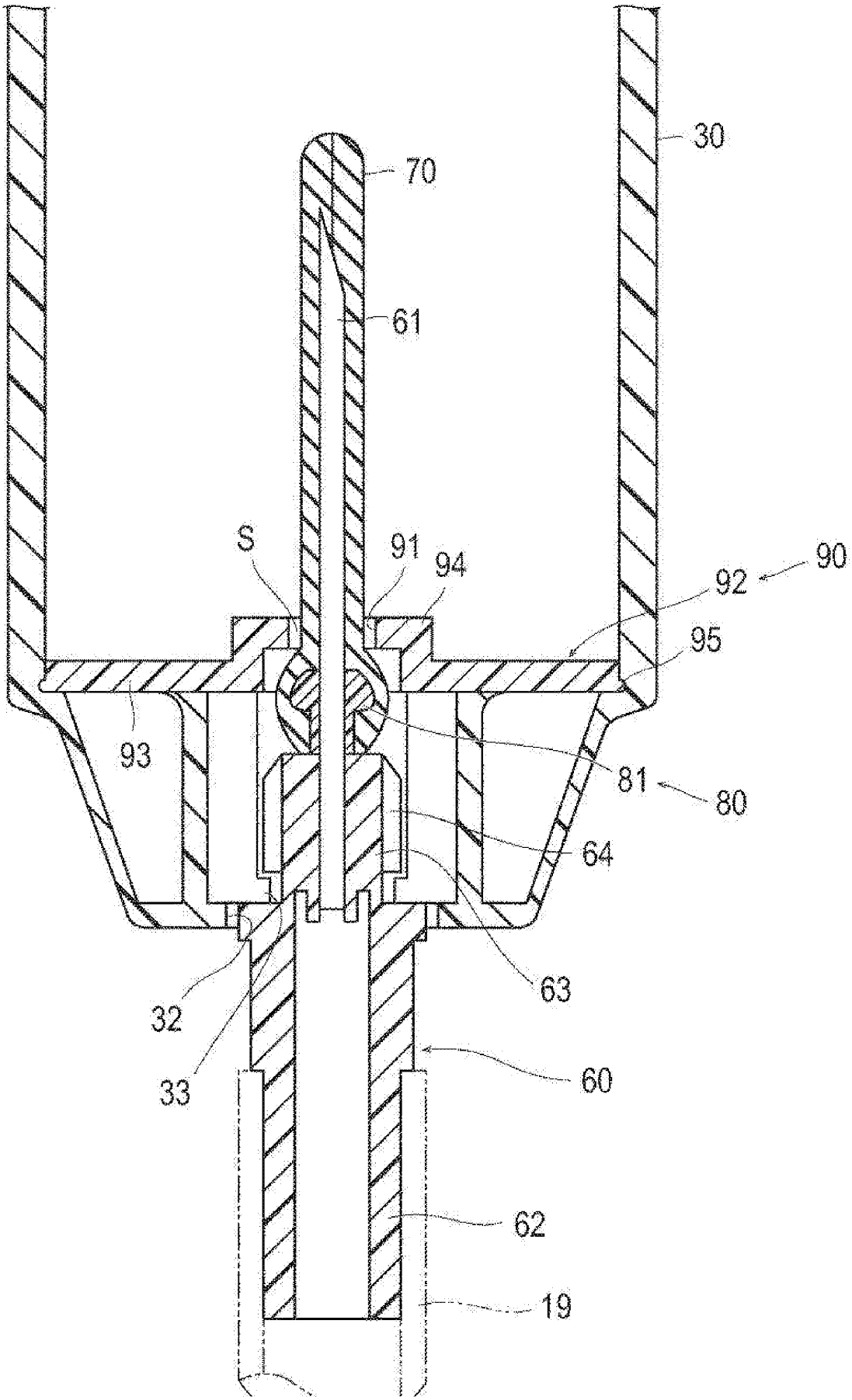


[Figure 2]

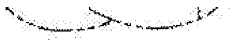

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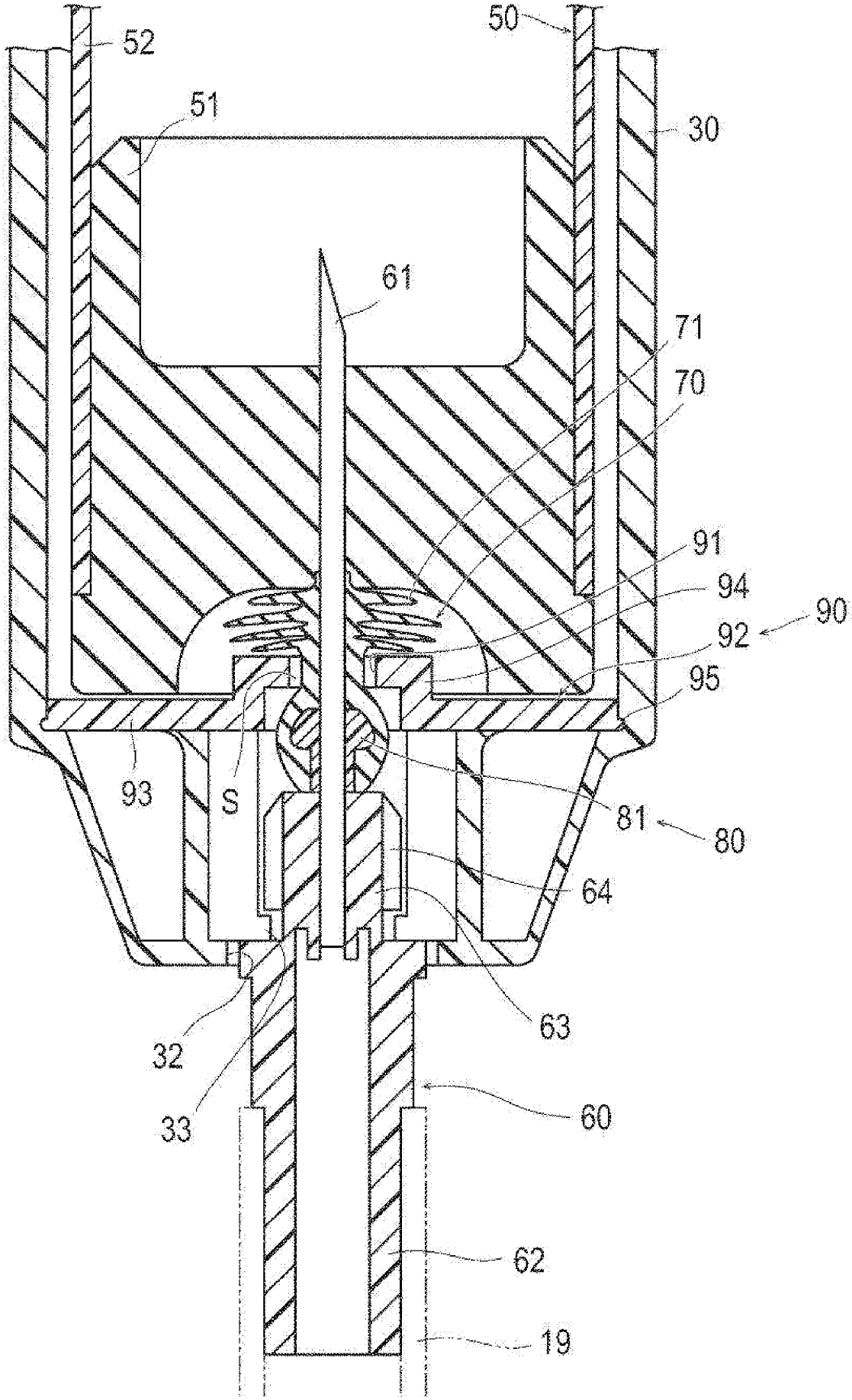
[Figure 3]




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[Figure 4]

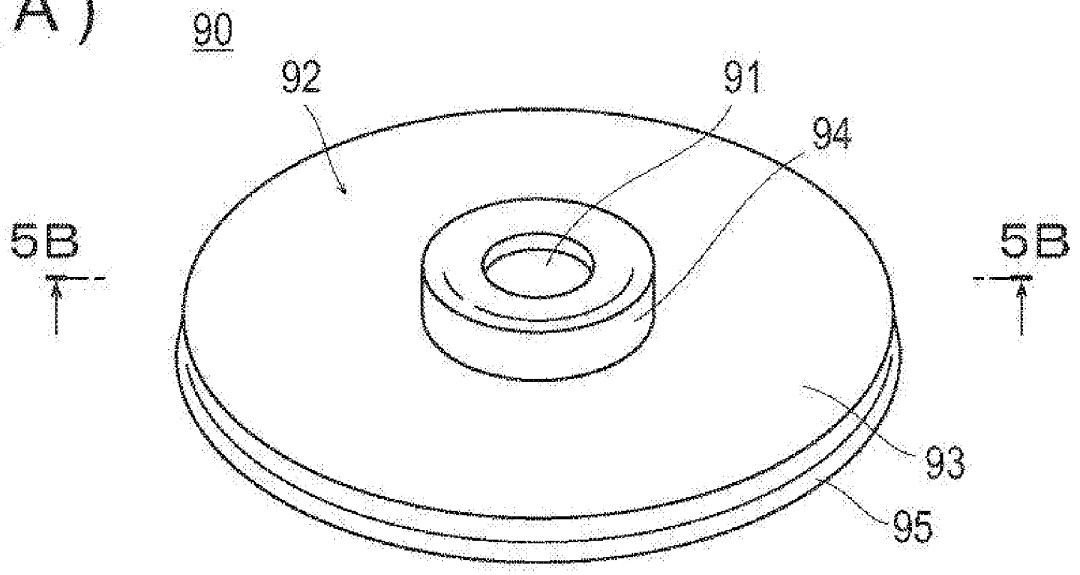



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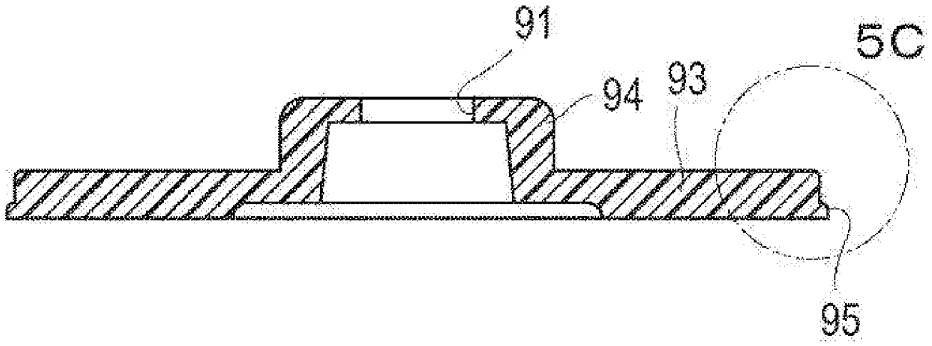
[Figure 5]



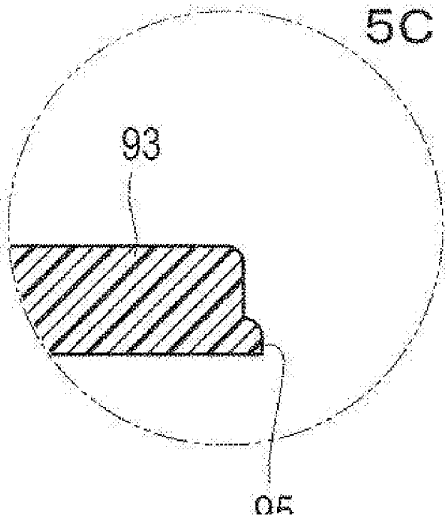
(A)



(B)

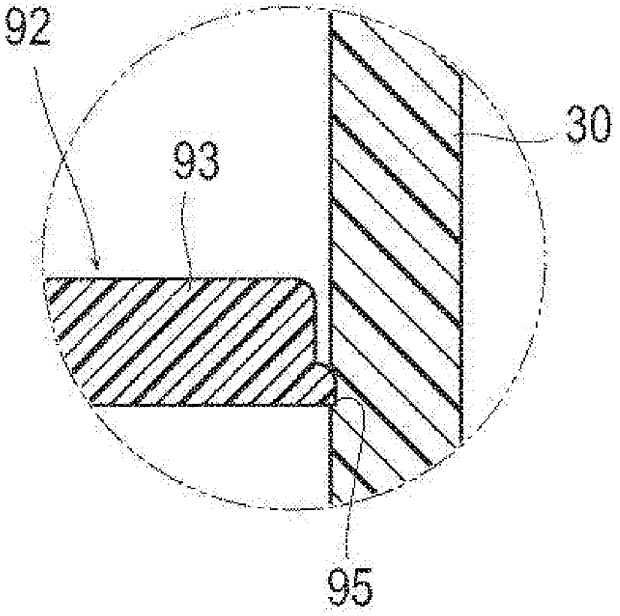


(C)

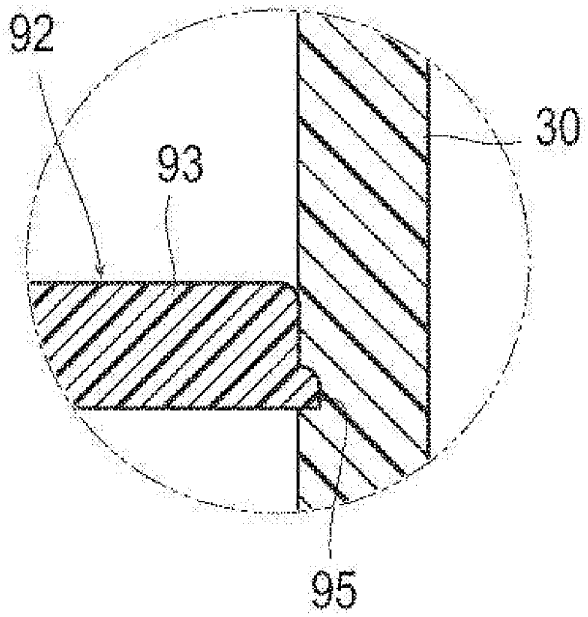


[Fig. 6]

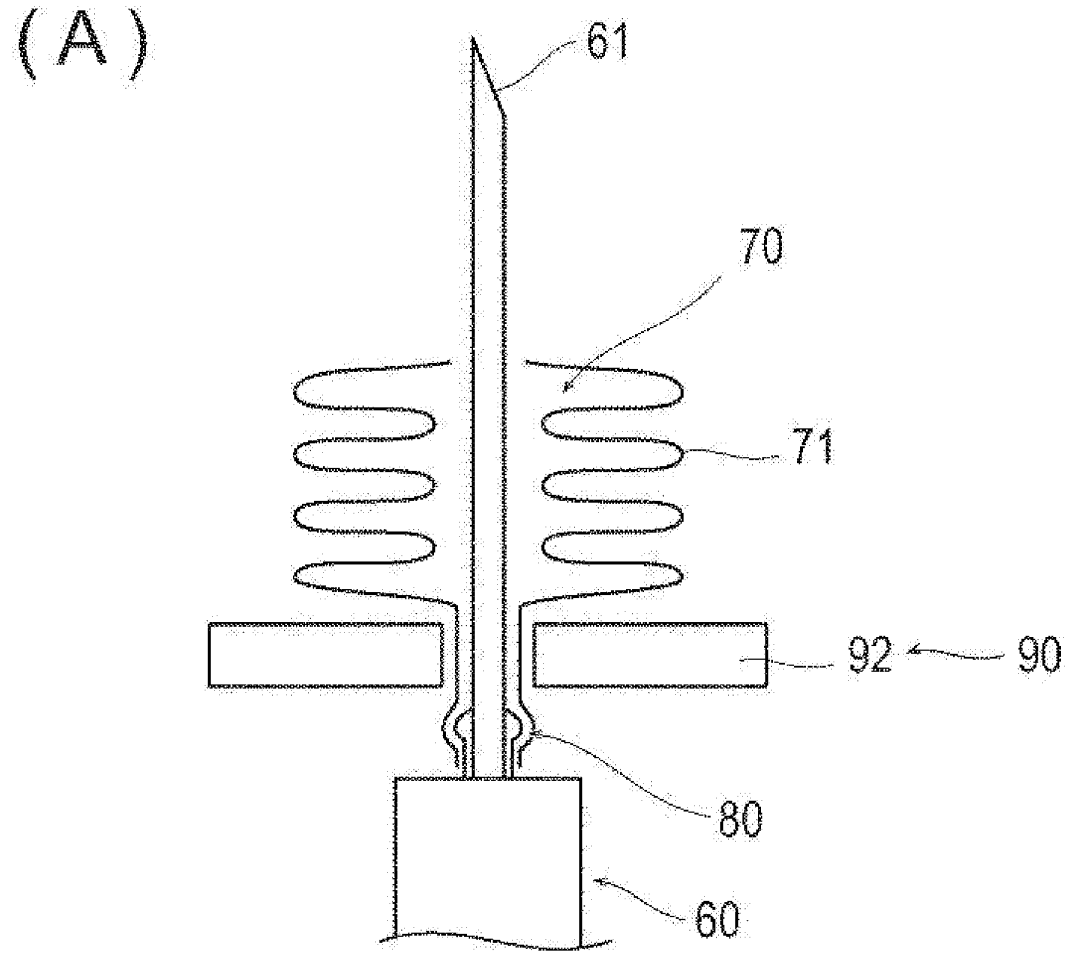
(A)

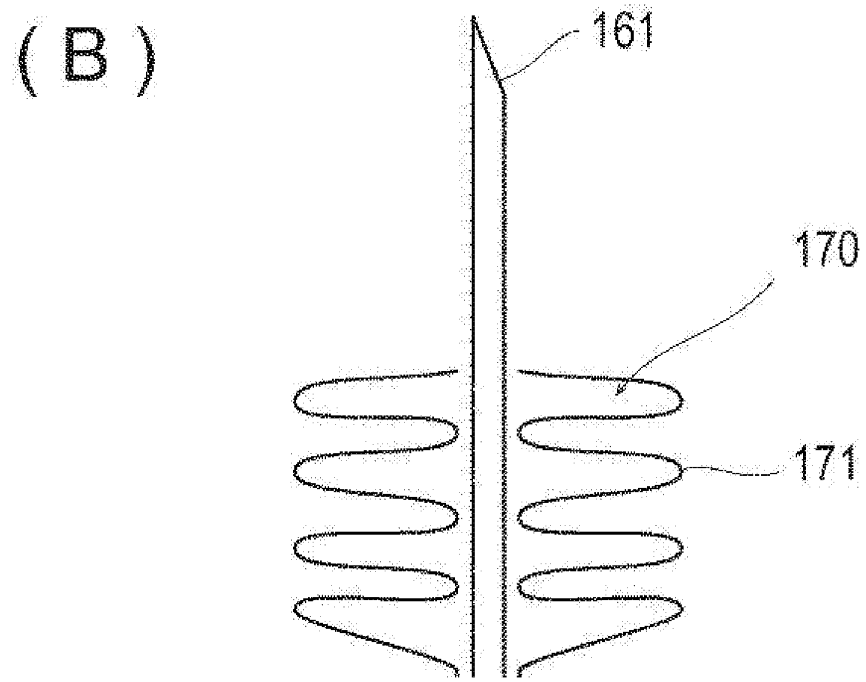


(B)

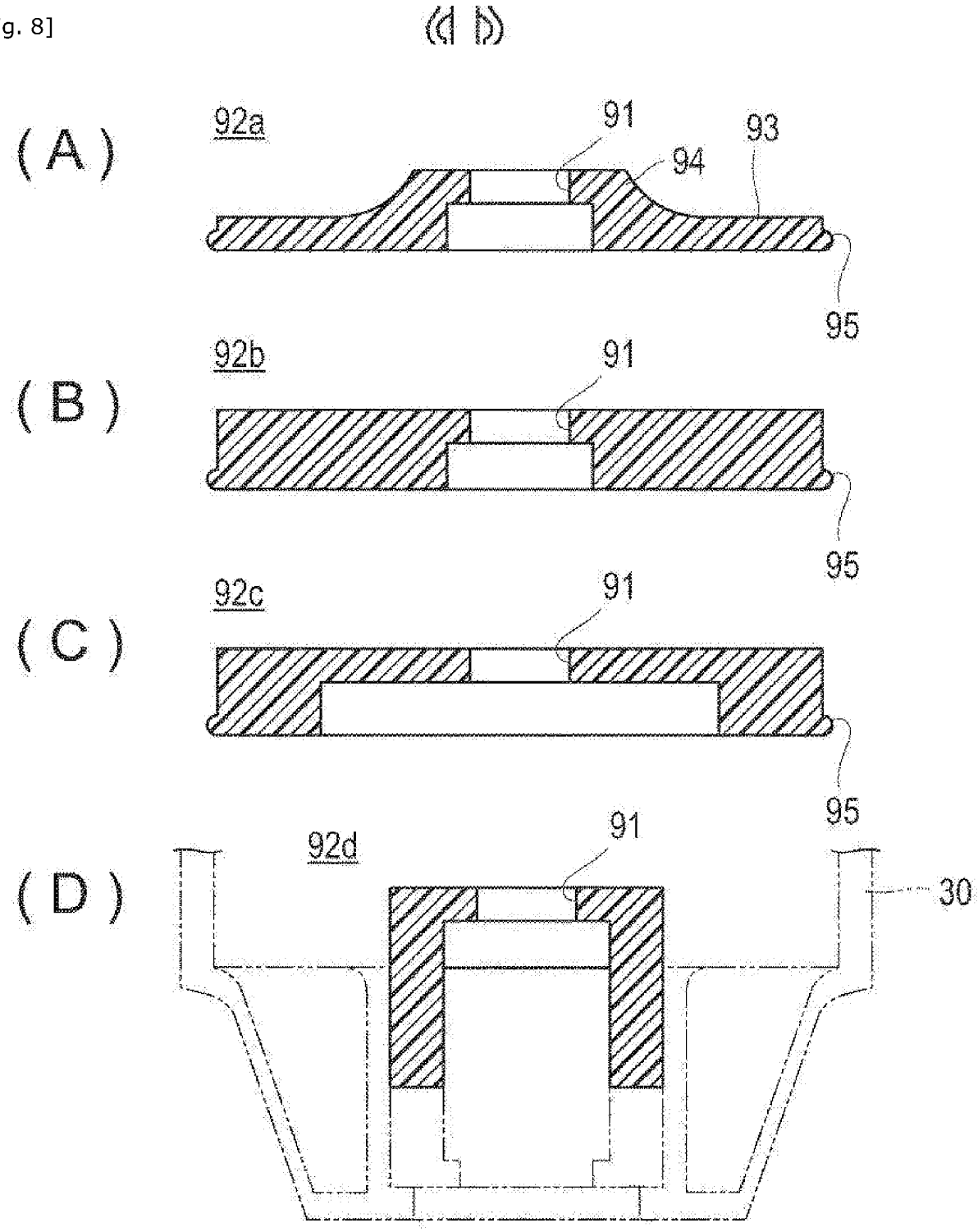


[Fig. 7]

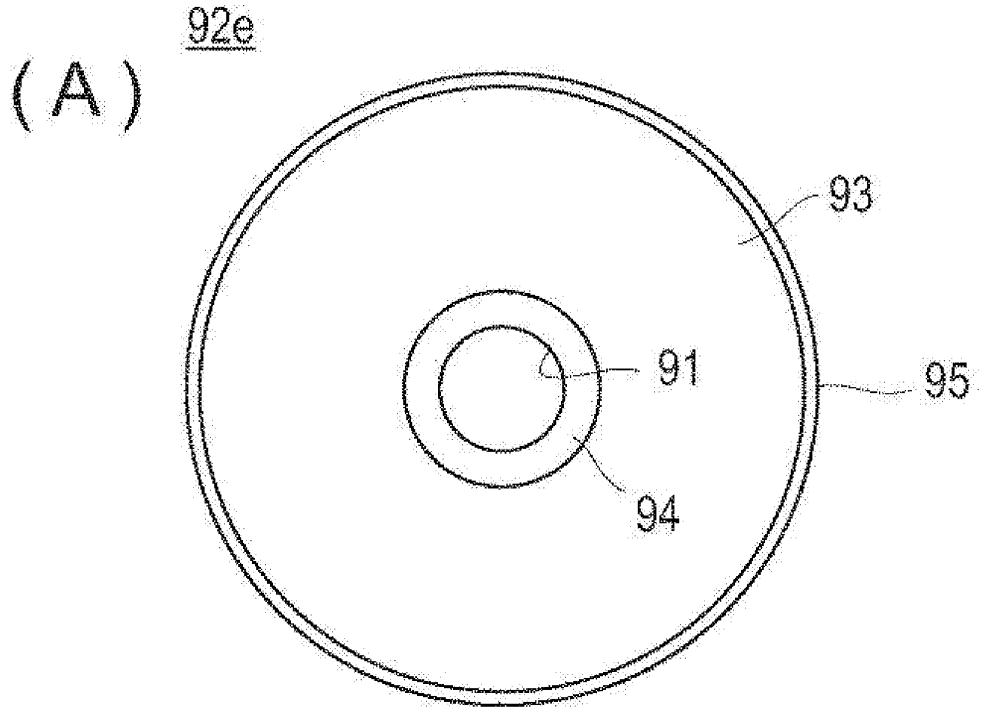

(A)
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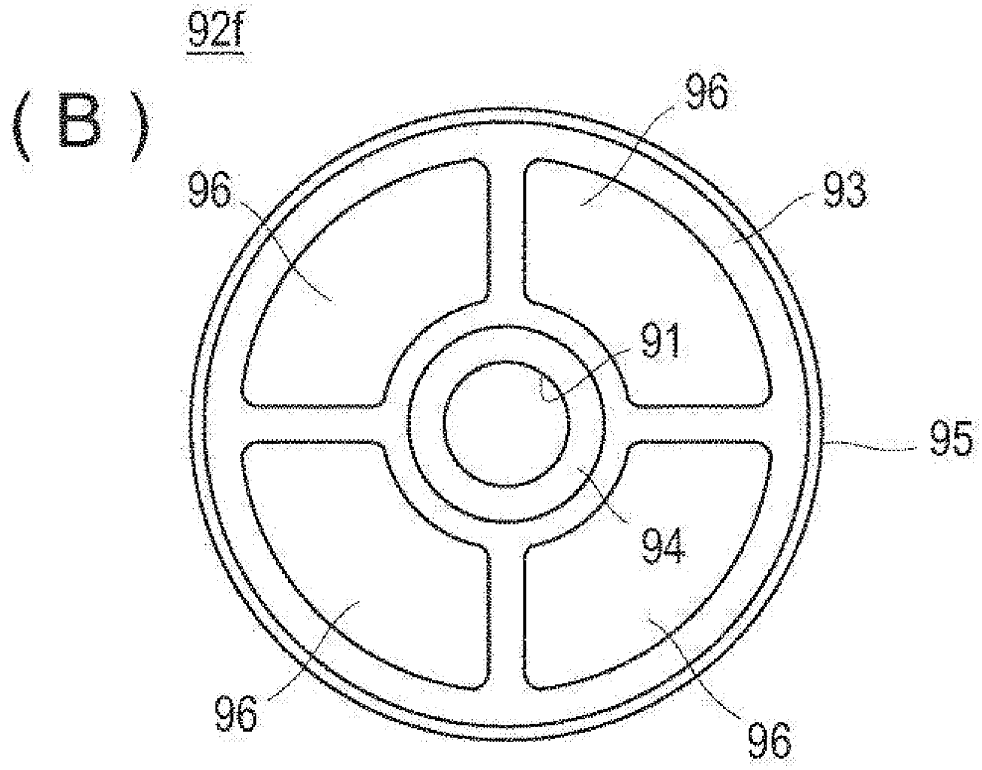

(B)
161
170
171

[Fig. 8]



[Fig. 9]

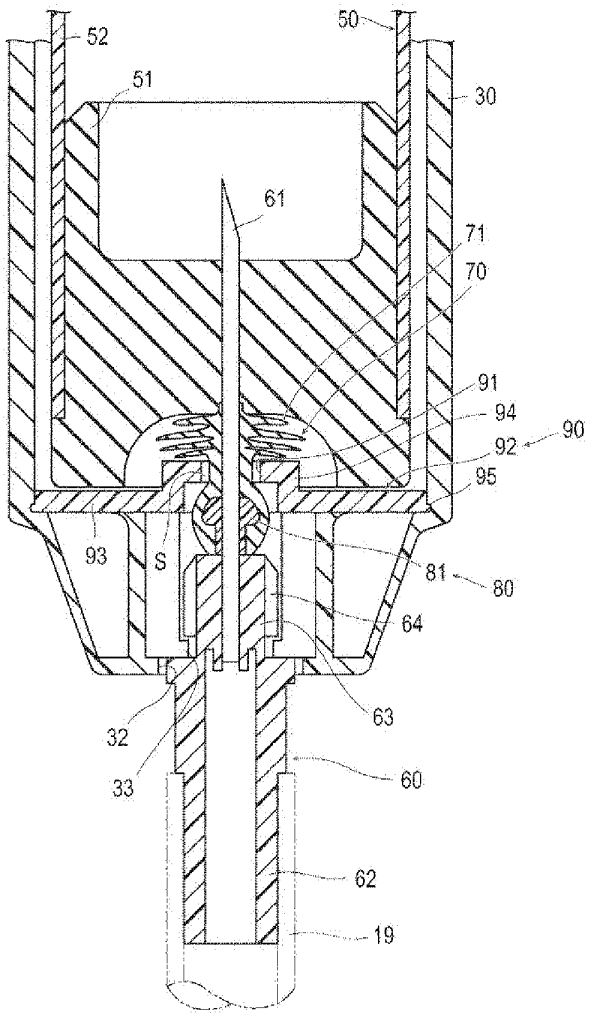

92e
(A)
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drawing open

Representative drawing 1 2 3 Four Five 6 7 8 9

Magnify and Rotate



Representative drawing

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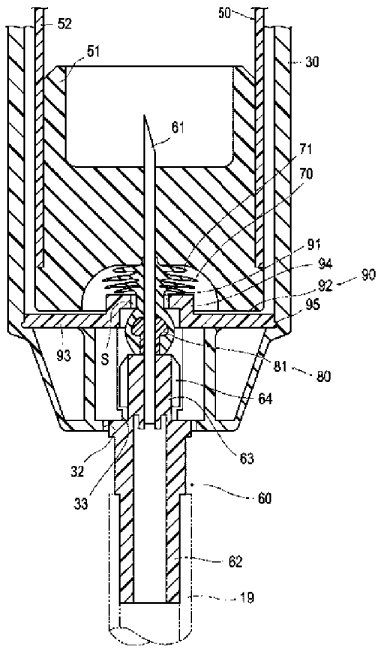
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(54)【発明の名称】サンプリングポート

(57)【要約】
【課題】採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポートを提供する。
【解決手段】サンプリングポート２０は、ゴム栓５１を備える採血管５０を挿入するための開口部３１が形成された本体部３０と、採血管のゴム栓に挿通自在な中空針６１と、中空針の基端部を支持するハブ６４と、中空針に被せられた弾性を有するゴムキャップ７０と、ゴムキャップを保持する保持部８０と、を備え、本体部に取り付けられた針組立体６０と、ゴムキャップが被せられた中空針が貫通する貫通孔９１を備え、ゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺７１が保持部に達することを抑制する抑制部材９０としてのプレート９２と、を有している。
【選択図】図４



【特許請求の範囲】
【請求項１】
ゴム栓を備える採血管を挿入するための開口部が形成された本体部と、
前記採血管の前記ゴム栓に挿通自在な中空針と、前記中空針の基端部を支持するハブと、前記中空針に被せられた弾性を有するゴムキャップと、前記ゴムキャップを保持する保持部と、を備え、前記本体部に取り付けられた針組立体と、
前記ゴムキャップが被せられた前記中空針が貫通する貫通孔を備え、前記ゴム栓への前記中空針の挿通に伴って前記ゴムキャップが弾性的に縮められることによって生じる皺が前記保持部に達することを抑制する抑制部材と、を有することを特徴とするサンプリングポート。
【請求項２】
前記本体部は、前記針組立体に対して回動自在に取り付けられ、
前記抑制部材は、前記本体部に固定されており、前記貫通孔と前記ゴムキャップとの間に、前記本体部の回動を許容するクリアランスを有する、請求項１に記載のサンプリングポート。
【請求項３】
前記本体部は、円筒形状であり、
前記抑制部材は、円盤形状であり、前記本体部の前記開口部の側に向けて突出する凸部を備えている、請求項１または請求項２に記載のサンプリングポート。
【請求項４】
前記抑制部材の外周縁には、径方向外方に突出するリング状突起が設けられている、請求項１～３のいずれか１つに記載のサンプリングポート。
【請求項５】
前記本体部は、熱を印加したときに前記抑制部材を形成する樹脂材料よりも大きく収縮する樹脂材料から形成されており、滅菌のための熱を印加することによって、前記抑制部材を前記本体部に対して固定する、請求項１～４のいずれか１つに記載のサンプリングポート。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は、採血管を保持するサンプリングポートに関する。
【背景技術】
【０００２】
ゴム栓を備える採血管を用いて採血するときには、採血管を保持するサンプリングポートが使用される（特許文献１を参照）。サンプリングポートは、採血管を挿入するための開口部が形成された本体部を有し、この本体部には、採血管のゴム栓に挿通自在な中空針を備えた針組立体が取り付けられている。中空針には、血液の漏洩を防止するために、弾性を有するゴムキャップが被せられている。
【０００３】
サンプリングポートの本体部に採血管を挿入し、中空針をゴム栓に挿通させるのに伴って、ゴムキャップは、弾性的に縮められて皺を生じながら中空針を露出させる。露出した中空針は、採血管に採血する。採血後に採血管を引き抜くと、ゴムキャップは、縮んだ状態から、皺を伸ばすように弾性的に伸び、中空針に再び被せられる状態まで復元する。これによって、中空針からの血液の漏洩を防止する。ゴムキャップは、例えば根元部分を針組立体に密着させることによって、針組立体に保持されている。
【先行技術文献】
【特許文献】
【０００４】
【特許文献１】特開２００２－２９１７２４
【発明の概要】

【発明が解決しようとする課題】
【０００５】
しかしながら、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺が、ゴムキャップの根元部に達することがある。このような場合には、ゴムキャップの根元部が膨らんでしまい、ゴムキャップを針組立体に保持するための保持力が弱くなる。このため、採血管のゴム栓の微小な挿通孔にゴムキャップの先端部が食い込んでいるような場合においては、採血管を引き抜くときにゴムキャップが一緒に引っ張られてしまい、ゴムキャップの位置などがずれてしまい、血液の漏洩の防止が不十分になる虞がある。
【０００６】
本発明は、上記従来技術に伴う課題を解決するためになされたものであり、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポート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】
【０００７】
上記目的を達成するための本発明のサンプリングポートは、ゴム栓を備える採血管を挿入するための開口部が形成された本体部と、
前記採血管の前記ゴム栓に挿通自在な中空針と、前記中空針の基端部を支持するハブと、前記中空針に被せられた弾性を有するゴムキャップと、前記ゴムキャップを保持する保持部と、を備え、前記本体部に取り付けられた針組立体と、
前記ゴムキャップが被せられた前記中空針が貫通する貫通孔を備え、前記ゴム栓への前記中空針の挿通に伴って前記ゴムキャップが弾性的に縮められることによって生じる皺が前記保持部に達することを抑制する抑制部材と、を有している。
【発明の効果】
【０００８】
抑制部材によって、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺が保持部に達することが抑制されているので、保持部の部分でゴムキャップが膨らむことがなく、ゴムキャップを針組立体に保持するための保持力が弱くならない。このため、採血後に採血管を引き抜くときにゴムキャップが一緒に引っ張られてしまっても、ゴムキャップの位置などがずれることがなく、血液の漏洩を十分に防止することが可能となる。このように、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポートを提供できる。
【図面の簡単な説明】
【０００９】
【図１】サンプリングポートが組み込まれた血液バッグシステムを示す構成図である。
【図２】図１に示される初流血バッグと、サンプリングポートとを示す斜視図である。
【図３】採血管を挿入する前のサンプリングポートの要部を示す断面図である。
【図４】採血管を挿入した後のサンプリングポートの要部を示す断面図である。
【図５】図５（Ａ）は、抑制部材としてのプレートを示す斜視図、図５（Ｂ）は、図５（Ａ）の５Ｂ－５Ｂ線に沿う断面図、図５（Ｃ）は、図５（Ｂ）の５Ｃ部分を拡大して示す断面図である。
【図６】図６（Ａ）（Ｂ）は、抑制部材としてのプレートを本体部に対して固定する様子を示す断面図である。
【図７】図７（Ａ）は、本実施形態の作用の説明に供する概念図、図７（Ｂ）は、プレートを設けていない対比例の場合の作用の説明に供する概念図である。
【図８】図８（Ａ）～（Ｄ）は、プレートの改変例を示す断面図である。
【図９】図９（Ａ）（Ｂ）は、プレートのさらなる改変例を示す平面図である。

【発明を実施するための形態】

【００１０】

以下、添付した図面を参照しながら、本発明の実施形態を説明する。なお、図面の説明において同一の要素には同一の符号を付し、重複する説明を省略する。また、図面の寸法比率は、説明の都合上誇張されており、実際の比率とは異なる場合がある。

【００１１】

図１を参照して、図示する血液バッグシステム１０は、血液を採取する際に、採取された血液の初流（初流血）を除去し、その初流血を検査用血液として利用する採血器具である。皮膚上や皮下に存在する細菌が穿刺時の皮膚のかけらとともに侵入するため、初流血を除去している。

【００１２】

血液バッグシステム１０は、採血針１１と、採血針１１を介して採取された血液を収納する血液バッグ１２と、採血針１１と血液バッグ１２とを連通する採血チューブ１３と、採血チューブ１３の途中に配置した分岐コネクタ１４と、分岐コネクタ１４に接続した分岐チューブ１５を介して採血チューブ１３に連通する初流血バッグ１６と、初流血バッグ１６の端部に接続されたサンプリングポート２０と、を有している。分岐コネクタ１４には血液バッグ１２への連通を封止する封止部材１７が設けられている。初流血バッグ１６への初流血の採血が終わるまで、封止部材１７は血液バッグ１２への連通を封止している。分岐チューブ１５には、初流血バッグ１６への血流を遮断するクランプ部材１８が設けられている。初流血の採血が終わると、クランプ部材１８によって分岐チューブ１５をクランプし、初流血バッグ１６への血流が遮断される。その後、封止部材１７を開放し、血液バッグ１２への採血を開始する。

【００１３】

図２には、初流血バッグ１６に収納した初流血を検査用血液として回収するときの状態が示されている。初流血バッグ１６に接続された血液取出チューブ１９にサンプリングポート２０が接続されている。サンプリングポート２０には、開口部３１を開閉する蓋部材４０がヒンジ４１を介して回動自在に接続されている。初流血バッグ１６に収納した初流血を検査用血液として回収するときには、ゴム栓５１を備える減圧採血管５０（採血管に相当する）が開口部３１からサンプリングポート２０内に挿入される。

【００１４】

減圧採血管５０は、初流血バッグ１６内に貯留された初流血を採取するための器具である。この減圧採血管５０は、採血管本体５２と、この採血管本体５２の開口に嵌め込まれているゴム栓５１と、を有している。減圧採血管５０内は、真空または減圧状態になっている。減圧採血管５０は、サンプリングポート２０に接続されたとき、ゴム栓５１が中空針６１によって刺通される。これによって、減圧採血管５０内と血液取出チューブ１９とが連通し、当該血液取出チューブ１９からの初流血が減圧採血管５０に回収される。

【００１５】

図３および図４を参照して、実施形態に係るサンプリングポート２０は、概説すれば、ゴム栓５１を備える採血管５０を挿入するための開口部３１が形成された本体部３０と、採血管５０のゴム栓５１に挿通自在な中空針６１と、中空針６１の基端部を支持するハブ６４と、中空針６１に被せられた弾性を有するゴムキャップ７０と、ゴムキャップ７０を保持する保持部８０と、を備え、本体部３０に取り付けられた針組立体６０と、を有している。サンプリングポート２０はさらに、ゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１（図４を参照）が保持部８０に達することを抑制する抑制部材９０を有している。抑制部材９０は、ゴムキャップ７０が被せられた中空針６１が貫通する貫通孔９１を備えている。なお、図３および図４において図中上側を各部材における「上部側」とし、図中下側を各部材における「下部側」とする。以下詳述する。

【００１６】

本体部３０は、円筒形状を有し、下部側は先細りの形状を有している。本体部３０には

、針組立体６０を差し込むための差込口３２と、差し込まれた針組立体６０の抜けを防止する係止部３３とが設けられている。

【００１７】

本体部３０は、針組立体６０に対して回動自在に取り付けられている。回動自在にすることによって、本体部３０を針組立体６０に対して回動させて、初流血バッグ１６に対する蓋部材４０の位置などを簡単に微調整することができる。

【００１８】

針組立体６０は、先端に鋭利な針先を有する中空針６１と、血液取出チューブ１９に接続される接続部６２と、中空針６１の基端部を保持するボス部６３と、を有している。ハブ６４は、ボス部６３の径方向外方へ突出するように設けている。針組立体６０は、本体部３０の差込口３２に差し込むときにハブ６４が係止部３３を乗り越えて、本体部３０に取り付けられる。ハブ６４の図中上端は、差し込むときに係止部３３を乗り越え易いように傾斜面に形成されている。

【００１９】

本体部３０を針組立体６０に対して回動自在に取り付けるために、針組立体６０の接続部６２と本体部３０の差込口３２との間のクリアランス、およびハブ６４の外周と本体部３０との間のクリアランスの寸法が調整されている。

【００２０】

ゴムキャップ７０は、本体部３０に採血管５０を挿入させ、中空針６１をゴム栓５１に挿通させるのに伴って、弾性的に縮められて皺７１を生じながら中空針６１を露出させる。採血管５０を引き抜くと、ゴムキャップ７０は、縮んだ状態から、皺７１を伸ばすように弾性的に伸び、中空針６１に再び被せられる状態まで復元する。これによって、中空針６１からの血液の漏洩を防止する。

【００２１】

保持部８０は、中空針６１が挿通されるとともに針組立体６０のボス部６３に取り付けられたロック部材８１から構成されている。ロック部材８１は、中空針６１の基端部側が先端側よりも小径部となったアンダーカット形状を有している。ロック部材８１におけるアンダーカット形状によって、ゴムキャップ７０を保持している。

【００２２】

図５（Ａ）（Ｂ）を参照して、抑制部材９０は、本体部３０内に嵌り込む円盤形状の平板部９３と、平板部９３の中央部分において上部側に向けて突出する凸部９４とを有するプレート９２から構成されている。凸部９４に、ゴムキャップ７０が取り付けられた中空針６１が貫通する貫通孔９１が形成されている。図５（Ｃ）に示すように、平板部９３の外周縁には、径方向外方に突出するリング状突起９５が、平板部９３と一体的に設けられている。

【００２３】

図３および図４を再び参照して、プレート９２は、保持部８０をなすロック部材８１よりも上部側の位置において、本体部３０内に取り付けられている。本体部３０に採血管５０を挿入し、中空針６１をゴム栓５１に挿通させるのに伴って、ゴムキャップ７０は、弾性的に縮められて皺７１を生じながら中空針６１を露出させている。プレート９２の貫通孔９１とゴムキャップ７０との間のクリアランスＳは比較的小さい。したがって、プレート９２によって、ゴムキャップ７０が弾性的に縮められることによって生じる皺７１が保持部８０に達することが抑制される（図４）。

【００２４】

前述のように本体部３０は、針組立体６０に対して回動自在に取り付けられている。そして、本体部３０に固定されたプレート９２の貫通孔９１とゴムキャップ７０との間に、本体部３０の回動を許容するクリアランスＳを設定してある。クリアランスＳを本体部３０の回動を阻害しない寸法に設定することによって、針組立体６０に対する本体部３０の回動位置や、初流血バッグ１６に対する蓋部材４０の位置などを簡単に微調整することが可能となる。

【００２５】
プレート９２に凸部９４を備えさせることによって、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくすることができる。その結果、ゴムキャップ７０を針組立体６０に保持するための保持力の低下をより一層抑えることができる。プレート９２の配置位置を図４に示される位置から上部側にずらしても、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくすることができる。但し、この場合には、採血管５０の位置も上部側にずれるため、本体部３０の長手方向の長さ寸法を若干大きくする必要が生じる場合がある。したがって、プレート９２に本体部３０の開口部３１の側に向けて突出する凸部９４を備えさせることによって、本体部３０の長手方向の長さを維持したまま、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくして、ゴムキャップ７０を針組立体６０に保持するための十分な保持力を確保することが可能となる。

【００２６】
本体部３０、蓋部材４０、中空針６１を除いた針組立体６０、保持部８０、およびプレート９２の構成材料としては、特に限定されないが、例えば、ポリカーボネート、ポリエチレン、ポリプロピレン、エチレン－酢酸ビニル共重合体等のポリオレフィン、変性ポリオレフィンが挙げられる。

【００２７】
中空針６１の構成材料としては、特に限定されないが、例えば、ステンレス鋼、アルミニウムまたはアルミニウム合金、チタンまたはチタン合金、Ｎｉ－Ｔｉ合金等の超弾性合金等の各種金属材料、ポリフェニレンサルファイド等の各種硬質樹脂材料等が挙げられる。

【００２８】
また、ゴムキャップ７０の構成材料としては、特に限定されないが、例えば、天然ゴム、イソプレンゴム、ブタジエンゴム、スチレン－ブタジエンゴム、ニトリルゴム、クロロプレンゴム、ブチルゴム、アクリルゴム、エチレン－プロピレンゴム、ヒドリンゴム、ウレタンゴム、シリコーンゴム、フッ素ゴムのような各種ゴム材料が挙げられる。

【００２９】
図６（Ａ）（Ｂ）に、プレート９２を本体部３０に対して固定する様子が示される。本実施形態においては、本体部３０は、熱を印加したときにプレート９２を形成する樹脂材料よりも大きく収縮する樹脂材料から形成してある。滅菌のための熱を印加することによって、プレート９２を本体部３０に対して固定することができるからである。

【００３０】
さらに詳しくは、図６（Ａ）に示すように、熱を印加する前では、本体部３０の内径が比較的大きく、プレート９２のリング状突起９５が若干寸法だけ本体部３０に食い込んでいる。プレート９２を比較的簡単に本体部３０内に挿入できることから、プレート９２の組み込み作業を行いやすい。

【００３１】
そして、図６（Ｂ）に示すように、滅菌のために行われる例えば高圧蒸気滅菌法（オートクレーブ）における熱を印加すると、本体部３０がプレート９２よりも大きく収縮する。これによって、プレート９２のリング状突起９５が本体部３０にさらに食い込み、プレート９２を本体部３０に対して簡単に固定することができる。

【００３２】
上記のような樹脂材料の組み合わせ例として、例えば、本体部３０の成形材料としてポリプロピレンを適用し、プレート９２の成形材料としてポリカーボネートを適用することができる。

【００３３】
本実施形態の作用を説明する。

【００３４】
採血するときには、サンプリングポート２０の本体部３０に採血管５０を挿入し、中空

針６１をゴム栓５１に挿通させる。ゴム栓５１に中空針６１が挿通するのに伴って、ゴムキャップ７０は、弾性的に縮められて皺７１を生じながら中空針６１を露出させる。

【００３５】

図７（Ｂ）を参照して、プレート９２を設けていない対比例の場合には、採血管５０のゴム栓５１への中空針１６１の挿通に伴ってゴムキャップ１７０が弾性的に縮められることによって生じる皺１７１が、ゴムキャップ１７０の根元部に達することがある。このような場合には、ゴムキャップ１７０の根元部が膨らんでしまい、ゴムキャップ１７０を針組立体１６０に保持するための保持力が弱くなる。このため、採血管５０を引き抜くときにゴムキャップ１７０が一緒に引っ張られてしまい、ゴムキャップ１７０の位置などがずれてしまい、血液の漏洩の防止が不十分になる虞がある。

【００３６】

これに対して、図４および図７（Ａ）を参照して、本実施形態にあっては、プレート９２を、保持部８０をなすロック部材８１よりも上部側の位置において、本体部３０内に取り付けている。このプレート９２によって、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１がロック部材８１に達することが抑制される。ロック部材８１の部分でゴムキャップ７０が膨らむことがないので、ゴムキャップ７０を針組立体６０に保持するための保持力が弱くならない。

【００３７】

露出した中空針６１は、ゴム栓５１に挿通されて、採血管５０に採血する。採血後に採血管５０を引き抜くと、ゴムキャップ７０は、縮んだ状態から、皺７１を伸ばすように弾性的に伸び、中空針６１に再び被せられる状態まで復元する。これによって、中空針６１からの血液の漏洩を防止する。ゴムキャップ７０は、ロック部材８１の部分で針組立体６０に保持されている。

【００３８】

採血管５０のゴム栓５１の微小な挿通孔にゴムキャップ７０の先端部が食い込んだ状態で採血管５０を引き抜くと、ゴムキャップ７０が一緒に引っ張られる。しかし、ロック部材８１の部分は皺７１の影響を受けていないので、保持力は初期に設定したままである。このため、ゴムキャップ７０は、中空針６１から抜けずに、採血管５０のゴム栓５１への食い込みが解除される。これによって、ゴムキャップ７０の位置などがずれることがなく、血液の漏洩を十分に防止することが可能となる。

【００３９】

このように、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められて皺７１が生じても、ゴムキャップ７０を針組立体６０に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポート２０を提供できる。

【００４０】

また、本体部３０は針組立体６０に対して回動自在に取り付けられ、プレート９２は本体部３０に固定されており、貫通孔９１とゴムキャップ７０との間に本体部３０の回動を許容するクリアランスＳを有するため、針組立体６０に対する本体部３０の回動位置などを簡単に微調整することが可能となる。

【００４１】

また、プレート９２は、本体部３０の開口部３１の側に向けて突出する凸部９４を備えているため、本体部３０の長手方向の長さを維持したまま、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくして、ゴムキャップ７０を針組立体６０に保持するための十分な保持力を確保することが可能となる。

【００４２】

また、プレート９２の外周縁に径方向外方に突出するリング状突起９５を設けているため、リング状突起９５を若干寸法だけ本体部３０に食い込ませるようにしてプレート９２を本体部３０内に挿入させることができ、簡単にプレート９２の組み込み作業を行うこと

が可能となる。

【００４３】

また、本体部３０は、熱を印加したときにプレート９２を形成する樹脂材料よりも大きく収縮する樹脂材料から形成されており、滅菌のための熱を印加することによって、プレート９２を本体部３０に対して固定するため、熱を印加する前ではプレート９２を比較的簡単に本体部３０内に挿入でき、プレート９２の組み込み作業を行いやすい。一方、滅菌のための熱を印加すると、本体部３０がプレート９２よりも大きく収縮する。これによって、プレート９２を本体部３０に対して簡単に固定することができる。

【００４４】

（プレートの改変例）

プレートは、ゴムキャップ７０が取り付けられた中空針６１が貫通する貫通孔９１を備え、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１が保持部８０に達することを抑制する限りにおいて適宜の形状に改変することができる。

【００４５】

例えば、図８を参照して、凸部９４を平板部９３から滑らかに突出させたプレート９２ａ（図８（Ａ））、全体の厚みを厚くし上面を平坦面としたプレート９２ｂ、９２ｃ（図８（Ｂ）（Ｃ））、本体部３０の底面全体を覆わずに保持部８０に被せるようなキャップ形状を有するプレート９２ｄ（図８（Ｄ））などを例示することができる。

【００４６】

また、図９を参照して、平板部９３に貫通部を形成しないタイプのプレート９２ｅ（図９（Ａ））、平板部９３に貫通部９６を形成したタイプのプレート９２ｆ（図９（Ｂ））とすることもできる。

【００４７】

（その他の改変例）

ゴムキャップ７０を保持する保持部８０として、アンダーカット形状を有するロック部材８１を例示したが、保持部８０はこの場合に限定されるものではない。保持部８０は、針組立体６０に設けられゴムキャップ７０の抜けを防止して保持する機能を有している限りにおいて適宜改変することができる。例えば、保持部８０は、接着剤によってゴムキャップ７０を中空針６１に接着させて保持する形態、超音波融着によってゴムキャップ７０を中空針６１に融着させて保持する形態、クリップなどを用いた嵌め込みによってゴムキャップ７０を中空針６１に保持する形態などを例示することができる。これらの保持部８０を単独で用いてもよいし、２種以上を組み合わせた保持部８０であってもよい。

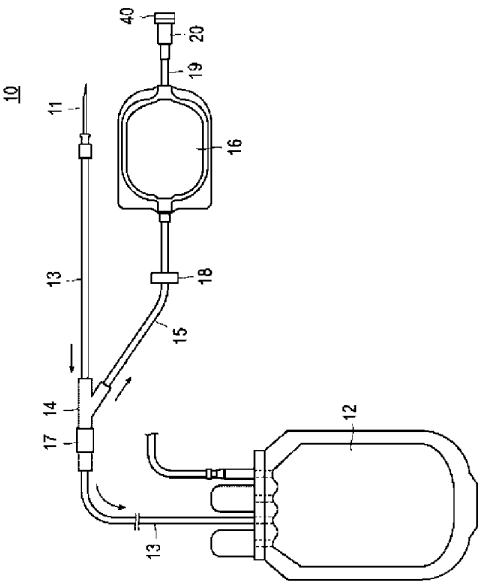
【符号の説明】

【００４８】

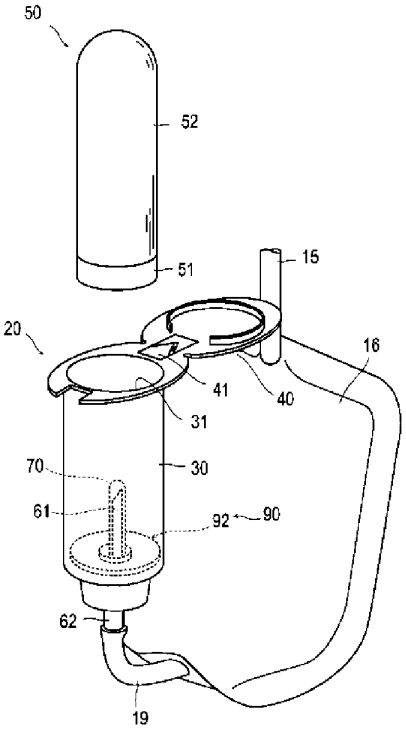
２０　サンプリングポート、
３０　本体部、
３１　開口部、
５０　減圧採血管（採血管）、
５１　ゴム栓、
６０　針組立体、
６１　中空針、
６４　ハブ、
７０　ゴムキャップ、
７１　皺、
８０　保持部、
８１　ロック部材、
９０　抑制部材、
９１　貫通孔、
９２　プレート（抑制部材）、

９３　　平板部、
９４　　凸部、
９５　　リング状突起、
Ｓ　　クリアランス。

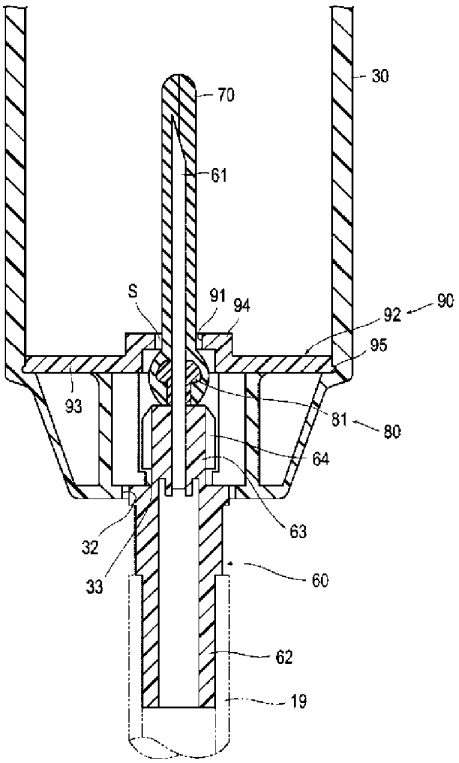
【図１】



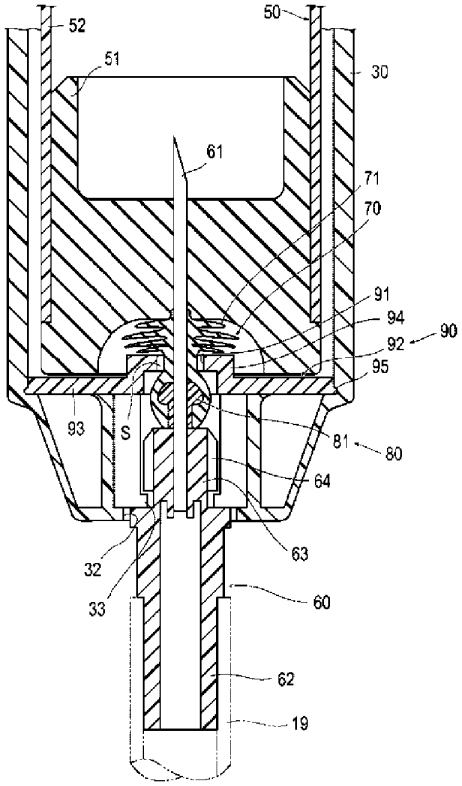
【図２】



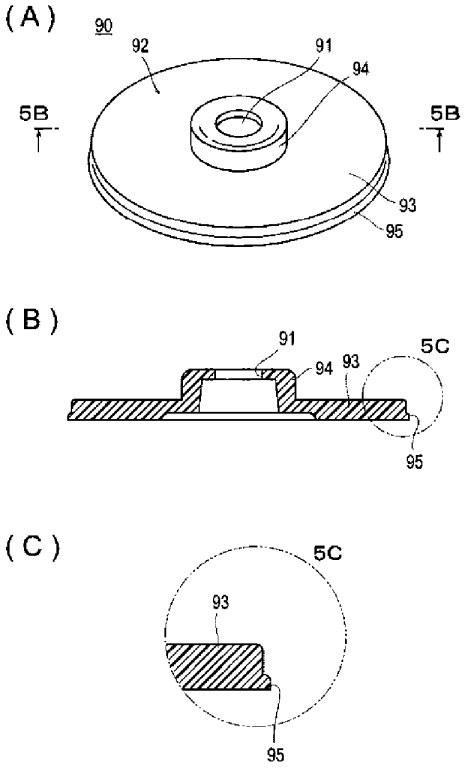
【図３】


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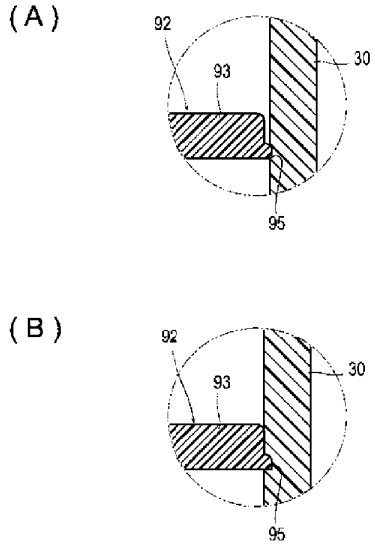
【図４】


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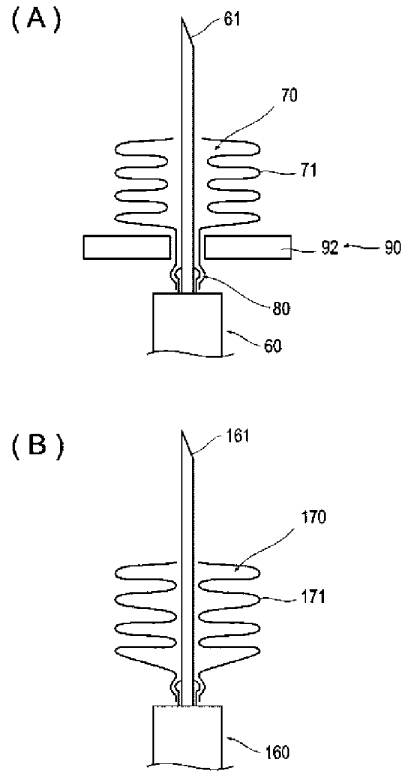
【図５】


(A)
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94
5B
5B
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(B)
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94
93
5C
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(C)
5C
93
95

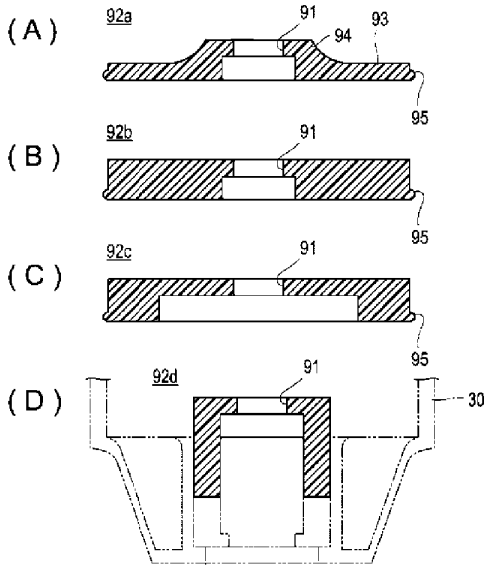
【図６】


(A)
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93
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(B)
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93
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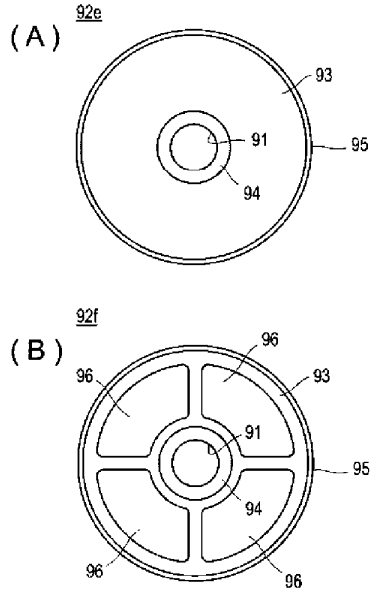
【図７】


(A)
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(B)
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【図８】


(A)
92a
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94
93
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(B)
92b
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95
(C)
92c
91
95
(D)
92d
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【図９】


(A)
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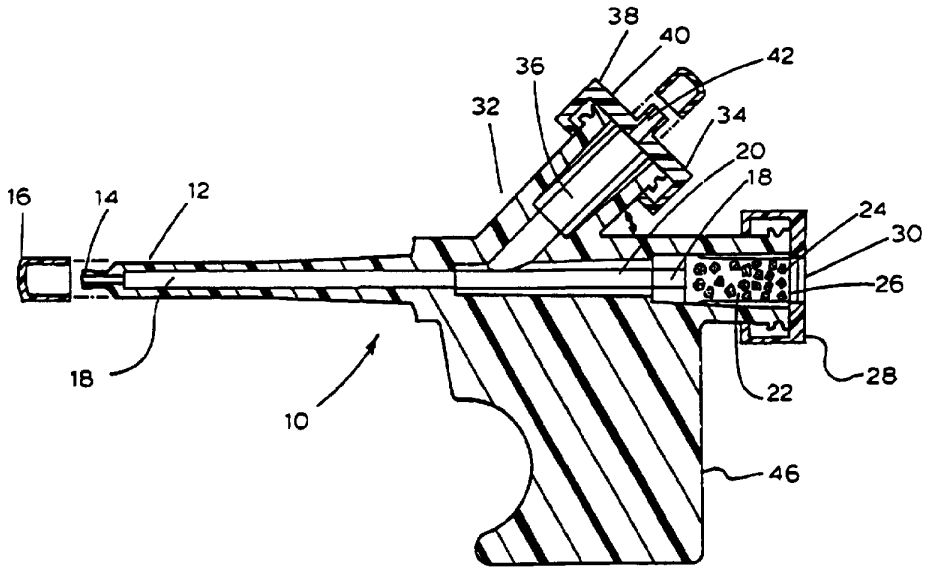
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(57) Abstract

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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CLOSED SYSTEM BLOOD SAMPLING DEVICE

FIELD OF THE INVENTION

The invention relates to closed system blood sampling devices.

BACKGROUND OF THE INVENTION

Arterial blood gas sampling is a standard procedure often used to help assess respiratory function in the critically ill. In some cases, samples can be drawn as many as 20 times a day. For the typical neonatal patient weighing 1000 grams and having approximately 85 cc of total body fluid capacity, the volume of blood samples becomes a critical factor.

A technique called the 3 drop method is gaining substantial clinical acceptance in neonatal units across the country. This method calls for inserting a blunt hypodermic needle as far as possible into a standard sleeve stoppered T-Connector. Three drops of blood estimated to be approximately .06 cc are allowed to drip onto a gauge pad, thereby clearing the cannula of heparinized or non-circulating blood while providing a fresh arterial sample to the surface. 3 more drops are then collected in a micro container followed by cannula withdrawal. Blood cannula contents within the cannula lumen and the previously collected micro container sample are then aspirated into a tuberculin type syringe for transport to the blood lab for testing. A flush of the T-Connector to eliminate residual blood then ensues. This procedure provides the ability to withdraw a controlled blood volume; .06 cc as necessary

discard and .12 cc to perhaps .20 cc for actual blood gas testing.

Several opportunities for procedural improvement exist. One challenge is the open environment method of collection which could foster blood contamination and/or the spread of infectious diseases. Secondarily, the collection process in regard to volume accuracy is difficult to control and highly sensitive to variations in clinician technique, catheter positioning and arterial pressure. If a device can be designed for closed system collection which could also insure consistency of sample volume time after time, treatment of neonatal patients where blood volume levels are critical, accuracy improvements could be a major clinical benefit.

THE DRAWINGS

Fig. 1 is a horizontal cut away side view showing the closed system blood sampling device of the invention.

Fig. 2 is a vertical, partial schematic view showing the closed system blood sampling device connected to an injection site which, in turn, is fitted into a venipuncture device used to withdraw arterial blood.

In the drawings, like parts have like numbers.

THE INVENTION

The invention is a closed system blood sampling device comprising a bifurcated capillary tube which has a first branch having a cannula shaped end for withdrawing and conveying blood to a communicating blood collection zone. The blood

collection zone is for storing a quantity of withdrawn blood. It also feeds an initial fraction of withdrawn blood to a communicating blood disposal chamber which has an air permeable liquid sealed end.

The second branch of the bifurcated capillary tube 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.

In preferred embodiments the closed system blood sampling device the cannula shaped end is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and the blood disposal chamber contains a porous blood adsorbent. The second branch has an interior angle not greater than 90 degrees and preferably the interior angle is 60 degrees. It is also desirable that the cannula shaped end be tapered so that it snugly fits into the preferred injection sites more fully described hereafter.

Preferably, the closed system blood sampling device is removed from the injection site before the blood sample is withdrawn therefrom by means such as a tuberculum syringe or aspirated directly into a blood gas analyzer.

While the closed blood sampling device is particularly suited for obtaining neonatal blood samples it is readily adapted to obtain samples from a variety of patient types.

DETAILED DESCRIPTION OF THE INVENTION

In Fig. 1 the closed system blood sampling device is designated generally by the numeral 10. It is preferably constructed of a clear chemically inert non-toxic plastic such as polycarbonate. It comprises a blood withdrawal cannula shaped end 12. The cannula tip 14 is blunt and necked down to prevent injection site from blood flash back during arterial sampling. To maintain sterility the cannula tip is fitted with a removable cap 16 which is removed just before the blood sampling device is to be used.

Fig. 1 shows the cannula shaped end 12 to be tapered. This particular configuration was selected so that the cannula may engage and generally mate with a particular injection site, the details of which will be more fully described hereafter. The interior bore 18 of the cannula shaped end is dimensioned to allow withdrawn blood to move along the bore by means of capillary action driven by normally positive arterial blood pressure.

The interior capillary bore 18 connects with and continues into a larger outer diameter lumen 20. The continuous bore 18 of the cannula 12 and the lumen 20 comprise a blood collection zone. Bore 18 as it exits the lumen 20 empties into blood disposal chamber 22. In a preferred embodiment of the invention, blood disposal chamber 22 contains a blood retaining means such as adsorbing material 24 which may be rayon or cellulosic wadding. The open end 26 of the blood disposal

chamber 22 is closed with a cap 28 that has its top fitted with a liquid tight, air permeable hydrophobic membrane 30 which allows air to be evacuated from the blood sampling device 10 of the invention. A suitable membrane material is sheet polytetrafloroethylene having a thickness of about 0.8 microns.

Fitted to the lumen 20, and in fluid communication therewith, is the second branch or port 32. It is positioned so as to have an interior angle 34 not exceeding 90 degrees. The interior angle is preferably about 60 degrees. The bore 36 connects with and corresponds in dimension with bore 18. Port 32 terminates and is sealed by adapter cap 38 whose top 40 is fitted with a capillary luer 42. The capillary luer is protected from contamination by means of protective cap 44 which is removed just prior to blood being withdrawn from the closed blood sampling device. The port 32 and its bore 36 form a part of the blood collection zone previously described. For convenience of use, the closed blood sampling device is fitted with pistol grip handle 46.

The blood collection zone has a larger liquid capacity than the liquid capacity of the blood disposal chamber. If the closed blood sampling device described were to be used in neonatal blood sampling, the liquid capacity of the blood collection zone might be 0.12 cc and the liquid capacity of the blood disposal chamber 22 would be about 0.06 cc.

The use of the closed blood sampling device of the invention to withdraw and sample blood is illustrated in Fig. 2 which shows artery 48 in communication with a venipuncture

device 50 which was inserted through subcutaneous tissue 52. The neck 54 of the venipuncture device 50 is adapted to receive an injection site 56. While conventional injection sites may be used as such or adapted to be used in the practice of the invention, it is preferred that the injection site be of the type having a resilient resealable septum which is preferably pre-slit. An injection site of this type is available from Baxter Healthcare Corporation and is a Neonatal T-Connector Luer sold under the brand name, InterLink, a registered trademark of Baxter Healthcare Corporation.

Such pre-slit, resilient, resealable injection sites and their method of fabrication are described in U.S. 5,188,620 the disclosure of which is incorporated herein by reference. The pre-slit resilient resealable injection sites described in this patent are designed to receive blunt cannulas. Another injection site related to the injection sites detailed in U.S. 5,188,620 is described in U.S. 5,300,034. This patent also details numerous publications and references which describe the preferred injection sites used in the practice of this invention. This patent and the publications listed therein also are incorporated herein by reference.

The injection site 56 is fitted with T-connector 58 which, in turn, is fitted with microbore tubing which, through female luer 62, is connected to IV line 64. The distal end 64 of the injection site 56 is connected to the neck 54 of the venipuncture device 50. The proximal end 66 of the injection site 56 is fitted with a pre-slit resilient resealing septum 68 adapted to receive

the blood withdrawal cannula 12 which is dimensioned to fit snugly into the injection site. Inserted into the second branch or port 32 is a conventional syringe 70, such as a tuberculum blood draw syringe, or an arterial blood gas loss of resistance syringe.

The device's cannula 12 would be inserted through the septum 68 of the injection site 56 and positioned so that the tip 14 of the cannula 12 was fully inserted into the injection site adjacent to the venipuncture device. In doing so, the residual volume of the actual T-Housing would be eliminated as a measurable factor in blood draw volume. Arterial pressure would cause blood flow to enter and flow up the device via capillary action. As blood moved up the hydrophobic membrane 30 of the device, air would escape via the upstream hydrophobic membrane 30. Original blood first present in the catheter would be pushed beyond the luer bifurcation for retention in the device and eventual disposal. The device would be withdrawn from the T-Connector as soon as visual confirmation of the blood filled lumen was made. The vented removal cap 44 would be removed from the bifurcated luer 42 and replaced by the syringe 70 which would be aspirated to remove the arterial blood sample. Residual blood volume upstream of the bifurcation would remain in the device for subsequent disposal.

WE CLAIM:

1. A closed system blood sampling device comprising a bifurcated capillary tube comprising:

a. a first branch having a cannula shaped end for withdrawing and conveying blood to a communicating;

b. blood collection zone for storing a quantity of withdrawn blood and feeding an initial fraction of withdrawn blood to a communicating;

c. blood disposal chamber having an air permeable liquid sealed end; and,

d. a second branch connected to and in fluid communication with the blood collection zone which terminates in an opening adapted to receive a blood withdrawal device.

2. The closed system blood sampling device of Claim 1 where the cannula shaped end is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and the blood disposal chamber contains a porous blood adsorbent.

3. The closed system blood sampling device of Claim 1 where the second branch has an interior angle not greater than 90 degrees.

4. The closed system blood sampling device of Claim 3 where the second branch has an angle of about 60 degrees.

5. The closed system blood sampling device of Claim 2 where the cannula shaped end is tapered.

6. The closed system blood sampling device of Claim 2 where the blunt cannula shaped end is adapted to be received by a injection site which contains a resilient resealing means.

7. The closed system blood sampling device of Claim 6 where the injection site is a pre-slit injection site.

8. The closed system blood sampling device of Claim 2 where the blood collection zone has a volume greater than the volume of the blood disposal chamber.

9. A method of sampling blood from a patient having an artery fitted with a venipuncture device which is attached to an injection site containing the closed blood sampling device of Claim 1 which comprises the steps of:

a. withdrawing blood through the cannula shaped end of the closed blood sampling device thereby sequentially filling the blood disposal chamber and then the blood collection zone;

b. withdrawing through the opening in the second branch the blood contained in the blood collection zone for subsequent processing; and, then,

c. discarding the closed system blood sampling device

10. The method of Claim 9 where the cannula is blunt, the blood disposal chamber has its end fitted with a cap containing an air permeable hydrophobic membrane, and contains a porous blood adsorbent.

11. The method of Claim 9 where the second branch has an interior angle not greater than 90 degrees.

12. The method Claim 11 where the second branch has an angle of about 60 degrees.

13. The method of Claim 10 where the cannula shaped end is tapered.

14. The method of Claim 10 where the blunt cannula shaped end is adapted to be received by a injection site which contains a resilient resealing means.

15. The method of Claim 14 where the injection site is a pre-slit injection site.

16. The method of Claim 10 where the blood collection zone has a volume greater than the volume of the blood disposal chamber.

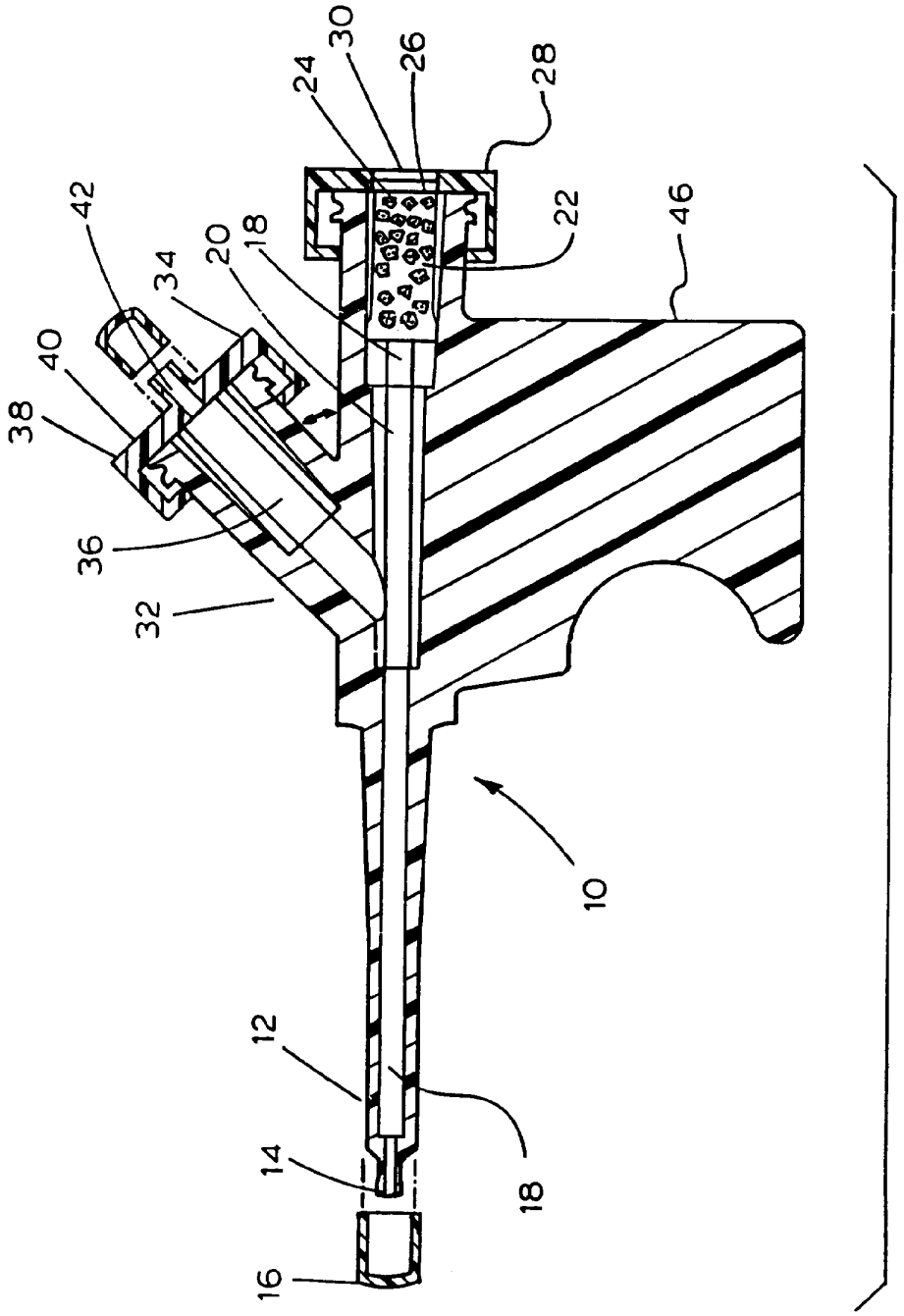


FIG. 1

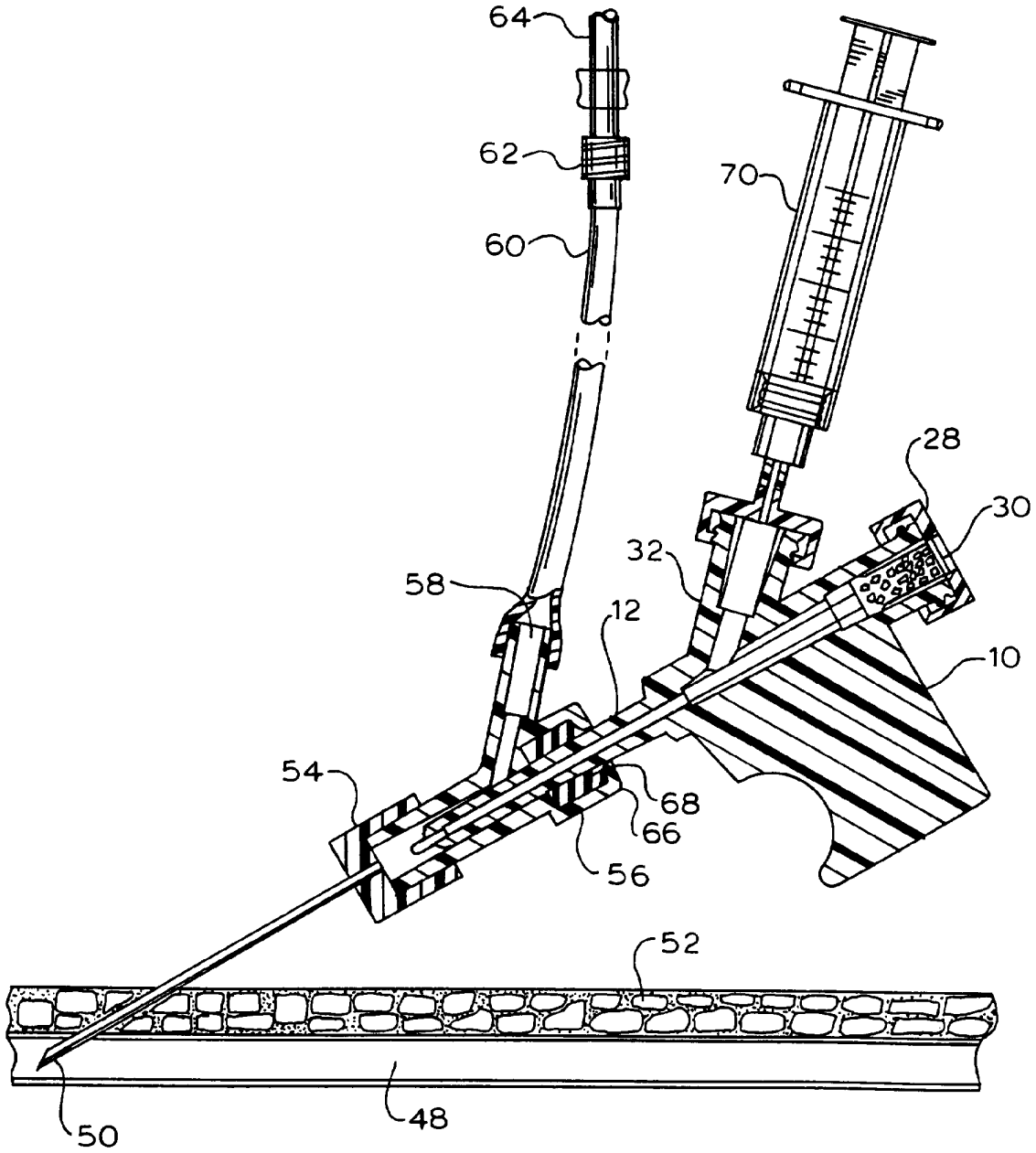


FIG. 2

SUBSTITUTE SHEET (RULE 26)

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
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"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
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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)★

Bibliographic data: DE10038026 (A1) — 2001-02-22

Blood extractor for patient has extraction container with needle housing to receive retractable hollow needle to extract blood

Inventor(s):

Applicant(s): ZIERDEN PETER [DE] ± (ZIERDEN, PETER)

Classification: - **international:** ***A61B5/15;*** (IPC1-7): A61B5/15; A61M1/00
- **cooperative:** **A61B5/15003 (EP)**; **A61B5/150152 (EP)**; **A61B5/150389 (EP)**; **A61B5/150503 (EP)**; **A61B5/150656 (EP)**; **A61B5/150732 (EP)**; **A61B5/153 (EP)**; **A61B5/155 (EP)**; A61B5/150748 (EP)

Application number: DE20001038026 20000802

Priority number(s): DE20001038026 20000802 ; DE19992013417U 19990806

Also published as: DE29913417 (U1)

Abstract of DE10038026 (A1)

The blood extractor has a housing (1) with a hollow needle (10) extending through the wall of the patients blood vessel (B) to aspirate blood from it. The needle can move between a retracted position in which it is behind the surface of the housing and an extended position in which the end of the needle extends from the housing.

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DESCRIPTION DE10038026A1

[0001]

13 The invention relates to a device for removing blood from a blood vessel of the type corresponding to the preamble of claim 1.

[0002]

18 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 .

[0003]

25 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.

[0004]

32 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.

35 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.

[0005]

41 For the latter reason, it is also known to pre-evacuate the vessels that have the volume for receiving the blood taken and to seal them with a closure or

43 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.

[0006]

49 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.

[0007]

57 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.

[0008]

62 This object is solved by the invention presented in claim 1.

[0009]

66 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.

74 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.

76 The risk of "wobbling" during insertion of the hollow needle is therefore significantly reduced.

77 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.

80 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.

[0010]

87 The means with which the hollow needle can be displaced from its retracted into its extended position preferably have an arrangement which exerts an elastic force on the hollow needle acting in the direction of the retracted towards the extended position.

90 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.

[0011]

98 In terms of its design, the arrangement for generating the elastic force can have a compression spring.

[0012]

103 However, it is also possible to generate the elastic force with the help of a compressed air reservoir or in a completely different way.

[0013]

108 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.

110 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.

[0014]

115 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.

119 With this configuration, depending on the requirements, either a plurality of containers can be connected to the adapter at the same time or--if this is not desired or possible--a plurality of containers can also be connected one after the other.

[0015]

125 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.

127 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.

[0016]

134 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.

[0017]

141 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.

145 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.

148 Because the suction in this preferred embodiment of the invention already exists when the hollow needle enters 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 into the vessel has penetrated or partially exited the opposite vessel wall.

152 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.

[0018]

158 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.

162 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.

[0019]

167 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.

[0020]

176 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.

[0021]

182 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, in a particularly preferred 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 thus from is positioned on the lateral boundary surfaces of the recess.

[0022]

190 If blood from a patient is used to carry out various diagnostic or

191 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.

[0023]

197 The inner volumes or the containers can then optionally communicate with one another in series or also in parallel.

[0024]

202 In the drawing, exemplary embodiments of the invention are shown schematically.

203 Show it:

[0025]

207 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;

[0026]

212 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.

[0027]

217 FIG. 3--in a detail--the same exemplary embodiment as in FIG. 1 in a partially sectional plan view (view A in FIG. 1);

[0028]

222 FIG. 4 shows another embodiment of a device according to the invention in a view corresponding to FIG. 3;

[0029]

227 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;

[0030]

233 6 - schematically - different positions of the beveled end of the hollow needle relative to the position of the blood vessel;

[0031]

238 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);

[0032]

244 8 shows an embodiment of a device according to the invention in a view corresponding to FIG

[0033]

248 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.

[0034]

254 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.

258 The housing 1 has, on its end face 5 pointing downwards in FIG. 1, a housing extension 6, the end 7 of which shown at the bottom in FIG. 1 is open.

[0035]

263 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.

[0036]

271 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 .

[0037]

276 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.

[0038]

281 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 .

[0039]

286 Furthermore, in the side wall of the housing extension 6 shown on the right in FIG.

[0040]

290 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 is released.

293 Due to the force exerted by the spiral spring 14 on the hollow needle arrangement 9, the latter snaps down according to FIG.

295 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.

[0041]

301 As can also be seen from FIG.

[0042]

305 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

308 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.

310 Fig. 6e)).

[0043]

314 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.

319 The cuff 24 and the housing extension 6 can be equipped with locking 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 adapted to the conditions usual in children, normal-weight adults or overweight adults .

[0044]

326 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.

[0045]

334 In principle, it is possible for the hollow needle 10 to pierce the blood vessel B essentially perpendicularly to its course.

336 However, such a procedure presupposes that the "penetration depth" must be predetermined almost exactly.

338 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°.

340 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.

342 In the exemplary embodiments shown in the drawing, the angle α is fixed.

343 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.

[0046]

348 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.

351 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.

[0047]

357 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.

363 5).

[0048]

367 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.

369 Thus, several volumes 28, 29, 30--three in FIG.

[0049]

373 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.

[0050]

379 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.

382 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.

[0051]

387 In the exemplary embodiment shown in FIG. 9, the volumes 34, 35 provided for receiving the blood removed are arranged externally and designed as piston/cylinder units 36/37 in such a way that the pistons 36 can be displaced into the cylinder 37 by manually operable piston rods 38 .

391 To attach the piston/cylinder unit 36/37 to this device, which is designated as a whole by 200, an adapter arrangement 39 is used, from which the housing extension 206 in turn extends downward according to FIG.

394 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.

397 Reference List

[0052]

401 The blood is taken in the device according to FIG. 9 in a manner already described with reference to FIGS. 1 to 3, whereby by pulling out the piston rods 38 into the position shown in FIG Cylinder 37 are held against the action of the negative pressure created prior to the needle propelling and penetrating the blood vessel.

1

408 Housing2 Channel3 Internal volume4 Internal volume5 Front side6 Housing extension7 End8 Interior9 Hollow needle arrangement10 Hollow needle11 Hollow needle carrier12 Inner lateral surface13 Front side14 Spiral spring15 Contact surface .16 Locking device17 Contact surface18 Inner channel19 Tip20 Opening21 Channel22 End23 Stop24 Cuff25 Contact surface26 Compressed air reservoir27 Recess28 Volume29 Volume30 Volume31 Volume32 Volume33 Volume34 volume 35 volume 36 piston 37 cylinder 38 piston rod 39 adapter assembly 40 locking projections 100 device 206 housing extension 209 hollow needle assembly 202 channels H skin B Blood vessel A view P arrow

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CLAIMS DE10038026A1

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 the connection of at least one container, the internal volume (34, 35) of which is used to hold the 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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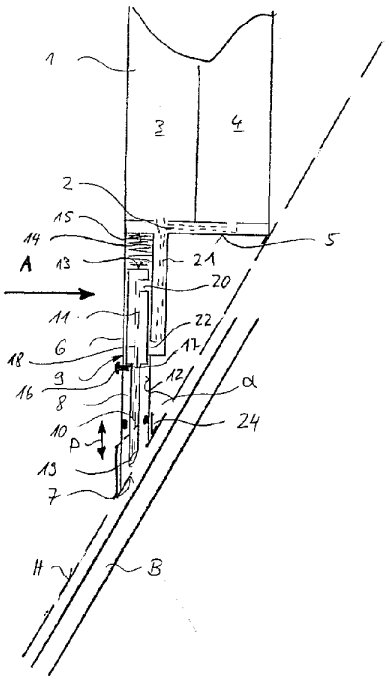
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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) Vorrichtung zur Entnahme von Blut aus einem Blutgefäß

(57) Die Vorrichtung umfaßt ein Gehäuse mit einer durch die Blutgefäßwandung ins Innere des Blutgefäßes einführbaren Hohlnadel und Mittel zum Saugen des Blutes durch das Innere der Hohlnadel.
Zwecks Blutentnahme aus einem Blutgefäß in für den Patienten weniger schmerzhafter Weise ist die Hohlnadel zwischen einer zurückgezogenen Position, in der die Hohlnadel zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß einführende Ende der Hohlnadel aus dem Gehäuse um eine Länge hervorragt, verlagerbar angeordnet. Ferner sind Mittel vorgesehen, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist.



DE 100 38 026 A 1

Beschreibung

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, weisen 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 Kindern, 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/Zylindereinheiten **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
2 Kanal
3 Innenvolumen
4 Innenvolumen
5 Stirnseite
6 Gehäusefortsatz
7 Ende
8 Inneres
9 Hohlnadelanordnung
10 Hohlnadel
11 Hohlnadelträger
12 innere Mantelfläche
13 Stirnseite
14 Spiralfeder
15 Anlagefläche
16 Arretiereinrichtung
17 Anlagefläche
18 Innenkanal
19 Spitze
20 Öffnung

21 Kanal
22 Ende
23 Anschlag
24 Manschette
25 Anlagefläche
26 Druckluftreservoir
27 Aussparung
28 Volumen
29 Volumen
30 Volumen
31 Volumen
32 Volumen
33 Volumen
34 Volumen
35 Volumen
36 Kolben
37 Zylinder
38 Kolbenstangen
39 Adapteranordnung
40 Arretiervorsprünge
100 Vorrichtung
206 Gehäusefortsatz
209 Hohlnadelanordnung
202 Kanäle
H Haut
B Blutgefäß
A Ansicht
P Pfeil

Patentansprüche

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 (**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 Abstützung 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.

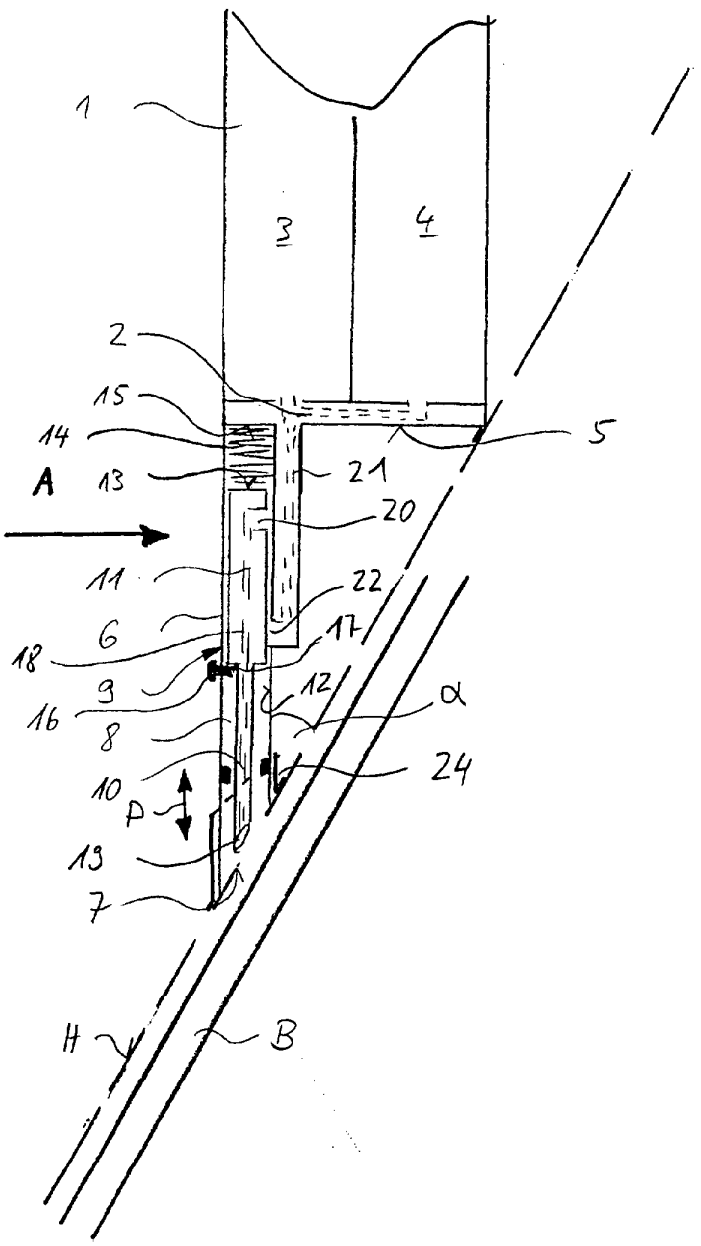
17. Vorrichtung nach Anspruch 15, dadurch gekennzeichnet, daß die Innenvolumina (**31**, **32**, **33**) oder die Behälter parallel miteinander kommunizieren.

Hierzu 6 Seite(n) Zeichnungen

- Leerseite -

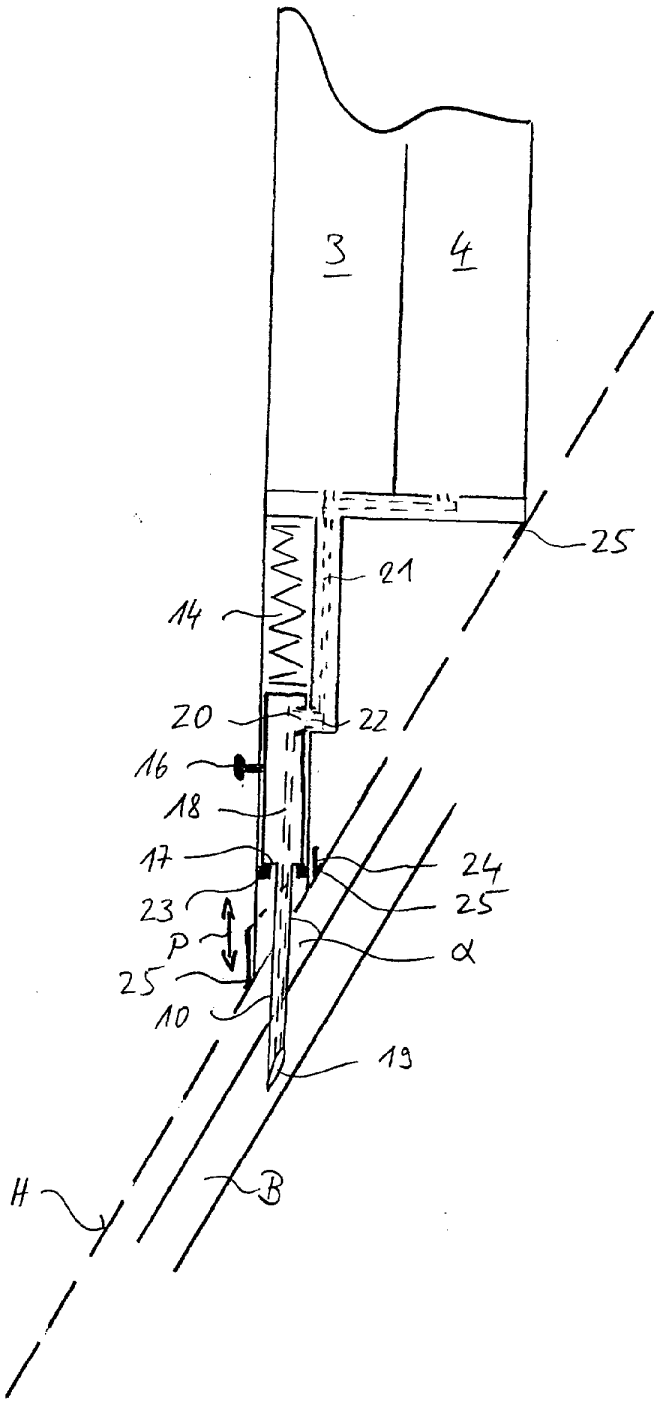
Nummer: **DE 100 38 026 A1**
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Fig. 1



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Fig. 2



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Fig. 3

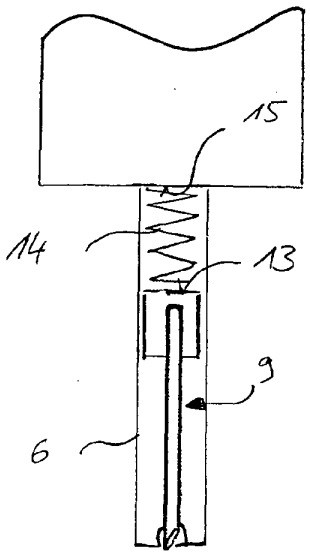
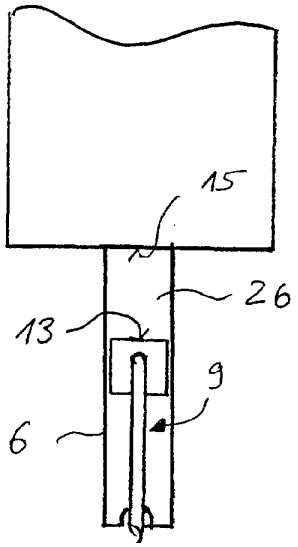


Fig. 4



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Offenlegungstag: 22. Februar 2001

Fig. 5

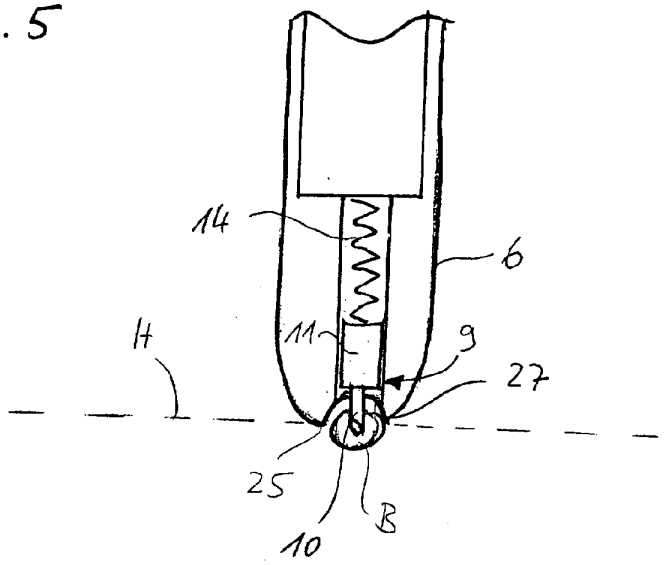
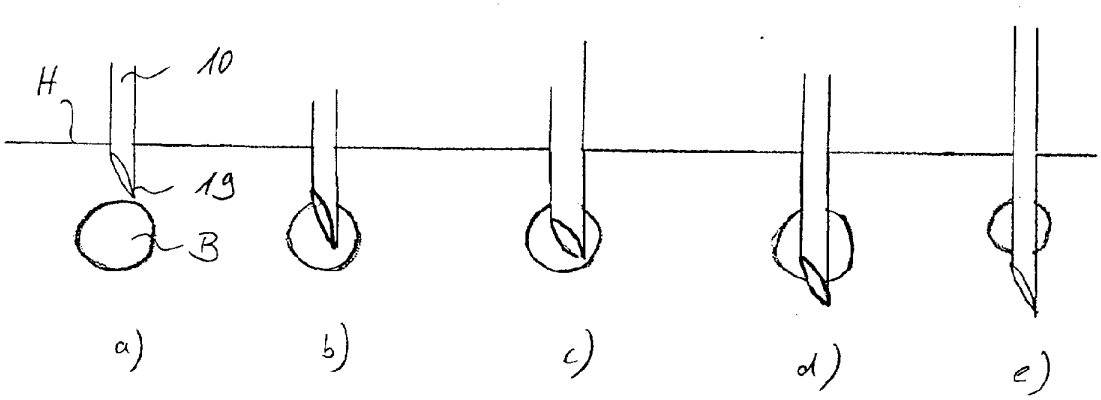


Fig. 6



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Fig. 7

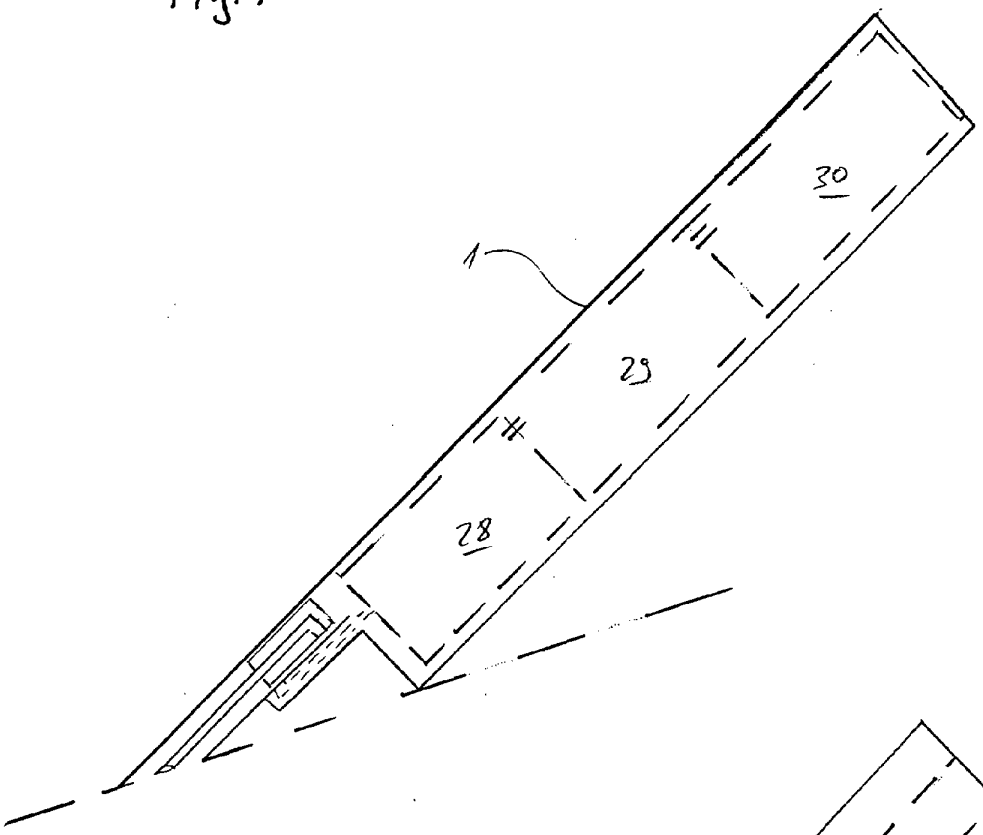
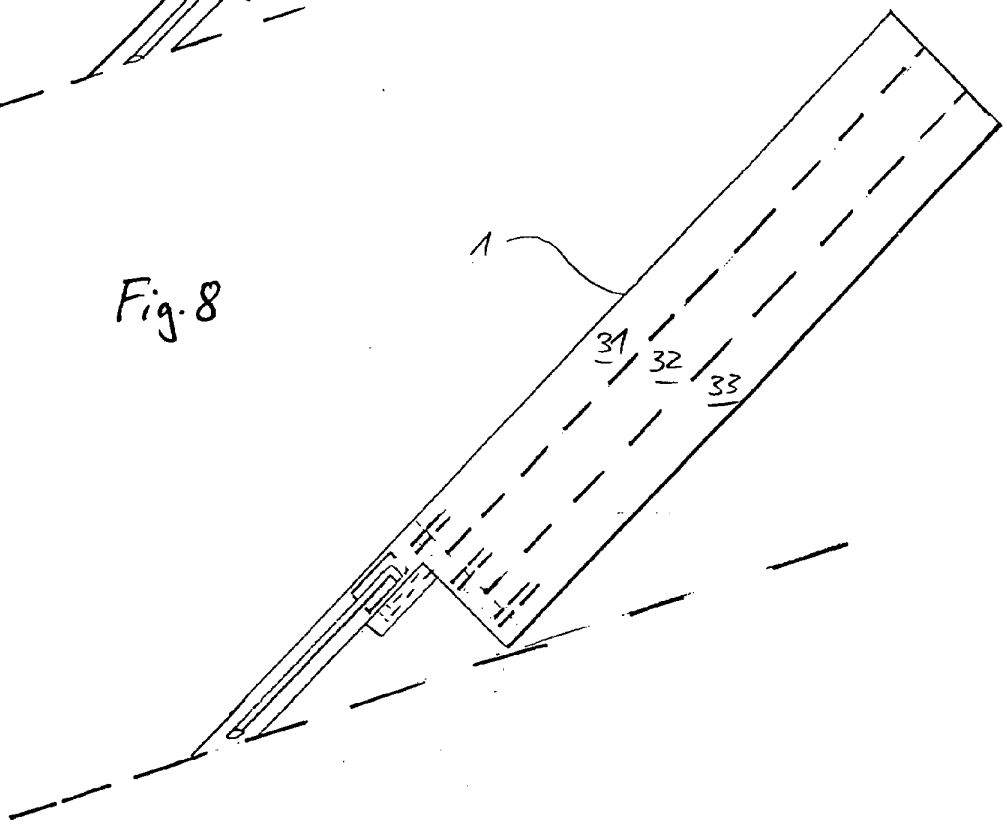
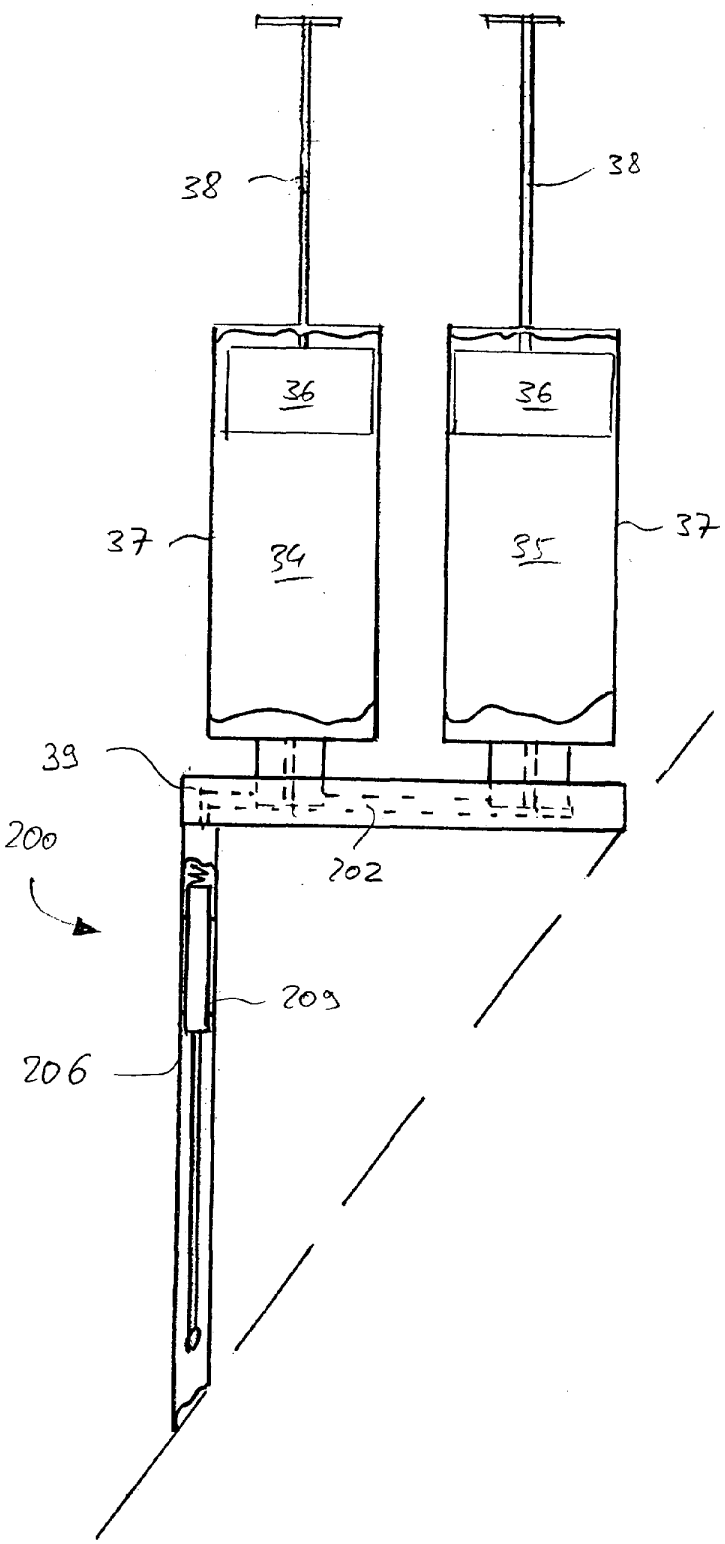


Fig. 8



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Fig. 9



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Karasawa [Examiner] Nobuhide Kato

(56) [Reference]
[Reference] Japanese Unexamined Patent Publication No. 2000-228126 (JP, A) [Reference] Japanese Unexamined Patent Publication No. 2007-076491 (JP, A) [Reference] Japanese Utility Model Laid-Open No. 61-161852 (JP, U) [Reference] JP-A-06-156114 (JP, A) (58) [Field investigated] (Int.Cl., DB name) B60R 16/02 B60R 16/027

The scope of the claims open ---

(57) [Scope of Claims]

[Claim 1] A sensor

having a plurality of detection areas and is mounted in a predetermined range of a grip portion of a steering wheel of a vehicle so as to cover the grip portion gripped by the driver. a sensor data generation unit that generates sensor data including position data indicating which detection area is being touched based on a contact detection signal obtained from the touch sensor

; a detection unit that detects whether or not the grip is gripped and an input operation to the touch sensor; the detection unit

detects that the driver is gripping the grip, and the touch sensor detects a control unit that controls an operation target device to be operated by the touch sensor in response to the specific input operation when it is detected that a specific input operation has been performed on the control device

; A control device for an operation target device in

a vehicle, characterized in that , when a direction indicator is operated , the vehicle is in a specific state , and the section disables control of the operation target device. 2. A contact detection signal obtained from a touch sensor which has a plurality of detection areas and is mounted in a predetermined range of a grip portion of a steering wheel of a vehicle so as to cover the grip portion gripped by the driver. a sensor data generator that generates sensor data including position data indicating which detection area is being touched, based on

a detection unit that detects whether or not the driver is gripping the grip based on the sensor data and an input operation to the touch sensor

; and when it is detected that a specific input operation has been performed on the touch sensor, the operation target device to be operated by the touch sensor in response to the specific input operation. and a control unit for controlling the operation target device,

wherein

the control unit invalidates the control of the operation target device by determining that the vehicle is in a specific state when the shift position of the shift lever is reversed. A control device for an operation target device in a vehicle. 3. The touch sensor includes a part of the plurality of detection areas and includes a grip detection area for detecting contact of a driver's palm and another part of the plurality of detection areas, and includes a grip detection area for detecting contact with the driver's palm. and an operation detection area for detecting the specific input operation caused by the contact of the grip detection area, and the detection unit detects when the driver grips the grip based on sensor data based on the contact detection signal obtained from the grip detection area. 3. The specific input operation is detected by sensor data based on a contact detection signal obtained from the operation detection area . Con

trol device. [Claim 4]

Based on a contact detection signal obtained from a touch sensor that has a plurality of dete ction areas and is attached to a predetermined range of a grip portion gripped by a driver on a steering wheel of a vehicle so as to cover the grip portion. a sensor data generation unit tha t generates sensor data including position data indicating whether a detection area is being to uched; and based on the sensor data, whether or not the driver is gripping the grip and the to uch

sensor a detection unit that detects an input operation to the touch sensor, and the

detection unit detects that the driver is gripping the grip, and detects that a specific input op eration has been performed on the touch sensor and a control unit

that controls an operation target device to be operated by the touch sensor in response to th e specific input operation, wherein the touch sensor includes a part of the plurality of detectio n areas

. , a grip detection area for detecting the contact of the driver's palm, and an operation dete ction area for detecting the specific input operation by finger contact, including other parts of the plurality of detection areas, are set,

The detection unit detects whether or not the driver is gripping the grip by sensor data base d on the contact detection signal obtained from the grip detection area, and the sensor based on the contact detection signal obtained from the operation detection area. A control device fo r an operation target device in a vehicle, wherein the specific input operation is detected by d ata, and the

control unit disables control of the operation target device when the vehicle is in a specific st ate.

5.

The controller controls, as the specific input operation, two points spaced apart in the circum ferential direction in a cross section of the steering wheel when the grip is cut in the radial dir ection with respect to the operation detection area. is operated with two fingers to control the operation target device5. The control device for an operation target device in a vehicle accordi ng to claim 3 or 4, characterized in that :

6.

The controller determines that the vehicle is in a specific state when the rotation angle of th e steering wheel exceeds a predetermined angle, and invalidates the control of the device to b e operated . A control device for an operation target device in a vehicle according to any one of claims 1 to 4 .

7.

The touch sensor comprises a first touch sensor mounted in a predetermined range of the gr ip portion gripped with the left hand of the driver and a second touch sensor mounted in a pre determined range of the grip portion gripped with the right hand of the driver. a touch sensor;

The control unit controls, as the specific input operation, the operation target device accordi ng to a pattern of a combination of a first input operation on the first touch sensor and a seco nd input operation on the second touch sensor. The control

device for an operation target device in a vehicle according to any one of claims 1 to 6, char acterized in that it controls the

8.

A driver grips a touch sensor which has a plurality of detection areas and is mounted within a predetermined range of a grip of a steering wheel of a vehicle so as to cover said grip. detec ting whether or not

a specific input operation has been performed on the touch sensor; detecting whether or not a direction indicator has been operated; When it is detected that the driver is not in a specifi c state, it is detected that the driver is gripping the touch sensor, and it is detected that the s pecific input operation is performed, the touch sensor detects An operation target device to be operated is controlled , and control of the operation target device is disabled when it is detec ted that the vehicle is in a specific state in which a direction indicator is operated. A control m ethod for an operation target device in a vehicle. 9. A driver grips a touch sensor which has a plurality of detection areas and is mounted within a predetermined range of a grip portion of a steering wheel of a vehicle so as to cover said grip portion to be gripped by the driver. It is detected whether or not a specific input operation has been performed on the touch sensor, and the shift position of the shift lever is reversed.

It is detected that

the vehicle is not in a specific state in which the shift position of the shift lever is in reverse , it is detected that the driver is gripping the touch sensor, and the specific When it is detected that the input operation is performed, the touch sensor controls the operation target device to be operated, and the vehicle is in a specific state in which the shift position of the shift lever is in reverse.

A control method for an operation target device in a vehicle, comprising: invalidating control of the operation target device when the operation target device is detected .

10.

The touch sensor includes a part of the plurality of detection areas, a grip detection area for

detecting a contact of the driver's palm, and another part of the plurality of detection areas, w herein and an operation detection area for detecting the specific operation due to contact with the

grip detection area, and detecting that the driver is gripping the touch sensor by contact of t he palm with the

grip detection area. 10. The method of controlling an operation target device in a vehicle acc ording to

claim 8, wherein the execution of the specific input operation is detected by finger contact . 11.

A driver grips a touch sensor which has a plurality of detection areas and is mounted within a predetermined range of a grip portion of a steering wheel of a vehicle so as to cover said gri p portion. detecting whether or not there is,

detecting whether or not a specific input operation has been performed on the touch sensor,

detecting whether the vehicle is in a specific state,

detecting that the vehicle is not in a specific state, detecting that the driver is gripping the to uch sensor, and performing the specific input operation When the operation is detected, the o peration target device to be operated is controlled by the touch sensor, and the touch sensor

includes a part of the plurality of detection areas and detects the contact of the driver's pal m. A grip detection area for detection and an operation detection area for detecting the specifi c operation by finger contact, which includes another part of the plurality of detection areas, a re set,

A palm contact with the grip detection area detects that the driver is gripping the touch sens or, and a finger contact with the operation detection area detects

that the specific input operation has been performed.

A control method for an operation target device in a vehicle characterized by:

12.

As said specific input operation, two points spaced apart in a circumferential direction in a cr oss section of said steering wheel when said grip is cut in said operation detection area by two fingers. 12. The method of controlling an operation target device in a vehicle according to clai m 10, wherein the operation target device is controlled according to an operation pattern . 13. When the rotation angle of the steering wheel exceeds a predetermined angle, it is deter mined that the vehicle is in a specific state, and the

control of the device to be operated is invalidated. The method for controlling an operation t arget device in a vehicle according to any one of Claims 1 to 1 .

14.

The touch sensor comprises a first touch sensor mounted in a predetermined range of the gr ip held by the driver's left hand and a second touch sensor mounted in a predetermined range of the grip held by the driver's right hand. and a touch sensor, and

according to a pattern of a combination of a first input operation on the first touch sensor an

d a second input operation on the second touch sensor as the specific input operation, the ope ration target.

14. The method for controlling an operation target device in a vehicle according to any one o f claims 8 to 13, characterized in that the device is controlled .

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to a vehicle operation control system for controlling the operation of a vehicle, such as an on-vehicle device such as a navigation syste m installed in a vehicle, or a transmission, a direction indicator, or the like. The present invent ion relates to a control device and a control method for controlling an operation target device, which is an operation target device. 2. Description of the Related Art Vehicles in which opera tion switches for operating vehicle-mounted equipment such as a navigation system are arran ged on a steering wheel have become widespread (see Patent Document 1). By arranging the operation switch on the steering wheel, the driver does not have to reach for the in-vehicle eq uipment when operating the in-vehicle equipment, thereby improving operability. As described in Japanese Patent Application Laid-Open No. 2002-200015, the operation switch is actually n ot the annular portion of the steering wheel, which is the grip portion that the driver grips, bu t the central portion where the airbag is accommodated and the circular portion. It is usually arranged in the connecting part connecting between the annular parts. Therefore, in order to operate the operation switch, the driver needs to release his/her hand from the gripped annul ar portion or move the hand largely. Patent Literature 2 describes that operation switches are arranged on the back surface and the inner side surface of the annular portion. [Prior Art Doc uments] [Patent Documents] [Patent Document 1] Japanese Patent Laid- Open Publication N o. 2007-106353 [Patent Document 2] Japanese Patent Laid-Open Publication No. 2005-34812 3 [Patent Document 3] Japanese Patent Laid- Open Publication No. 2008-195220 [Invention] Overview] [Problems to be solved by the invention]

According to the invention disclosed in Patent Document 2, since the operation switches are arranged on the annular portion, the operation switches can be operated without releasing the hand from the annular portion or moving the hand largely . child
can be However, the operation switch described in Patent Literature 2 is a push-button key or a key with projections and depressions, and such keys may interfere with the driver's operation of the steering wheel. It is not preferable to provide large irregularities in the annular portion gripped by the driver. In addition, when an operation unit such as an operation switch is arranged in the annular portion, the driver does not have the intention to operate the operation target device, unlike the case where the driver grips the annular portion for normal driving. In such cases, it is required to prevent the operation target device from being operated carelessly. Furthermore, depending on the state of the vehicle, erroneous operations may be caused, and it is required to reduce erroneous operations as much as possible.
[0005]

In order to meet such a demand, the present invention enables a device to be operated to be operated without removing the hand from the grip or moving the hand largely, and the driver can operate the steering wheel. It is an object of the present invention to provide a control device and a control method for an operation target device in a vehicle, which can greatly reduce the possibility of hindrance during operation. Another object of the present invention is to provide a control device and a control method for an operation target device in a vehicle that can significantly reduce erroneous operations.
SUMMARY OF THE INVENTION In order to solve the above-described problems of the prior art, the present invention has a plurality of detection areas and a grip portion of a steering wheel
a driver . A sensor that generates sensor data including position data indicating which detection area is being touched, based on a contact detection signal obtained from a touch sensor attached to cover the grip in a predetermined range of data generator and
a detection unit for detecting whether or not a driver is gripping the grip based on the sensor data and an input operation to the touch sensor; an operation target to be operated by the touch sensor in response to the specific input operation when it is detected that a specific input operation is performed on the touch sensor. a controller for controlling a device , wherein the controller determines that the vehicle is in a specific state when the direction indicator is operated , and invalidates the control of the device to be operated. A controller for a target device is provided. [0007] In order to solve the above-described problems of the prior art, the prese

nt invention has a plurality of detection areas, and a steering wheel of a vehicle is provided with a grip portion within a predetermined range of the grip portion to be gripped by the driver. A sensor data generation unit that generates sensor data including position data indicating which detection area is being touched based on a contact detection signal obtained from a touch sensor that is mounted so as to cover it; and based on the sensor data, a detection unit that detects whether or not a driver is gripping the grip portion and an input operation to the touch sensor; the detection unit detects that the driver is gripping the grip portion; and a control unit that controls an operation target device to be operated by the touch sensor in response to the specific input operation when it is detected that a specific input operation has been performed on the touch sensor. A control device for an operation target device in a vehicle, wherein the control unit invalidates control of the operation target device by determining that the vehicle is in a specific state when the shift position of the shift lever is in reverse. I will provide a.

[0008]

In the above-described control device for an operation target device in a vehicle, the touch sensor includes a grip detection area ; An operation detection area set, and the detection unit is based on a contact detection signal obtained from the grip detection area. Preferably, sensor data is used to detect whether or not a driver is gripping the grip portion, and sensor data based on a contact detection signal obtained from the operation detection area is used to detect the specific input operation.

[0009]

In order to solve the above-described problems of the prior art, the present invention has a plurality of detection areas,

A position indicating which detection area is being touched based on a contact detection signal obtained from a touch sensor attached to a predetermined range of a grip portion of a steering wheel gripped by a driver so as to cover the grip portion. a sensor data generation unit that generates sensor data including data; a detection unit that detects whether or not a driver is gripping the grip based on the sensor data and an input operation to the touch sensor; When the detection unit detects that the driver is gripping the grip and also detects that a specific input operation has been performed on the touch sensor, the specific input operation is performed. Accordingly, a control unit for controlling an operation target device to be operated by the touch sensor, wherein the touch sensor includes part of the plurality of detection areas and detects contact of the driver's palm. A detection area and an operation detection area that includes other parts of the plurality of detection areas and detects the specific input operation by finger contact are set, and the detection unit obtains information from the grip detection area. Detecting whether or not the driver is gripping the grip by sensor data based on the contact detection signal obtained from the operation detection area, detecting the specific input operati

on by sensor data based on the contact detection signal obtained from the operation detection area, The control unit disables control of the operation target device when the vehicle is in a specific state.

[0010]

In the above-described control device for an operation target device in a vehicle, the control unit is configured to, as the specific input operation, cut the grip portion in the radial direction of the steering wheel with respect to the operation detection area. It is preferable that the operation target device is controlled in accordance with a pattern in which two locations spaced apart in the circumferential direction on the cross section of are operated with two fingers.

In the above control device for an operation target device in a vehicle, the control unit further disables control of the operation target device by determining that the vehicle is in a specific state when the rotation angle of the steering wheel exceeds a predetermined angle. It is preferable to

In the above-described control device for an operation target device in a vehicle, the touch sensors include a first touch sensor of a grip portion gripped by a driver's right hand. and a second touch sensor attached to the controller, and the control unit performs a first input operation on the first touch sensor and a second input operation on the second touch sensor as the specific input operation. It is preferable that the operation target device is controlled according to a combination pattern of and.

[0011] In order to solve the above-described problems of the prior art, the present invention has a plurality of detection areas, and a grip portion of a steering wheel

gripped by a driver , has a grip portion within a predetermined range. It detects whether or not the driver is gripping a touch sensor mounted so as to cover the part , detects whether or not a specific input operation has been performed on the touch sensor, and detects whether or not the direction indicator has been operated. detects whether the vehicle is not in a specific state in which the direction indicator is operated, detects that the driver is gripping the touch sensor, and detects whether the specific input operation is detected to be performed, control the operation target device to be operated by the touch sensorand, when it is detected that the vehicle is in a specific state in which the direction indicator is operated, the control of the operation target device is invalidated . offer.

[0012]

In order to solve the above-described problems of the prior art, the present invention has a plurality of detection areas, and a steering wheel of a vehicle is provided with a grip portion within a predetermined range of the grip portion to be gripped by the driver. It detects whether or not the driver is gripping a touch sensor mounted so as to cover it, detects whether or not a specific input operation has been performed on the touch sensor, and shifts the shift position of the shift lever to reverse. It is detected that the vehicle is not in a specific state in which the shift position of the shift lever is in reverse, it is detected that the driver is gripping the touch sensor, and the specific When it is detected that the input operation is performed, the tou

ch sensor controls the operation target device to be operated, and the vehicle is in a specific state in which the shift position of the shift lever is in reverse. If it is detected, the control of the operation target device is invalidated.

A control method for an operation target device in a vehicle is provided.

[0013]

In the above-described control method for a device to be operated in a vehicle, the touch sensor includes a grip detection area ; An operation detection area set, and the driver grips the touch sensor by contact of the palm with the grip detection area. It is preferable to detect that the specific input operation has been performed by a finger touching the operation detection area.

[0014]

In order to solve the above-described problems of the prior art, the present invention has a plurality of detection areas, and a steering wheel of a vehicle is provided with a grip portion in a predetermined range so as to cover the grip portion to be gripped by the driver. Detects whether the driver is gripping the attached touch sensor, detects whether a specific input operation has been performed on the touch sensor, and detects whether the vehicle is in a specific state. and when it is detected that the vehicle is not in a specific state, it is detected that the driver is gripping the touch sensor, and it is detected that the specific input operation is performed, A touch sensor controls an operation target device to be operated, and the touch sensor includes a grip detection area that includes a part of the plurality of detection areas and detects contact with the driver's palm, and the plurality of detection areas. and an operation detection area for detecting the specific operation by finger contact is set, and the driver is gripping the touch sensor by palm contact with the grip detection area and detecting that the specific input operation has been performed by touching the operation detection area with a finger.

[0015]

In the method for controlling an operation target device in a vehicle described above, the specific input operation is a circumferential direction in a cross section of the steering wheel when the grip portion is cut in the radial direction of the steering wheel with respect to the operation detection area. It is preferable that the device to be operated is controlled according to a pattern in which two locations spaced apart from each other are operated with two fingers.

In the above method for controlling an operation target device in a vehicle, it is preferable that control of the operation target device is invalidated on the assumption that the vehicle is in a specific state when the rotation angle of the steering wheel exceeds a predetermined angle.

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In the control method for the operation target device in the vehicle,The touch sensor includes a first touch sensor and a second touch sensor and controlling the operation target device according to a pattern of a combination of a first input operation on the first touch sensor and a second input operation on the second touch sensor as the specific input operation. is preferred.

EFFECTS OF THE INVENTION According to the control device and control method for the devi ce to be operated in the vehicle of the present invention, the device to be operated can be op erated without releasing the hand from the grip portion or moving the hand largely

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Therefore, it is possible to greatly reduce the possibility of hindrance when the driver operates the steering wheel. In addition, erroneous operations can be greatly reduced.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017]

FIG. 1 is a block diagram showing an embodiment of a control device for an operation target device in a vehicle according to the present invention;

FIG. 2 is a partial plan view showing an example of a vehicle provided with a control device fo r an operation-targeted device according to one embodiment;

FIG. 3 is a diagram showing an example of positions and ranges where touch sensors are mou nted on a steering wheel according to one embodiment;

4A and 4B are diagrams showing other examples of the positions and ranges where the touch sensor is mounted on the steering wheel according to the embodiment; FIG.

FIG. 5 is a diagram showing an example of attaching a touch sensor to a modified steering wh eel;

FIG. 6 is a partial perspective view showing an example of a portion of the steering wheel fro m which sensor data can be obtained while the touch sensor portion is being gripped;

FIG. 7 is a cross-sectional view showing coordinates in the circumferential direction of the cro ss-section of the touch sensor;

8 is a plan view showing a state in which the touch sensor shown in FIG. 6 is unfolded; FIG.

9 is a schematic diagram showing a state in which each area shown in FIG. 8 is converted into uniform sizes; FIG.

FIG. 10 is a diagram showing an example of requirements for determining that the touch sens or portion of the steering wheel is being gripped;

FIG. 11 is a schematic diagram showing an example of a specific input operation on the touch sensor;

FIG. 12 is a schematic diagram showing another example of a specific input operation on the t ouch sensor;

13A and 13B are schematic diagrams showing still another example of a specific input operati on on the touch sensor; FIG.

FIG. 14 is a flowchart for explaining the operation of one embodiment;

FIG. 15 is a diagram for explaining the rotation angle of the steering wheel;

16 is a flow chart showing a specific example of processing in step S4 of FIG. 14; FIG.

FIG. 17 is a schematic perspective view showing a configuration example for changing colors when a touch sensor is operated;

FIG. 18 is a schematic perspective view showing a configuration example for changing the tac

tile sensation when the touch sensor is operated;

19 is a plan view showing a configuration example of a steering wheel; FIG.

BEST MODE FOR CARRYING OUT THE INVENTION An embodiment of a control device and con trol method

for

an operation target device in a vehicle according to the present invention will be described b elow with reference to the accompanying drawings. 1 and 2, the in-vehicle device 100 is mou nted inside the dashboard of the vehicle. In the example shown in FIG. 1, the in-vehicle devic e 100 includes a control unit 10, a navigation processing unit 11, an audio reproduction unit 1 2, a television (TV) tuner 13, a video signal processing unit 14, a video display unit 15, an au dio signal processing unit 16. , a display element 17 and a storage unit 18 . The control unit 1 0 includes a detection unit 10a. The navigation processing unit 11 has a storage unit for hold ing map data, a GPS antenna, etc. The control unit 10 and the navigation processing unit 11 work together to provide route guidance

.

The audio reproducing unit 12 reproduces an audio signal recorded on an optical disk such as a compact disk or a semiconductor memory under the control of the control unit 10 . The TV t uner 13 receives TV broadcast wave signals from a predetermined broadcasting station under the control of the control unit 10 . A video signal output from the navigation processing unit 1 1 or the TV tuner 13 is input to the video signal processing unit 14 via the control unit 10, pro cessed, and displayed on a video display unit 15 such as a liquid crystal panel.

[0020]

Audio signals output from the navigation processing unit 11 , the audio reproduction unit 12 , and the TV tuner 13 are input to the audio signal processing unit 16 via the control unit 10 , processed, and produced by the external speaker 20 . The audio signal processor 16 includes an amplifier. The speaker 20 is installed inside the door of the vehicle or the like. The display element 17 is, for example, a light-emitting diode (LED), and is turned on or off according to t he contact state of the touch sensor 21 described later under the control of the control unit 10 . The display element 17 is arranged, for example, on the housing of the in-vehicle device 100 so that it can be visually recognized by the driver. The display element 17 may be separated f rom the in-vehicle device 100 and arranged near the steering wheel 200 of the vehicle. The st orage unit 18 is a non-volatile memory. As shown in FIG. 2, the touch sensor 21, which is an operation unit, is attached to an annular portion 200r of the steering wheel 200. As shown in FIG

.

The annular portion 200r is a grip portion that is gripped by the driver during driving. In the e xample shown in FIG. 2, the touch sensor 21 is located at the annular portion 200r.

It is mounted in a predetermined angle range on each of the left and right sides. The touch se nsor 21 is a so-called multi-point detection (multi-touch) touch sensor capable of detecting co

ntact at multiple points. The touch sensor 21 is preferably mounted on the circumference of t he cross section in the radial direction of the annular portion 200r within a range of 360°. Eve n if the range is less than 360°, it is sufficient that it covers substantially the entire circumfere nce of the cross section of the annular portion 200r.

The driver grips the portion of the annular portion 200r on which the touch sensor 21 is mounted. In FIG. 1 , the output of the touch sensor 21 is input to the sensor data generator 22 . When the touch sensor 21 is touched with a hand, a contact detection signal is input to t he sensor data generator 22 . Based on the input contact detection signal, the sensor data ge neration unit 22 generates sensor data including position data indicating from which position o n the touch sensor 21 the contact detection signal was obtained, and supplies the sensor data to the control unit 10 . The touch sensor 21 and the sensor data generator 22 may be integrat ed, or the sensor data generator 22 may be provided within the controller 10 .

As the touch sensor 21, for example, a projective capacitance (mutual capacitance) type touch sensor can be use d. As the touch sensor 21 attached to the annular portion 200r, for example, a flexible touch p anel developed by Micro Technology Laboratory can be adopted. This flexible touch panel has a structure in which an ultra-thin glass plate having a thickness of 0.02 to 0.05 mm is used as a sensor portion, and an ultra-thin glass plate and a PET (polyethylene terephthalate) film are bonded together. Even if the touch sensor 21 is attached to the annular portion 200r, the touc h sensor 21 does not have unevenness that can be sensed by the hand or fingers, so that it h ardly interferes with the operation of the steering wheel 200 by the driver. do not have.

[0024]

As shown by the dashed line in FIG. 2, it is preferable to wire the electric wire connecting th e touch sensor 21 and the in-vehicle device 100 through the inside of the steering wheel 200 and the dashboard. 1 and 2, a steering angle sensor 31 detects the rotation angle of a steeri ng wheel 200. As shown in FIG .

The direction indicator sensor 32 detects operation of the direction indicator 320 . The shift le ver sensor 33 detects where the shift position by the shift lever 330 is. Detection signals from the steering angle sensor 31 , direction indicator sensor 32 , and shift lever sensor 33 are sup plied to the control section 10 via the in-vehicle communication section 34 . An example of t he position and range of mounting the touch sensor 21 on the annular portion 200r of the ste ering wheel 200 will be described with reference to FIG .

Note that up, down, right, and left refer to up, down, right, and left when the steering wheel 2 00 is viewed from the driver's position when the steering wheel 200 is not rotated (the vehicle is traveling straight ahead). Suppose that FIG. 3A shows an example in which the touch senso r 21 is attached to the entire circumference of the annular portion 200r. FIG. 3B is the same a s FIG. 2, and shows an example in which the touch sensors 21 are mounted separately from e

ach other within predetermined angular ranges on the left and right above the annular portion 200r. FIG. 3C shows an example in which the touch sensor 21 is mounted in a predetermined angular range only on the upper right side of the annular portion 200r.

FIG.

3(D) shows an example in which the touch sensors 21 are spaced apart from each other wit hin predetermined angular ranges on the left and right sides below the annular portion 200r. F IG. 3(E) is an example in which the touch sensor 21 is mounted over a relatively wide angular range above the top of the annular portion 200r. FIG. 3(E) corresponds to connecting the left and right touch sensors 21 in FIG. 3(B).

FIG.

4 shows an example in which the left and right touch sensors 21 in FIG. 3B are divided into an upper touch sensor 21a and a lower touch sensor 21b. In the example of FIG. 4, the upper touch sensor 21a detects contact with the index finger and thumb of the hand, and the lower touch sensor 21b mainly detects contact with the palm, middle finger, and ring finger. Figure 5 shows a modified steering wheel that is not circular.

This is an example in which a touch sensor 21 is attached to a rule 201. FIG. The touch senso r 21 is attached to the left and right straight portions 201 s of the modified steering wheel 20 1 . The driver grips the linear portion 201s, which is the grip portion, while driving, and the to uch sensor 21 detects contact with the palm or fingers. Here, as shown in FIG. 2, the touch sensors 21 are mounted on the left and right sides above the annular portion 200r

.

Describe how palm and finger contact is detected. FIG. 6 shows an example of a range in whic h the palm and fingers are in contact when the driver grips the touch sensor 21 on the right si de of FIG. The manner in which the driver grips the annular portion 200r and the size of the h and are not uniform, and FIG. 6 is merely an example. In the example shown in FIG. 6, a pl urality of detection areas R indicated by hatched Tp are portions where the contact of the pal m is detected, and a plurality of detection areas R indicated by hatched Tt are those of the th umb

.

This is the part that detects contact. Hereinafter, they are referred to as a palm contact detect ion section Tp and a thumb contact detection section Tt. The back side of the touch sensor 2 1, which is not visible in FIG. 6, is in contact with the forefinger.

As shown in FIG .

6, the touch sensor 21 has a plurality of detection regions R as detection portions for detecti ng contact of palms and fingers. Coordinates are set in each detection area R of the touch sen sor 21 . As shown in FIG. 6, in the circumferential direction of the annular portion 200r, the de tection region R located at the lower end of the touch sensor 21 is set to 0, and the detection region R located at the upper end is 1, 2, 1, 2, 2, . . . , 30, 31 and the coordinates in the circu mferential direction are set. Let the circumferential coordinate of the annular portion 200r in t

he touch sensor 21 be the Y coordinate.

[0032]

FIG. 7 is a cross-sectional view of the annular portion 200r cut in the radial direction of the a nnular portion 200r at the portion where the touch sensor 21 is mounted. As shown in FIG. 7, in the cross-section of the annular portion 200r, a detection region R positioned, for example, on the inner diameter side of the annular portion 200r is assumed to be coordinate 0. As sho wn in FIG. 7 from the inner diameter side to the front side, from the front side to the outer di ameter side, from the outer diameter side to the back side, and from the back side to the inne r diameter side in the counterclockwise direction of FIG. are set to 1, 2, . . . , 21, 22. Let the c oordinate in the circumferential direction of the cross section of the touch sensor 21 be the X coordinate. The sensor data generator 22 can obtain position data indicating where on the tou ch sensor 21 the driver is touching from the X and Y coordinates of the detection area R from which the contact detection signal is obtained.

FIG.

8 shows the development of the touch sensor 21 shown in FIG. FIG. 9 schematically shows a state in which each area of the touch sensor 21 shown in FIG. 8 is converted into uniform size s. 8 and 9, in addition to the palm contact detection portion Tp and the thumb contact detecti on portion Tt, the index finger contact detection portion Ti, which is a plurality of detection re gions R in contact with the index finger, is also shown. If the touch sensor 21 is touched by th e middle finger, the ring finger, or the little finger, the touch sensor 21 also detects the contact of those fingers. In this embodiment, the driver uses the thumb or forefinger suitable for perf orming a specific input operation on the touch sensor 21 as a finger for operation.

[0034]

The details of the input operation with the thumb or index finger will be described later. Base d on the sensor data output from the sensor data generator 22, the detector 10a of the contro ller 10 detects that an input operation has been performed on the touch sensor 21 with the th umb or forefinger. Based on the sensor data output from the sensor data generation unit 22, t he detection unit 10a also detects that the annular portion 200r (touch sensor 21) is gripped. The control unit 10 controls the operation target device according to a specific input operation performed on the touch sensor 21 .

[0035]

An example of the device to be operated is the vehicle-mounted device 100 . Specifically, th e control unit 10

In accordance with the input operation, the navigation processing unit 11 can perform control related to route guidance, the audio reproduction unit 12 can reproduce or stop audio signals, and the track (music) to be reproduced can be advanced or reversed. In addition, the control unit 10 can switch the receiving channel in the TV tuner 13 or control the amplification unit of the audio signal processing unit 16 to decrease or increase the sound volume according to a s pecific input operation.

Another

example of the device to be operated is a vehicle motion control device for controlling the m otion of a vehicle. Specifically, the control unit 10 may control the transmission, the direction i ndicator, the on/off of the air conditioner, the set temperature of the air conditioner, and the li ke, through the in-vehicle communication unit 34 . When the operation target device is a vehi cle motion control device, it is preferable to input the sensor data output from the sensor data generator 22 to a control portion of the vehicle to control the vehicle motion control device. T he control unit that controls the operation target device may be the control unit 10 in the vehi cle-mounted device 100 or may be a control unit outside the vehicle-mounted device 100 pro vided in the vehicle. According to this embodiment, the extremely thin touch sensor 21 is att ached to the annular portion 200r gripped by the driver, and the device to be operated is oper ated by operating the touch sensor 21

.

The device to be operated can be operated without releasing the hand or moving the hand lar gely. In addition, since the touch sensor 21 has no irregularities on the surface of the annular portion 200r, there is almost no possibility that it will interfere with the operation of the steeri ng wheel 200 by the driver.

[0038]

By the way, when the driver does not intend to operate the operation target device, such as when the driver grips the annular portion 200r for normal driving, the operation target device should be prevented from being inadvertently operated. is required. Therefore, in this embodi ment, the following measures are taken to avoid erroneous operations not intended by the dri ver. As shown in FIGS. 8 and 9, a plurality of detection areas R on the touch sensor 21 are p rovided with a grip detection area Arg for detecting contact of the palm and an operation inpu t by the thumb or forefinger

.

An operation detection area Arv for detecting an input and an operation invalid area Ariv whic h is an intermediate area between the grip detection area Arg and the operation detection are a Arv and invalidates an operation input are set. The palm contact detection portion Tp is loca ted within the grip detection area Arg, and the thumb contact detection portion Tt and the for efinger contact detection portion Ti are located within the operation detection area Arv. Like the grip detection area Arg and the operation detection area Arv, the operation invalid area Ar iv has a detection area R for detecting the contact of the palm or fingers

.

22 can be made an operation invalid area by processing to invalidate the input operation from the operation invalid area Ariv. Further, by configuring the touch sensor 21 so that the detecti on area R is not provided in the range of the operation invalid area Ariv, the operation invalid area may be set. This case is substantially equivalent to the example shown in FIG.

[0041]

When the driver grips the annular portion 200r for normal driving, the palm contact detectio n portion Tp, the thumb contact detection portion Tt, and the index finger contact detection p ortion Ti are relatively close to each other. Therefore, in order to accurately distinguish betwee n the case where the driver simply grips the annular portion 200r and the case where the driv er touches the touch sensor 21 to operate the operation target device, the operation invalid ar ea Ariv is provided. When the driver intends to operate the device to be operated, the driver i ntentionally extends his or her thumb or forefinger to touch the touch sensor 21 to perform a specific input operation, which will be described later. The control unit 10 controls the operatio n target device according to the input operation when a specific input operation, which will be described later, is performed within the operation detection area Arv.

[0042]

It is also necessary to avoid erroneous operation of the operation target device when the dri ver carelessly touches the operation detection area Arv without gripping the annular portion 2 00r for driving. Therefore, in the present embodiment, the detection unit 10a determines that the annular portion 200r is gripped when a palm contact detection portion Tp having a predet ermined area or more is obtained in the grip detection area Arg. The control unit 10 is configu red to control the operation target device when the annular portion 200r is gripped and a spec ific operation is performed within the operation detection area Arv. The area of the palm conta ct detection portion Tp for determining that the annular portion 200r is being gripped may be appropriately set by statistically examining the area when a plurality of drivers grip the steeri ng wheel 200 in a normal gripping manner. Just do it.

The area of the palm contact detection portion Tp in the grip detection area Arg is an example of requirements for determining that the driver is gripping the annular portion 200r ,

and the requirements for determination are limited to this. isn't it. FIG. 10 shows a cross sec tion of the annular portion 200r cut at the portion of the grip detection area Arg of the touch s ensor 21. As shown in FIG. The detection unit 10a can determine that the annular portion 200 r is being gripped when the angle θ in the circumferential direction of the cross-section of the palm contact detection portion Tp is equal to or greater than a predetermined angle. The pred etermined angle is, for example, 180°.

[0044]

As described above, in the present embodiment, it is determined whether or not the driver is gripping the annular portion 200r (touch sensor 21), and operation input to the touch sensor 21 is performed only when the driver is gripping the annular portion 200r. is accepted, it is po ssible to avoid an erroneous operation when the operation detection area Arv is carelessly tou ched. In this embodiment, as a preferred configuration, the operation detection area Arv is pr ovided at a position separated from the grip detection area Arg by a predetermined distance, so that the driver intentionally performs a specific input operation on the touch sensor 21. You can detect exactly what you are doing. Therefore, erroneous operations can be greatly reduce d. In this embodiment, the area of the palm contact detection portion Tp in the grip detectio

n area Arg and the angle θ in the circumferential direction of the cross section are used as req uirements for determining whether or not the driver is gripping the annular portion 200r

.

Therefore, it can be accurately determined whether or not the user is gripping the annular por tion 200r. Therefore, it is possible to avoid an erroneous operation when the driver carelessly t ouches the operation detection area Arv without gripping the annular portion 200r. When the detection unit 10a detects that the driver is gripping the annular portion 200r (touch sensor 2 1) based on the sensor data based on the contact detection signal from the grip detection are a Arg, the control unit

10

The display element 17 is turned on in order to inform the driver that the operation input by t he operation detection area Arv is possible. The driver can determine whether or not the oper ation target device can be operated by the touch sensor 21 by turning on/off the display elem ent 17 . It is preferable to arrange the display element 17 near the steering wheel 200 .

[0047]

By the way, when the touch sensor 21 is attached to the entire circumference of the annular portion 200r as shown in FIG. , the position where the driver grips the touch sensor 21 is not fixed. Therefore, the positions of the grip detection area Arg and the operation detection area Arv described with reference to FIGS. 8 and 9 and the operation invalid area Ariv provided as necessary are dynamically changed according to the position at which the driver grips the tou ch sensor 21. Must be set.

Therefore ,

when the touch sensor 21 is gripped while the grip detection area Arg and the like are not se t, the control section 10 sets the area including the palm contact detection portion Tp as the g rip detection area Arg. A predetermined range of Y coordinates including the palm contact det ection part Tp is defined as a grip detection area A

rg. As described above, since the palm contact detection portion Tp has a predetermined area or more, a portion of the plurality of detection regions R on the touch sensor 21 that is detect ed to be touched with a predetermined area or more is the palm contact detection portion Tp. becomes. Alternatively, as described with reference to FIG. 10, in the circumferential direction of the cross section obtained by cutting the annular portion 200r at the portion of the touch s ensor 21, the portion detected to be touched at a predetermined angle or more becomes the palm contact detection portion Tp. . After setting the grip detection area Arg, the control unit 10 sets a predetermined range of Y coordinates above the grip detection area Arg as the oper ation detection area Arv

.

In this case, if necessary, a predetermined range of Y coordinates adjacent to the grip detecti on area Arg is set as the operation invalid area Ariv, and the grip detection area Arg is positio ned away from the grip detection area Arg. 11 to 13, examples of specific input operations p

erformed by the driver on the touch sensor 21 using his thumb or forefinger will now be descr ibed

.

11A to 11E schematically show half of the touch sensor 21, which is the front side or the back side facing the driver, in a plane view. The operations shown in FIGS. 11A to 11E are perform ed with the thumb on the front side and with the index finger on the back side. In FIG. 11A, D R is a rightward drag by sliding the thumb or forefinger on the touch sensor 21 (operation detection area Arv), and DL is a leftward dragging by sliding the thumb or forefinger to the right. It is a directional drag. D U is an upward drag that slides the thumb or forefinger upward; is a downward drag that slides in t he direction the thumb or index finger is pointing.

In FIG . 11(A), instead of the

rightward drag D R , leftward drag D L , upward drag D U , and downward drag D D , the tou ch sensor 21 is flicked with the thumb or forefinger in the respective directions. It may be a fli ck.

FIG.

11(B) shows a tap T of tapping the touch sensor 21 with the thumb or index finger. FIG. 11 (C) shows an arc drag DC in which the thumb or forefinger is dragged on the touch sensor 21 so as to draw an arc. F IG. 11(D) shows a zigzag drag DZ in which the thumb or forefinger is dragged on the touch sensor 21 in a zigzag p attern. FIG. 11(E) shows a symbol input drag DS that is dragged as if writing a symbol with the thumb or forefinger . FIG. 11E shows a state in which the number 3 is drawn as a symbol. As symbols, it is preferable to use numbers and alphabets that are relatively easy to recognize.

[0053]

FIGS. 12A to 12D show a schematic plan view of a front portion 21f, which is the front half o f the touch sensor 21, and a rear portion 21r, which is the rear half of the touch sensor 21, wh en the touch sensor 21 is opened. . The front portion 21f is the portion of X coordinates 0 to 1 1 shown in FIGS. 8 and 9, and the rear portion 21r is the portion of X coordinates 12 to 22. A s shown in FIG. Strictly speaking, in the examples shown in FIGS. 8 and 9, the front portion 2 1f and the back portion 21r do not have the same area, but in FIGS. Shown in area. 12A to 1 2D, for ease of understanding, the rear surface portion 21r is not viewed from the rear surfac e side of the annular portion 200r, but is seen through the rear surface portion 21r from the fr ont surface portion 21f. state. As shown in FIGS. 12A to 12D, a combination of an input oper ation with the thumb on the front portion 21f and an input operation with the index finger on t he back portion 21r can be used as a specific input operation on the touch sensor 21

.

good. FIG. 12A shows an example of performing both a rightward drag DTR in which the thum b slides rightward on the front portion 21f and a rightward drag DIR in which the index finger slides righ tward on the back portion 21r. FIG. 12A is realized by dragging both the thumb and index finger from the inner circumference side to the outer circumference side of the annular portion 200r. A pat tern in which both the thumb and the forefinger are dragged in the direction opposite to that i

n FIG. 12A may be employed.

FIG. 12B shows an example of performing both a leftward drag DTL

in which the thumb slides leftward on the front portion 21f and a rightward drag DIR in which the index finger slides rightward on the back portion 21r. is. FIG. 12B is realized by dragging t he thumb from the outer peripheral side to the inner peripheral side of the annular portion 20 0r and dragging the index finger from the inner peripheral side to the outer peripheral side of the annular portion 200r. FIG. 12C shows an example of performing both a rightward drag DTR in which the thumb slides rightward on the front portion 21f and a leftward drag DIL in which the i ndex finger slides leftward on the back portion 21r. FIG. 12C is realized by dragging the thumb from the in ner circumference side to the outer circumference side of the annular portion 200r and draggi ng the index finger from the outer circumference side to the inner circumference side of the a nnular portion 200r. FIG . 12(D) shows an example of performing both an upward drag D TU

in which the thumb slides upward on the front portion 21f and a downward drag D ID in whic h the index finger slides downward on the back portion 21r. is. A pattern in which the thumb i s dragged downward and the index finger is dragged upward may be adopted, or a pattern in which both the thumb and the index finger are dragged upward or downward may be adopte d. Here, various patterns are shown in which the input operation with the thumb on the front portion 21f and the input operation with the index finger on the back portion 21r are combine d. [0057]

As shown in FIGS. 12A to 12D, if a pattern combining an input operation with the thumb and an input operation with the index finger is used as a specific input operation for controlling the device to be operated, erroneous operations are greatly reduced. can be reduced. Furthermo re, as shown in FIGS. 3(A), (B), (D), (E) and FIGS. 4 and 5, when the touch sensors 21 (21a, 21b) can be operated with the left and right hands

,

, a combination of left and right hand operations can be used as a specific input operation for controlling the operation target device. FIGS. 13A to 13D show operations by the left and righ t hands when the left touch sensor 21 in FIG. 3B is the left touch sensor 21L and the right tou ch sensor 21 is the right touch sensor 21R. Examples of combined patterns are shown. Here, a plane corresponding to the front portion 21f of FIG. 12 operated by the thumb is shown as a schematic plane.

FIG. 13A shows a leftward drag DTL

for sliding the thumb leftward on the left touch sensor 21L and a rightward drag DTR for slidi ng the thumb rightward on the right touch sensor 21R. This pattern is a combination of FIG. 1 3B shows a combination of a rightward drag DTR in which the thumb slides rightward on the le ft touch sensor 21L and a leftward drag DTL in which the thumb slides leftward on the right to

uch sensor 21R . pattern. FIG. 13C shows an upward drag D in which the thumb is slid upwa rd on both the left touch sensor 21L and the right touch sensor 21R.

This pattern is a combination of TUs . FIG. 13(D) shows a pattern in which a downward drag DTD of sliding th e thumb downward is combined for both the left touch sensor 21L and the right touch sensor 21R. If a combination of input operations with left and right hands is used as a specific input operation for controlling the device to be operated, the driver grasps the annular portion 200r with both hands, which contributes to safe driving

.

It is possible to contribute. In particular, the example of FIG. 3B is most preferable in that it c ontributes to safe driving because the touch sensor 21 is mounted at the most appropriate po sition for gripping the annular portion 200r with both hands. An input operation may be accep ted when the left and right touch sensors 21 are gripped with both hands. A state may be ado pted in which input operations are not accepted when one hand is removed from the touch se nsor 21 . When one hand leaves the touch sensor 21, the state of accepting the input operatio n may be continued. Even when a specific input operation with only one hand is used, if the in put operation is accepted when the left and right touch sensors 21 are gripped with both hand s, it contributes to safe driving.

. When the driver grips the annular portion 200r for normal driving and does not intend to o perate the device to be operated, he accidentally combines the input operation with the thum b and the input operation with the index finger

.

It is considered that the possibility of becoming a specific pattern combining input operations with left and right hands is relatively low. Therefore, when using only a specific pattern in whi ch an input operation with the thumb and an input operation with the index finger are combin ed, or a specific pattern in which an input operation with the left and right hands is combined, one of the devices for avoiding the above-described erroneous operation. Some or all of them may be omitted. Of course, even when only a specific pattern combining input operations with the left and right hands is used, it is preferable to employ a device for avoiding the above-des cribed erroneous operation. The storage unit 18 stores a table that associates the above-des cribed specific input operations or patterns of combinations of specific input operations with ty pes of control for the device to be operated

.

The control unit 10 controls the operation target device according to the operation input to th e touch sensor 21 according to the table stored in the storage unit 18 . The storage unit 18 m ay be provided within the control unit 10 .

[0064]

The processing executed by the control unit 10 in this embodiment will be described again u sing the flowchart of FIG. 14 . In FIG. 13, the control unit 10 acquires sensor data output fro

m the sensor data generation unit 22 in step S1. In step S2, the control unit 10 determines w hether or not the annular portion 200r is being gripped based on the detection output from th e detection unit 10a. If it is determined that the annular portion 200r is gripped (YES), the co ntrol unit 10 shifts the process to step S3, and if it is not determined that the annular portion 200r is gripped (NO), the control unit 10 returns the process to step S1. At step S3, the cont rol section 10 determines whether or not there is an input operation based on the detection o utput from the detection section 10a

.

If it is determined that an input operation has been performed (YES), the control unit 10 mov es the process to step S4, and if it is not determined that an operation input has been perfor med (NO), the control unit 10 returns the process to step S1. In step S4, the control unit 10 d etermines whether or not to permit the operation of the operation target device by the input o peration in step S3. If it is determined that the operation is permitted (YES), the control secti on 10 moves the process to step S5, and if it is not determined that the operation is permitte d (NO), the control section 10 returns the process to step S1. As described above, the contr ol unit 10 permits the operation of the operation target device when a specific input operation is performed within the operation detection area Arv, and permits the operation of the operati on target device when a specific input operation is performed within the operation invalid area Ariv

.

, the operation to the operation target device is not permitted. Further, even if some input ope ration is performed within the operation detection area Arv, the control unit 10 does not permi t the operation to the operation target device unless the above-described specific input operat ion is performed, and only when the specific input operation is performed. Permission to opera te the operation target device.

[0067]

The control unit 10 confirms an operation based on the input operation in step S5, executes control according to the confirmed operation on the operation target device in step S6, and re turns the process to step S1. .

[0068]

Further, in step S4, when the vehicle is in a specific state, it is preferable to disallow (that is, disable) the control of the device to be operated. The rotation angle of the steering wheel 200 is set in the control unit 10 for determining whether or not to permit control of the device to b e operated. As shown in FIG. 15, a state in which the steering wheel 200 is not rotated is ass umed to be a rotation angle of 0°. Touch sensor 21 within a range of 30°

input operation to the touch sensor 21 is enabled and permitted, and if the rotation angle exc eeds ±30°, the input operation to the touch sensor 21 is disabled and not permitted.

When the turning angle exceeds ±30°, the vehicle is in a specific state

such as turning right or left, or cornering. If an attempt is made to control the device to be o

perated in such a specific state, there is a high possibility that an erroneous operation will occ ur. In other words, there is a high possibility that an operation input in such a specific state is an operation input unintended by the user. Moreover, it is not preferable in terms of safety. Th erefore, in this embodiment, when the vehicle is in a specific state, control of the operation ta rget device is disabled. As described above, the rotation angle of the steering wheel 200 det ected by the steering angle sensor 31 is input to the controller 10

.

The control unit 10 switches between enabling and disabling the input operation to the touch sensor 21 according to the rotation angle of the steering wheel 200 detected by the steering a ngle sensor 31 . A detection signal from the direction indicator sensor 32 is also input to the c ontrol unit 10 . Therefore, the control unit 10 may invalidate the input operation to the touch sensor 21 when the direction indicator 320 is operated by the detection signal from the directi on indicator sensor 32 . When the direction indicator 320 is operated, it can be considered to be in a specific state in which the steering wheel 200 is rotated over a predetermined rotation angle. In some cases, the direction indicator 320 is also used for operations other than signali ng a right turn or left turn, but the operation of the direction indicator 320 here is an operatio n for signaling a right turn or a left turn.

[0071]

Furthermore, it is not preferable to perform a specific input operation on the touch sensor 21 to control the operation target device while the vehicle is being reversed. There is a high possi bility that an erroneous operation will occur, and this is not preferable in terms of safety. Ther efore, it is preferable that the control unit 10 invalidates the input operation to the touch sens or 21 even when the shift position of the shift lever 330 is reversed by the detection signal fro m the shift lever sensor 33 . When the rotation angle of the steering wheel 200 exceeds a pre determined angle of ±30°, for example, or when the direction indicator 320 is operated, and when the shift position of the shift lever 330 is reversed, the operation target device Although it is preferable to disable the control for , only one of them may be disabled. It should be not ed that disabling the control of the operation target device means disabling the control of the operation target device by disabling the specific input operation even if the above-described s pecific input operation is performed

.

Even if some sensor data is input from the sensor data generation unit 22 to the control unit 1 0, the control unit 10 may invalidate the sensor data. As a result, it is sufficient to invalidate t he control on the operation target device.

[0073]

A specific example of the processing of step S4 in FIG. 14 will be described with reference to the flowchart in FIG. In FIG. 16, in step S41, the control unit 10 determines whether or not th e shift position of the shift lever 330 is reverse. If the shift position is reverse (YES), in step S 45, the control unit 10 disallows the input operation in step S3, and proceeds to step S1 in FI

G. If the shift position is not reverse (NO), control unit 10 determines in step S42 whether dir ection indicator 320 has been operated. If the direction indicator 320 is operated (YES), the c ontroller 10 disallows the input operation in step S3 in step S45, and proceeds to step S1 in F IG. If the direction indicator 320 has not been operated (NO), the controller 10 determines i n step S43 whether or not the rotation angle of the steering wheel 200 has exceeded a predet ermined angle

.

If the rotation angle of the steering wheel 200 exceeds the predetermined angle (YES), in ste p S45, the control unit 10 disallows the input operation in step S3, and proceeds to step S1 in FIG.

Let If the rotation angle of steering wheel 200 does not exceed the predetermined angle (N O), control unit 10 determines in step S44 whether or not a specific input operation has been performed within operation detection area Arv. If a specific input operation has not been perfo rmed (NO), in step S45, the control unit 10 disallows the input operation in step S3, and proc eeds to step S1 in FIG. If the input operation is disallowed in step S45, control of the operatio n target device is invalidated. If a specific input operation is performed (YES), the control unit 10 permits the input operation in step S3 in step S46, and proceeds to step S5 in FIG. Altho ugh all steps S41, S42 and S43 are provided in the example shown in FIG. 16, only one or tw o of these steps may be provided

.

Moreover, when providing all of steps S41, S42, and S43 or two of these steps, the order is ar bitrary. Although referred to as a shift lever 330 here, the shape of the operating portion for s witching between straight forward and backward movement of the vehicle and for changing th e gear ratio of the transmission is arbitrary, and may be any of floor shift, column shift, paddl e shift, and the like. All of these are included in the shift lever.

As described

above, when the vehicle is in a specific state such as right turn, left turn, cornering, or rever se, if the control of the device to be operated is disabled, the driver can No input operation is performed on the touch sensor 21 . Therefore, it contributes to the improvement of safety.

[0077]

The operation according to this embodiment is summarized as follows. The detection unit 10 a (first detection unit) detects a first area of the touch sensor 21 attached to the grip portion (annular portion 200r or straight portion 201s) of the steering wheels 200 and 201 held by th e driver. Detects that the An example of the first area is the grip detection area Arg. The dete ction unit 10a (second detection unit) performs a specific input operation on a second area of the touch sensor 21 located above the first area while the first area is being touched. Detect what has been done. An example of the second area is the operation detection area Arv. Since the thumb or forefinger is positioned higher than the palm during driving, the upper side of th e first area may be the second area. When the first area is touched and a specific input operat

ion is performed, the touch sensor 21 controls the operation target device to be operated acco rding to the specific input operation. The upper area is an area above the first area when the steering wheel 200 is not rotated and the driver grips the grip

.

It is preferable to determine that the first area is being touched when it is detected that the fir st area is being touched over a predetermined area.

[0079]

Moreover, from another viewpoint, it is as follows. The detection unit 10a (first detection uni t) is mounted in a predetermined range of the grip portion (annular portion 200r or linear port ion 201s) of the steering wheels 200 and 201 that the driver grips so as to cover the grip port ion. The touch sensor 21 touches the first area on the touch sensor 21 at a predetermined an gle or more in the circumferential direction of the cross section of the steering wheels 200 and 201 when the grip portion is cut in the radial direction. to detect The detection unit 10a (seco nd detection unit) detects that a specific input operation is performed on a second area of the touch sensor 21 that is different from the first area while the first area is being touched at a p redetermined angle or more. Detect what has been done. When the first area is touched at th e predetermined angle or more and a specific input operation is performed, the operation targ et device to be operated by the touch sensor 21 is controlled according to the specific input op eration.

The second

area is preferably an area located above the first area. The area located above is an area loc ated above the first area when the driver grips the grip portion while the steering wheel 200 i s not rotated.

FIGS.

17 and 18 show examples of construction for effectively informing the driver that the touch s ensor 21 has been operated. 17 and 18 are schematic diagrams in which the touch sensor 21 is expanded and converted into a rectangular shape, similar to FIG. FIG. 17 shows an exampl e in which a color changing sheet 41 containing a coloring substance is provided on the lower surface side of the touch sensor 21 . By using a transparent conductive film for the touch sens or 21 , the driver can see the color of the color change sheet 41 arranged on the lower surfac e of the touch sensor 21 through the touch sensor 21 . The driver can recognize that the touc h sensor 21 has been operated by changing the color of the color change sheet 41 at the porti on where the touch sensor 21 is touched under the control of the control unit 10 .

FIG.

18 shows an example in which a tactile feedback sheet 42 for changing the tactile sense (ha nd feeling) is provided on the upper surface side of the touch sensor 21 . As the tactile feedba ck sheet 42, for example, a sheet called "E-Sense" developed by Senseg of Finland can be ad opted. This sheet provides tactile feedback by charging the film. Even if the tactile feedback s heet 42 is provided on the upper surface side of the touch sensor 21, the touch sensor 21 can

detect the contact of a finger or the like. When the touch sensor 21 is operated via the tactile feedback sheet 42 , the driver can recognize that the touch sensor 21 has been operated by c hanging the tactile sensation of the tactile feedback sheet 42 under the control of the control unit 10 . can.

[0083]

Next, a configuration example of the steering wheel will be described with reference to FIG. 19 . A steering wheel 210 shown in FIG. 19 is configured to output a control signal to an oper ation target device from the steering wheel 210 . In FIG. 19, the same parts as those in FIGS. 1 and 2 are denoted by the same reference numerals, and the description thereof will be omit ted as appropriate. As shown in FIG. 19, the steering wheel 210 includes, for example, a sens or data generation unit 23 similar to the sensor data generation unit 22 in FIG. I have it. The controller 24 has a detector 24a similar to the detector 10a and a control signal generator 24 b. When the steering wheel 210 is mounted on the vehicle, the control signal generator 24b generates a control signal for controlling the device to be operated in accordance with a specif ic input operation to the touch sensor 21. FIG

.

The control signal output from the control signal generator 24b is output to the output termin al 26 via the cable 25. FIG. By connecting the output terminal 26 to the device to be operate d, the device to be operated can be controlled by the control signal. Examples of specific input operations are similar to FIGS. 11-13. The requirements for the control signal generator 24b t o generate the control signal are the same as those described above. The present invention i s not limited to the embodiments described above, and various modifications can be made wit hout departing from the gist of the present invention

.

The touch sensor 21 may be detachably attached to the annular portion 200r using a hook-an d-loop fastener. Although the annular portion 200r is used as the grip portion, the grip portion does not necessarily have to be annular.

[0086]

The touch sensor 21 need not be composed of one sheet, and may be composed of a pluralit y of touch sensor pieces. If the touch sensor 21 is composed of a plurality of touch sensor pie ces, the shape of each touch sensor piece can be simplified, which is advantageous in manufa cturing touch sensors. Note that when the touch sensor 21 is composed of a plurality of touch sensor pieces, the touch sensor pieces do not necessarily have to be arranged without gaps. T he touch panel 21 of the present embodiment is mounted so as to cover the grip portion. It al so includes that the sensor 21 is mounted over the grip portion with a gap between the pieces of the touch sensor.

[0087]

Furthermore, the range in which the touch sensor 21 is provided is not limited to the grip po rtion (annular portion 200r or the straight portion 201s) that the driver grips during driving. Y

ou may extend to the surface of the connection part which connects between. In FIG. 2, the c onnection part is the part located between the left and right hands in the state shown in FIG. 2, and in FIG. In this way, the touch sensor 21 may be extended to the surface of the connect ing portion, and the operation detection area Arv may be set at a position near the grip portio n of the connecting portion. If the position is close to the grip portion, the driver can operate t he operation target device without releasing the hand from the grip portion or moving the han d largely during driving. Therefore, even if the touch sensor 21 is extended to the surface of t he connecting portion, there is almost no possibility that the driver's operation of the steering wheels 200, 201, 210 will be hindered.

10 , 24 control units 10a

, 24a detection unit 11 navigation processing unit 12 audio reproduction unit 13 televisio n tuner 14 video signal processing unit 15 video display unit 16 audio signal processing u nit 17 display element 18 storage unit 20 speaker 21 touch sensors 22, 23 sensor data generator 24b control signal generator 25 cable

26 output terminal

31 steering angle sensor

32 direction indicator sensor

33 shift lever sensor

34 in-vehicle communication section

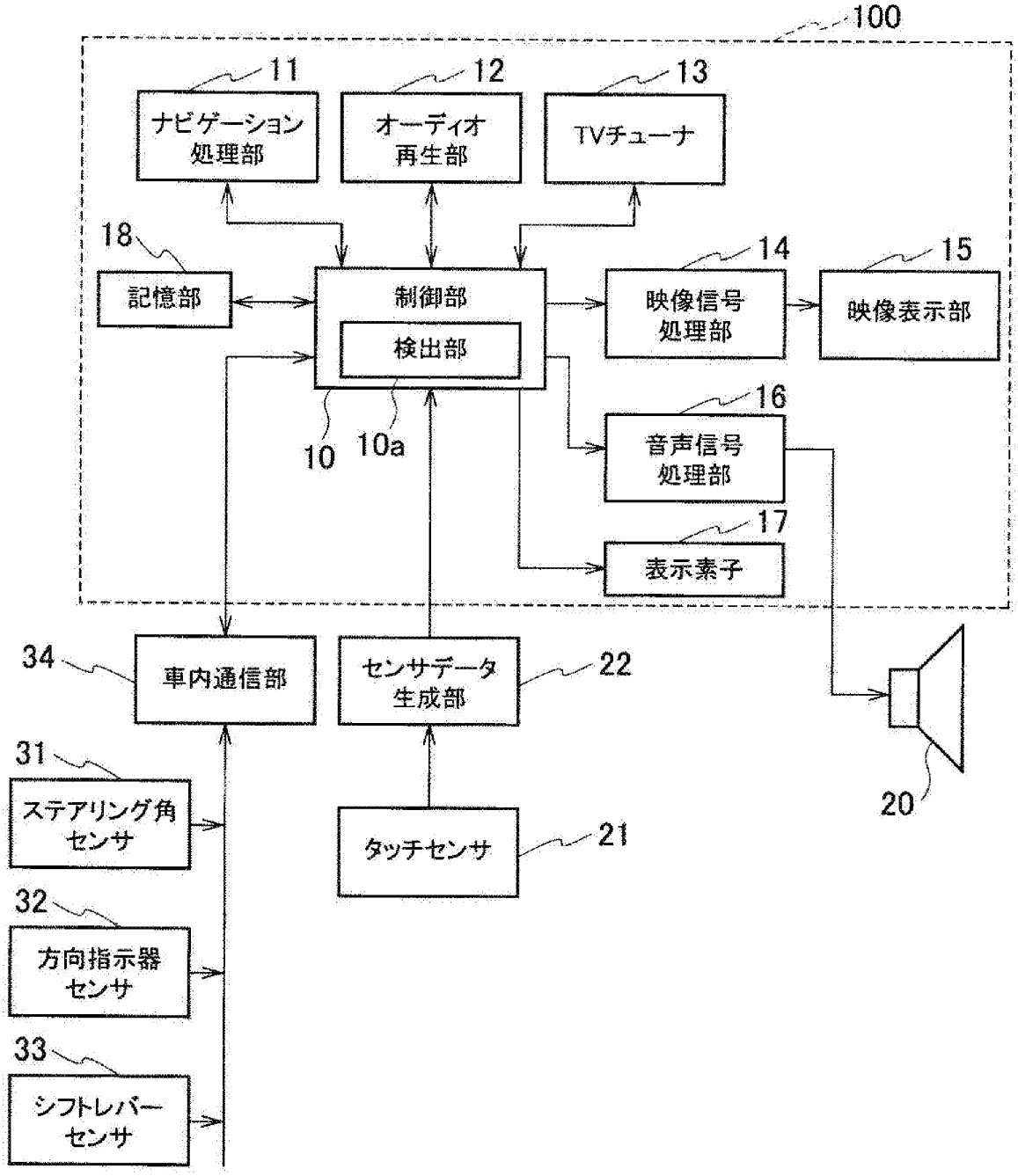
200, 201, 210 steering wheel

200r annular section (grip section)

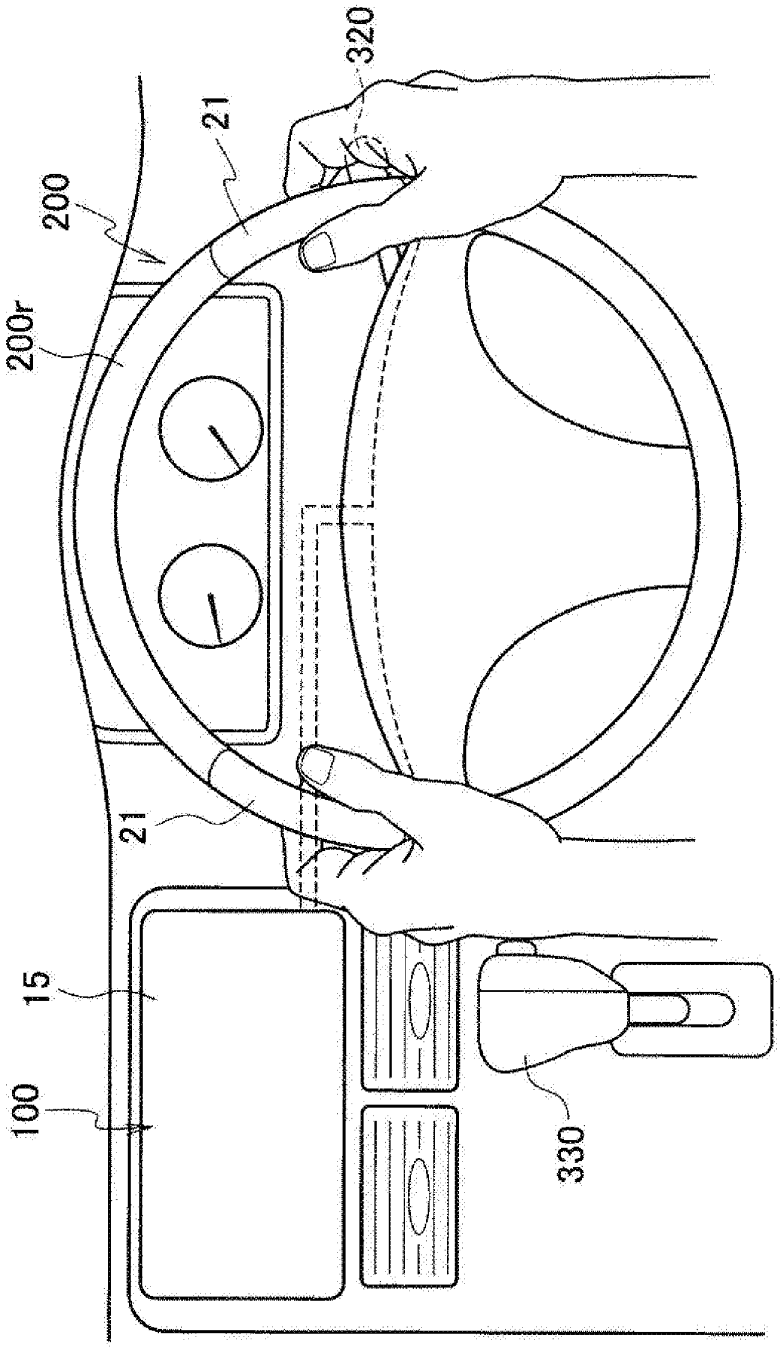
201s linear section (grip section)

drawing	open —

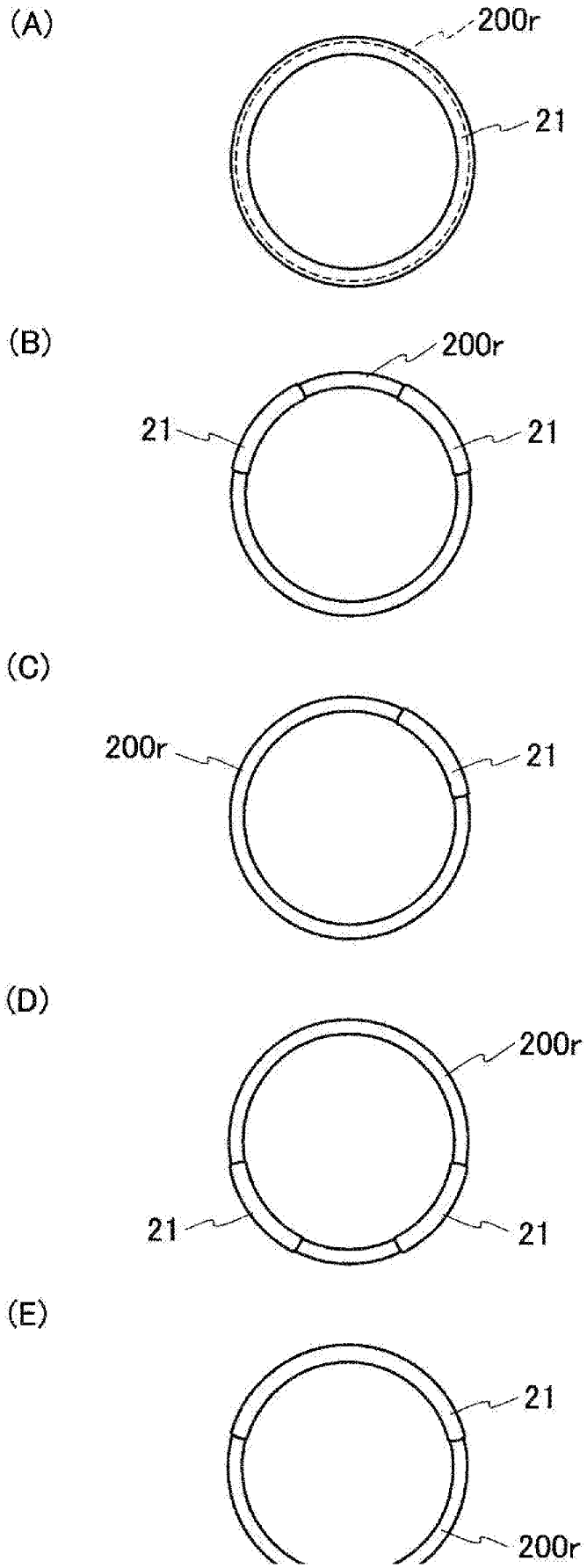
[Fig. 1]


100
11
ナビゲーション処理部
12
オーディオ再生部
13
TVチューナ
18
記憶部
制御部
検出部
14
映像信号処理部
15
映像表示部
10
10a
16
音声信号処理部
17
表示素子
34
車内通信部
センサデータ生成部
22
20
31
ステアリング角センサ
タッチセンサ
21
32
方向指示器センサ
33
シフトレバーセンサ

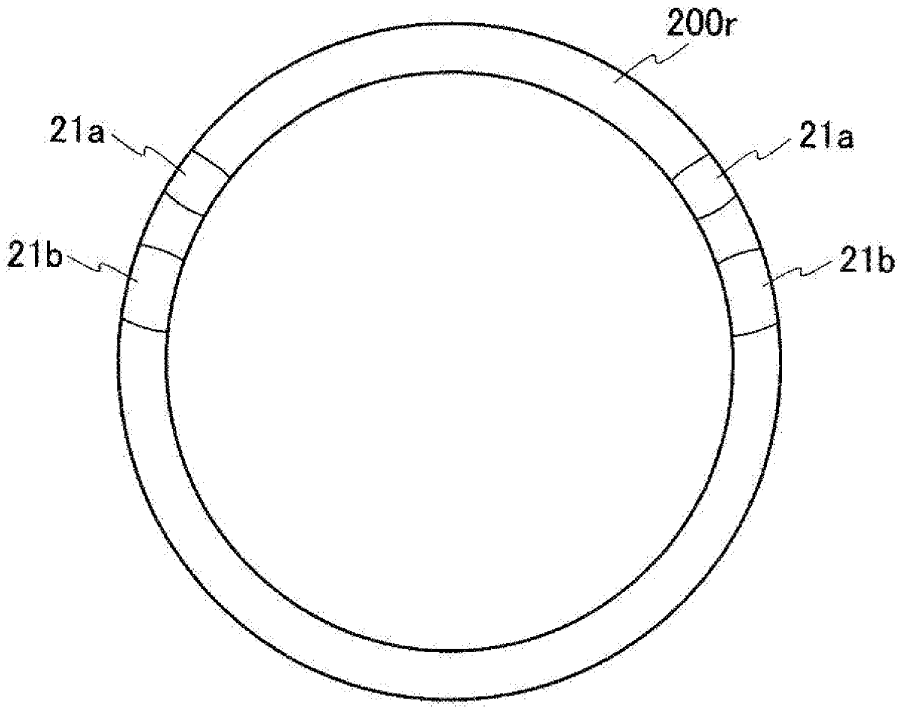
[Figure 2]


320
21
200
200r
21
15
100
330

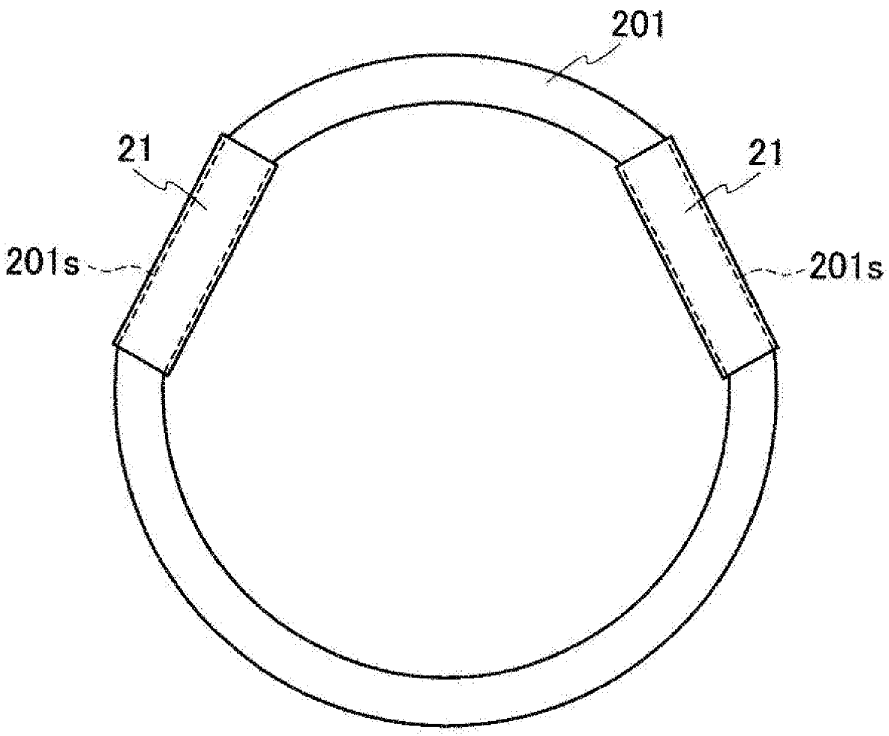
[Figure 3]


(A)
200r
21
(B)
200r
21
21
(C)
200r
21
(D)
200r
21
21
(E)
21
200r

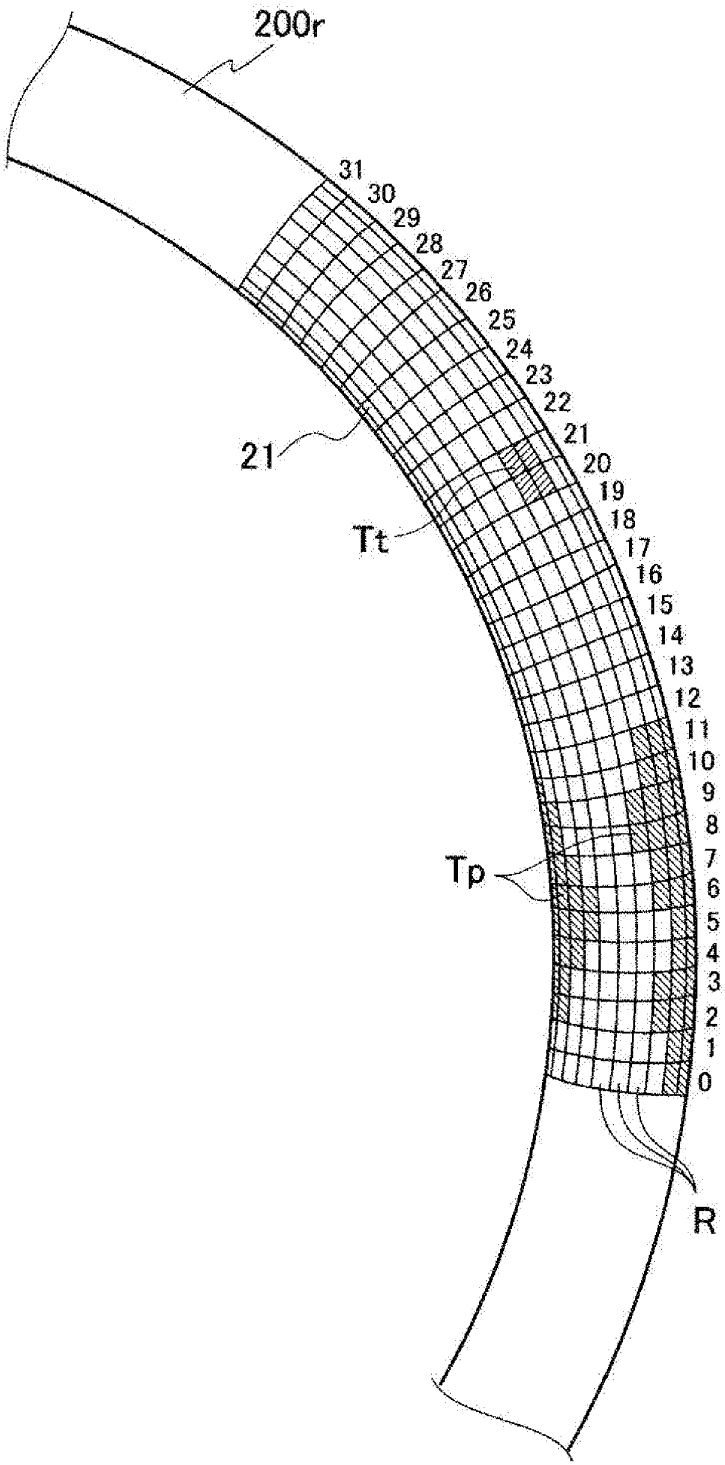
[Figure 4]



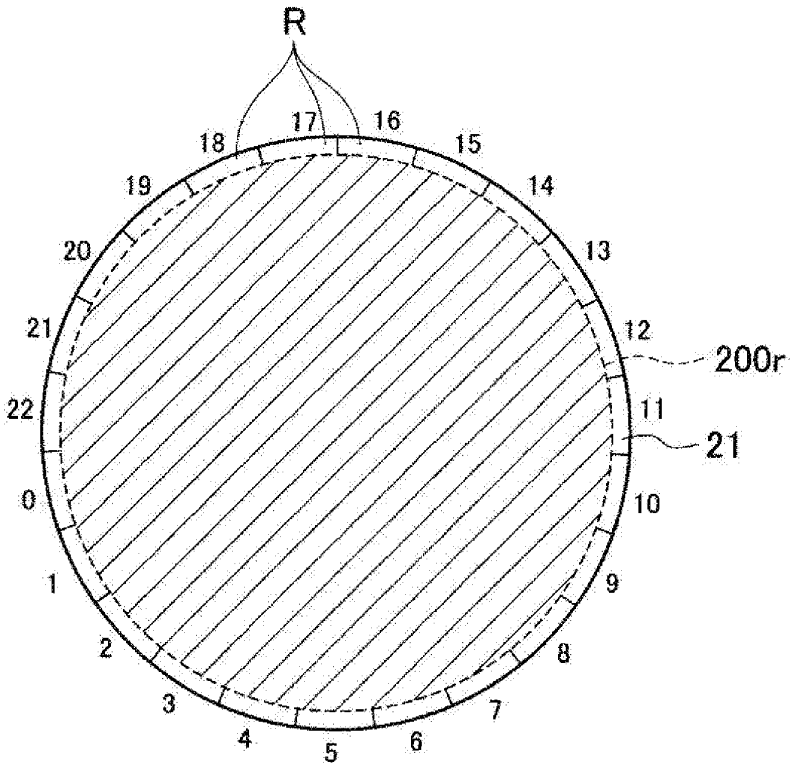
[Figure 5]



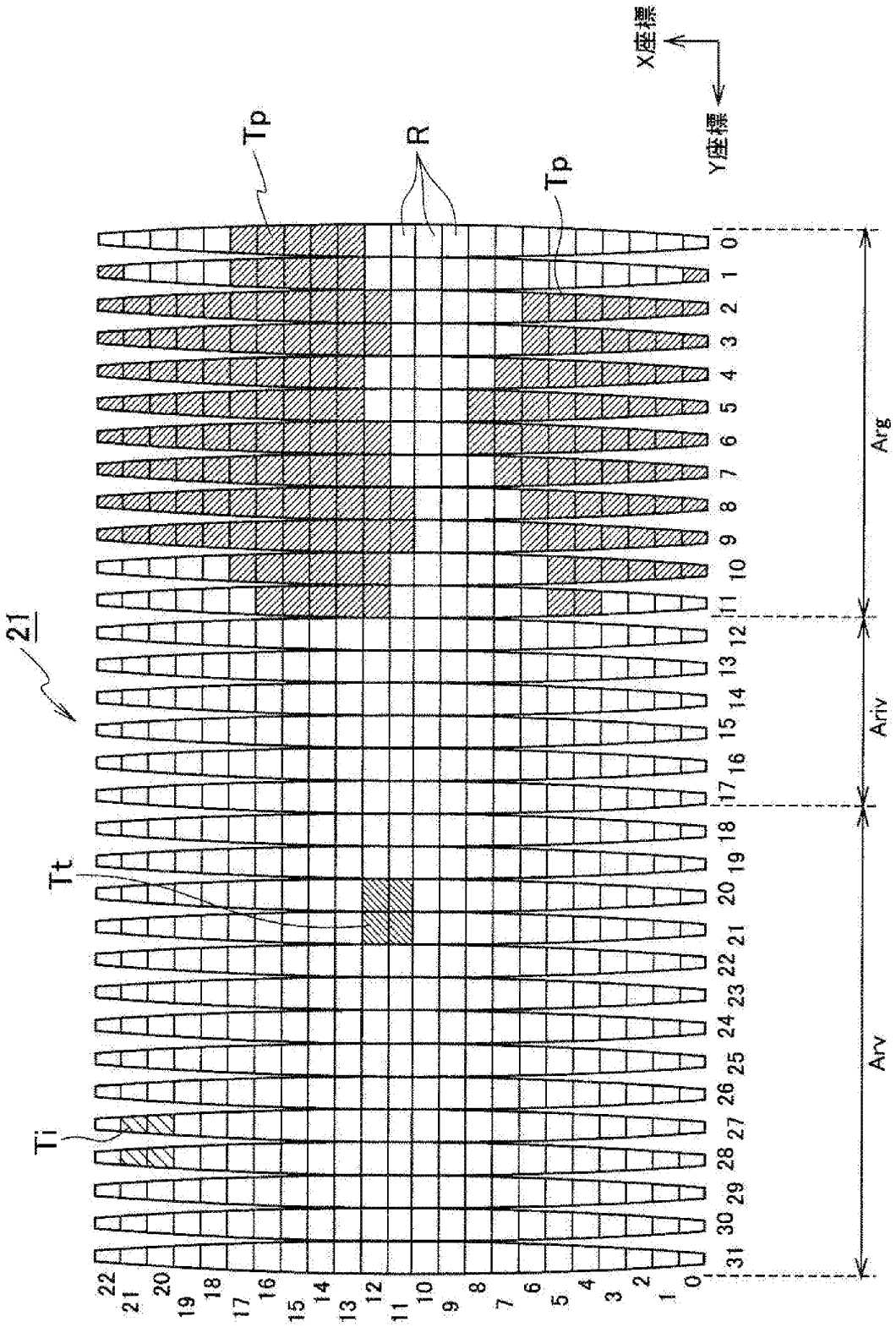
[Fig. 6]


200r
31
30
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
21
Tt
Tp
R

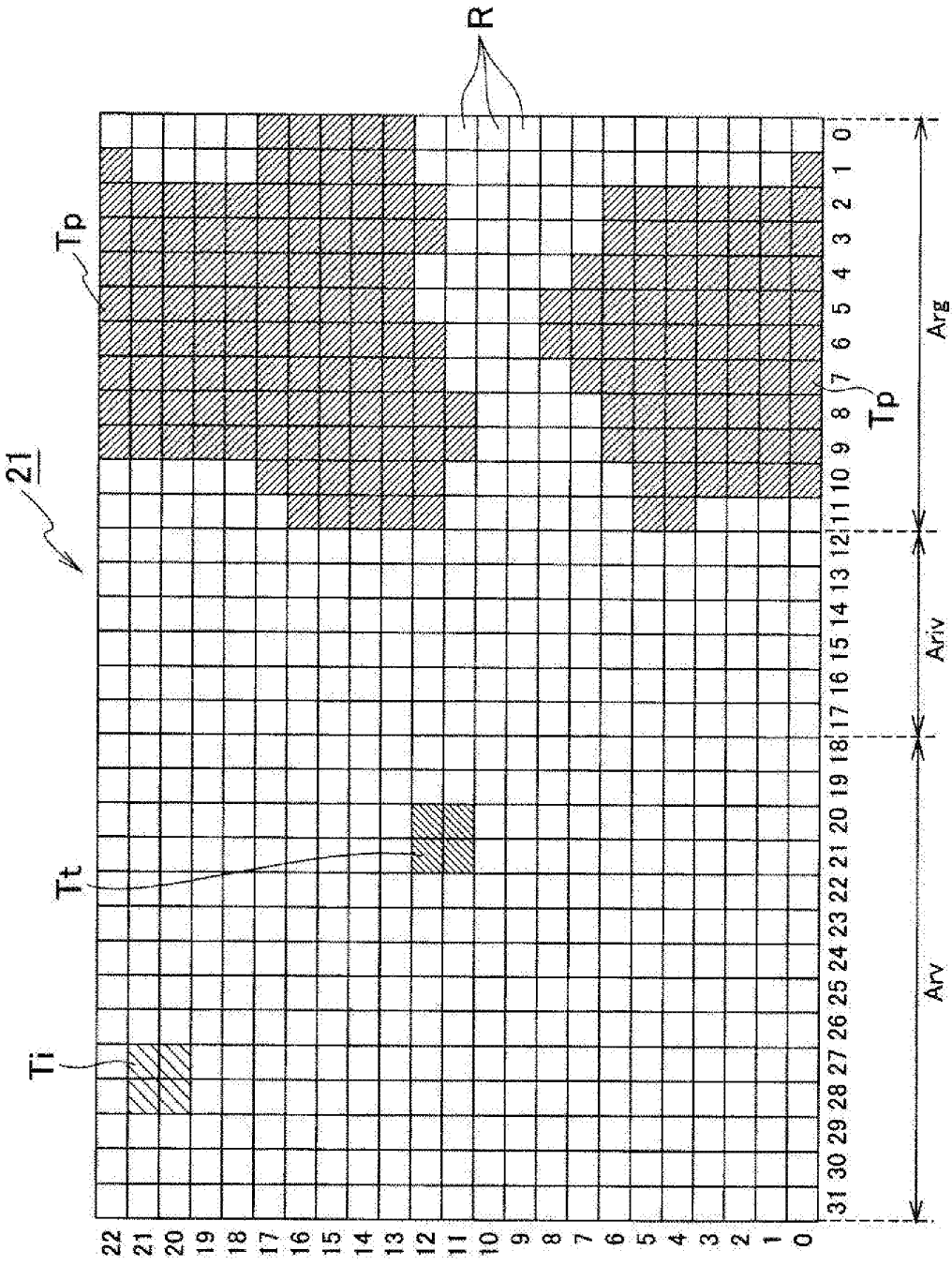
[Fig. 7]


R
17
16
18
15
19
14
20
13
21
12
200r
22
11
21
0
10
1
9
2
8
3
7
4
6
5

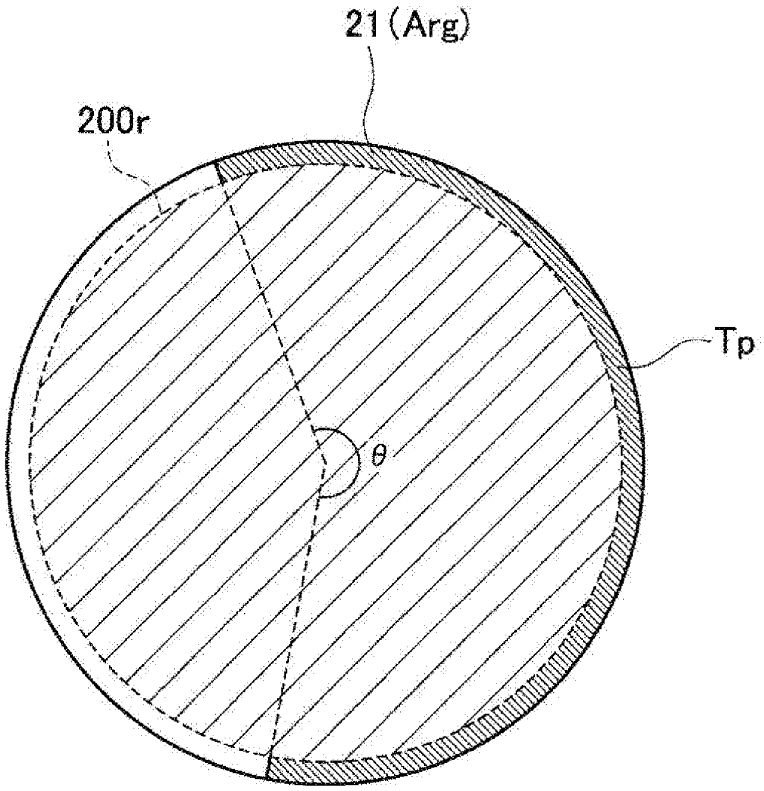
[Fig. 8]


X座標
Y座標
Tp
R
Tp
21
Tt
Ti
Arg
Ariv
Arv

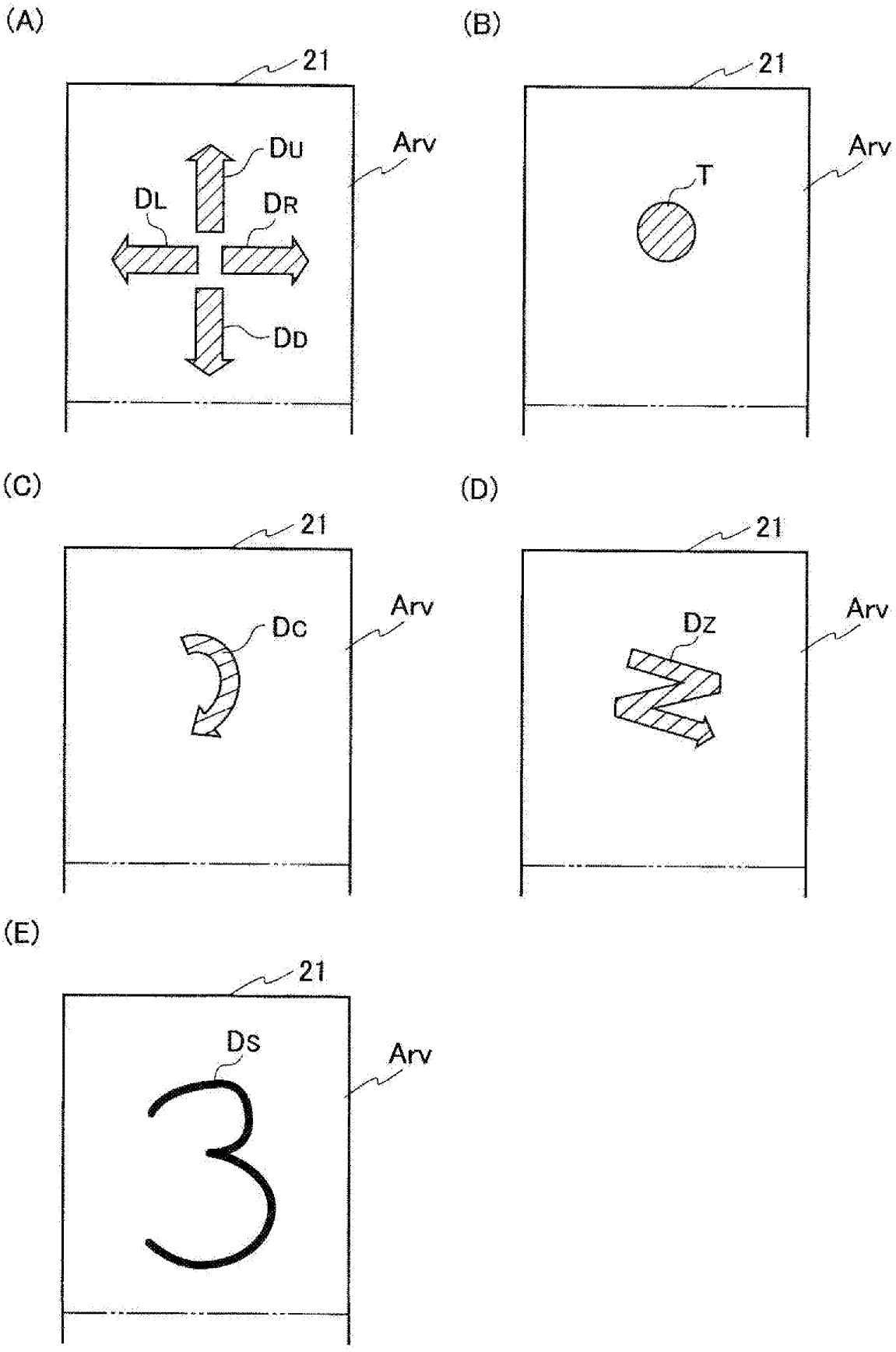
[Fig. 9]


R
Tp
21
Tt
Ti
Tp
Arg
Ariv
Arv
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
22 21 20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0

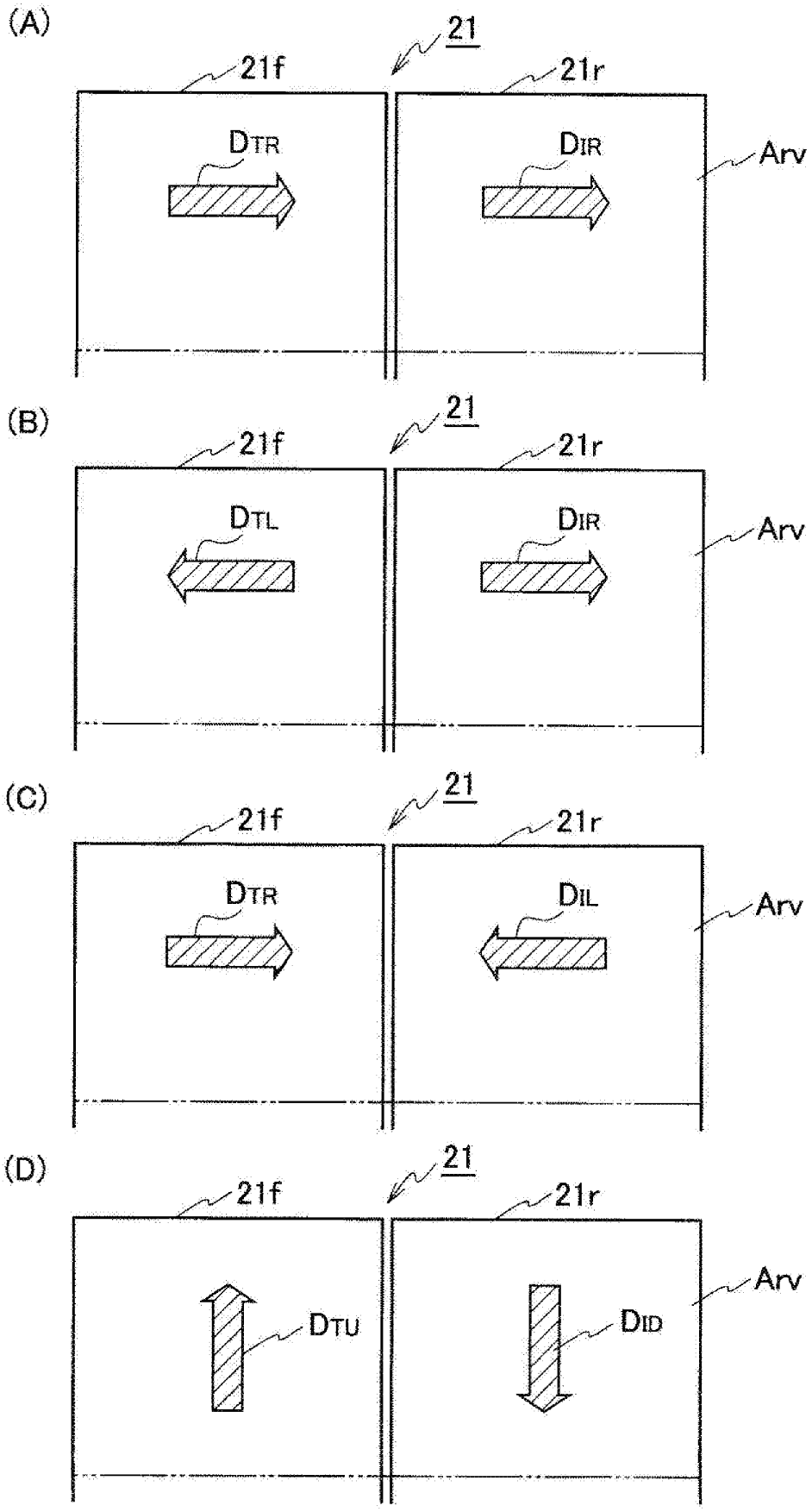
[Fig. 10]


21 (Arg)
200r
Tp
θ

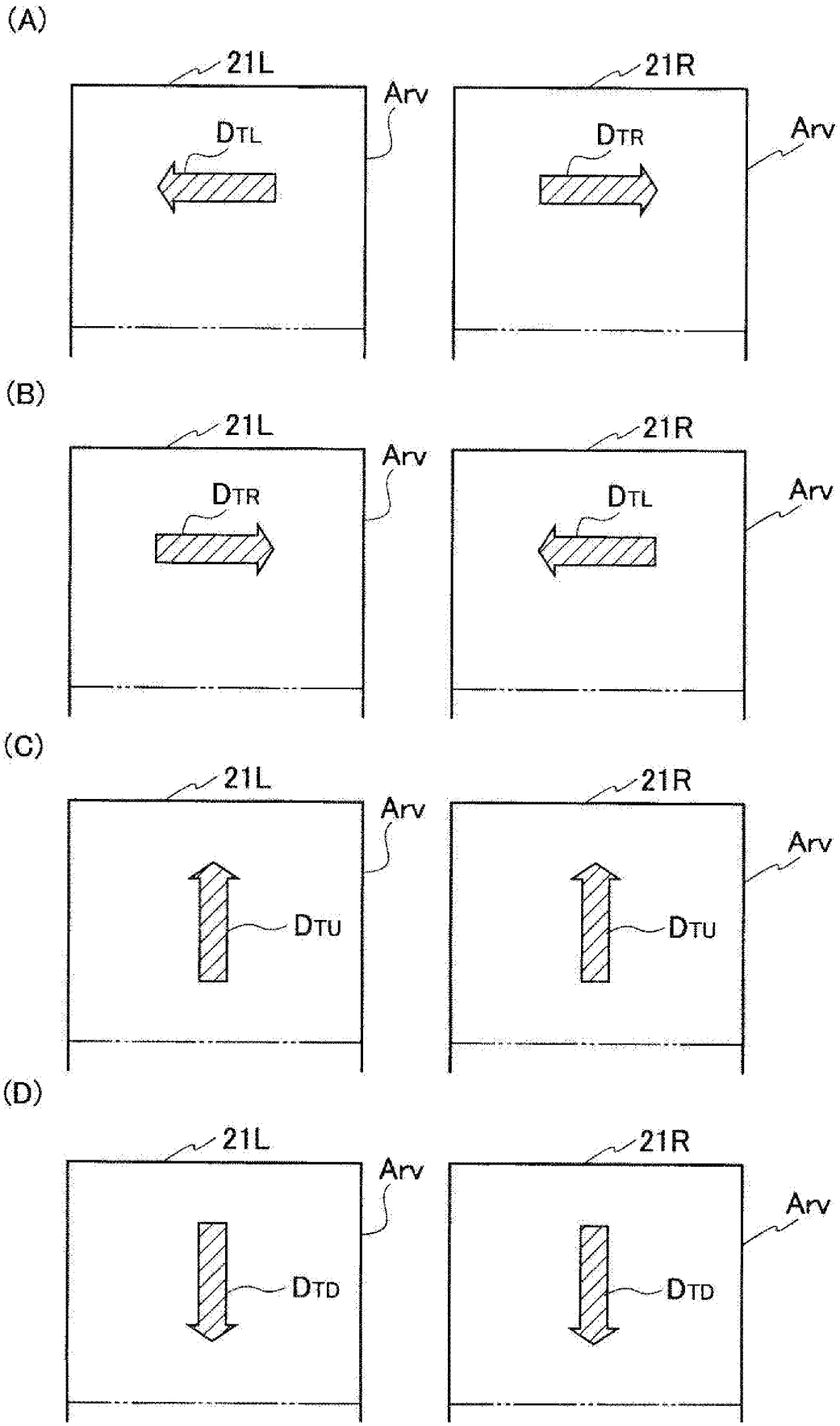
[Fig. 11]


(A)
21
Arv
DU
DL
DR
DD
(B)
21
Arv
T
(C)
21
Arv
DC
(D)
21
Arv
DZ
(E)
21
Arv
DS
3

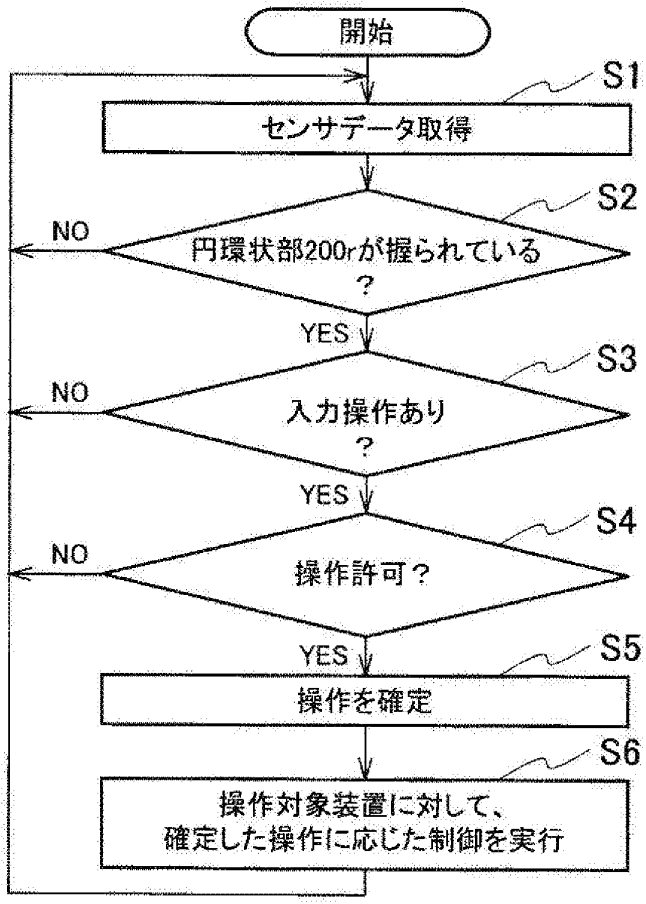
[Fig. 12]


(A)
21
21f
21r
DTR
DIR
Arv
(B)
21
21f
21r
DTL
DIR
Arv
(C)
21
21f
21r
DTR
DIL
Arv
(D)
21
21f
21r
DTU
DID
Arv

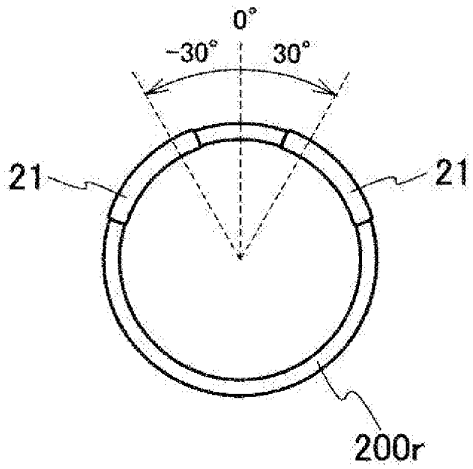
[Fig. 13]


(A)
21L
Arv
DTL
21R
Arv
DTR
(B)
21L
Arv
DTR
21R
Arv
DTL
(C)
21L
Arv
DTU
21R
Arv
DTU
(D)
21L
Arv
DTD
21R
Arv
DTD

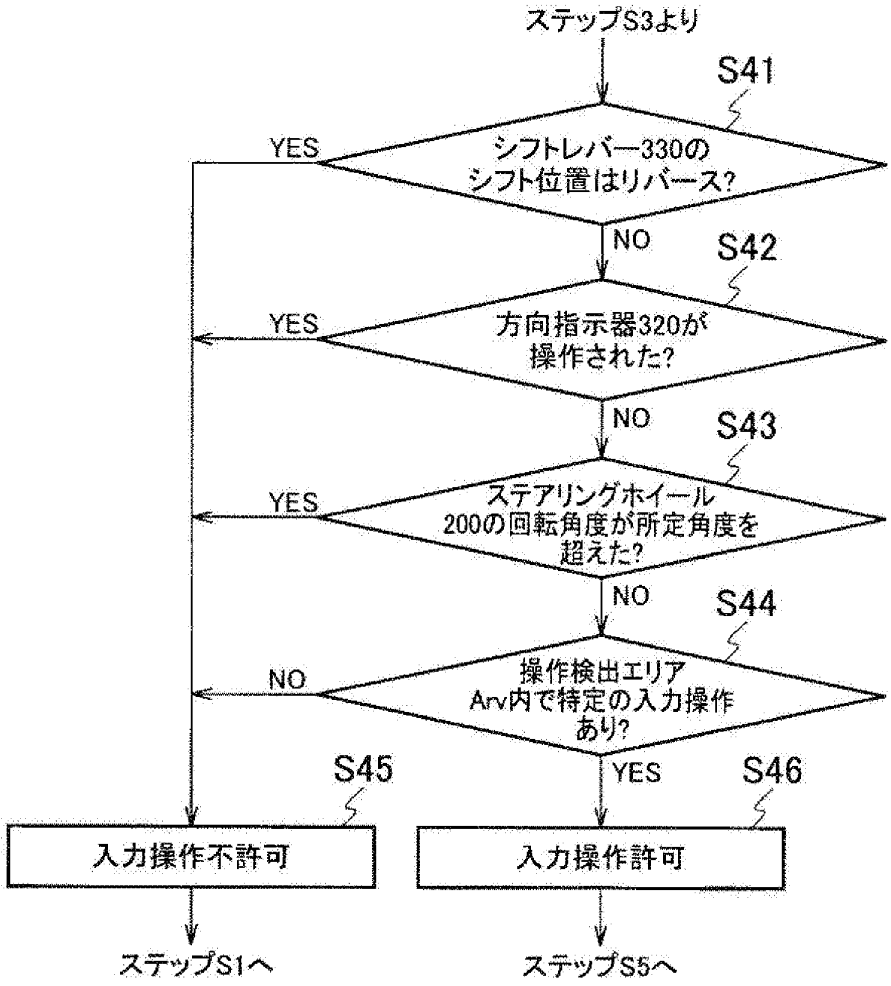
[Fig. 14]


開始
S1
センサデータ取得
S2
NO
円環状部200rが握られている
？
YES
S3
NO
入力操作あり
？
YES
S4
NO
操作許可？
YES
S5
操作を確定
S6
操作対象装置に対して、
確定した操作に応じた制御を実行

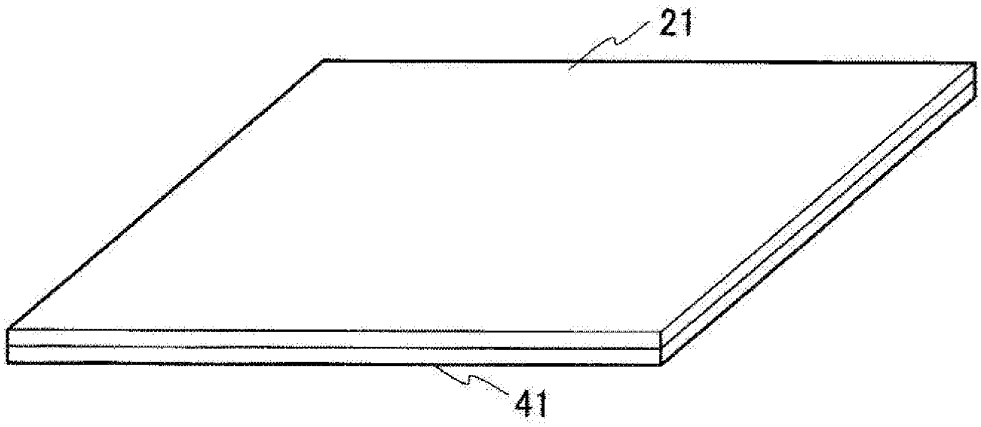
[Fig. 15]



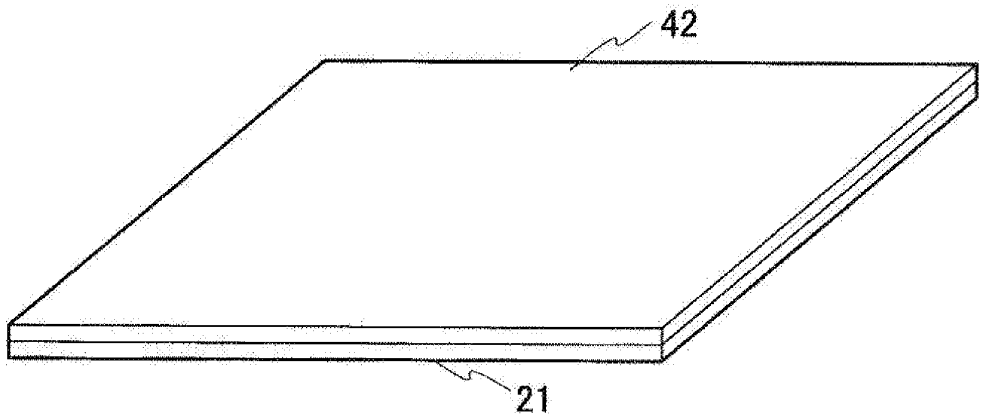
[Fig. 16]


ステップS3より
S41
シフトレバー330の
シフト位置はリバース?
YES
NO
S42
方向指示器320が
操作された?
YES
NO
S43
ステアリングホイール
200の回転角度が所定角度を
超えた?
YES
NO
S44
操作検出エリア
Arv内で特定の入力操作
あり?
NO
YES
S45
S46
入力操作不許可
入力操作許可
ステップS1へ
ステップS5へ

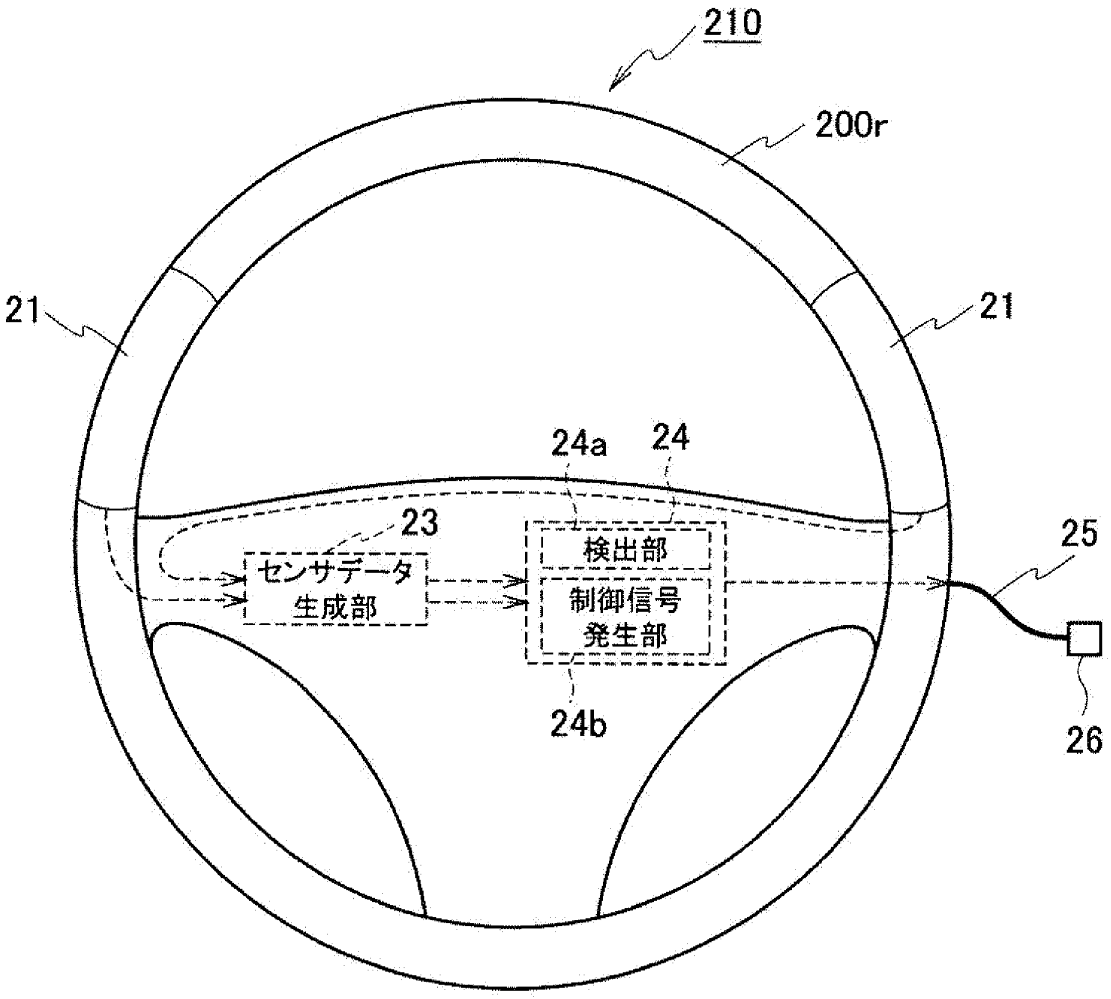
[Fig. 17]


21
41

[Fig. 18]



[Fig. 19]



drawing open —

1 2 3 Four Five 6 7 8 9 Ten ...

Magnify and Rotate

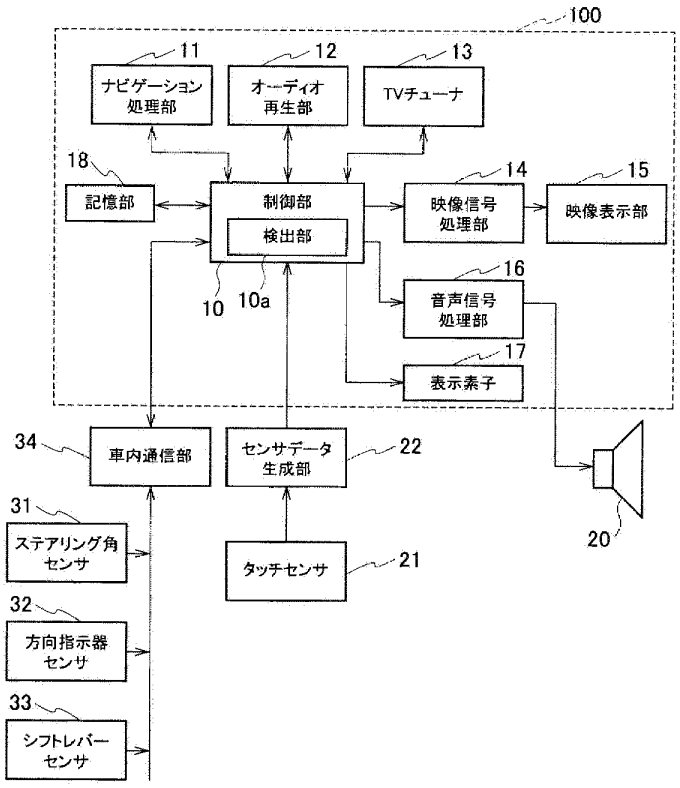


Figure 1

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DEVICE AND METHOD FOR CONTROLLING OPERATION TARGET DEVICE IN VEHICLE

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Applicant(s): JVC KENWOOD CORP, ; 株式会社ＪＶＣケンウッド

Classification: **- international:** ***B60R16/02; B60R16/027***
- cooperative:

Application number: JP20120043554 20120229 Global Dossier

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Abstract of JP2013075652 (A)

PROBLEM TO BE SOLVED: To provide a control device for controlling an operation target device in a vehicle, which can operate the operation target device without detaching or largely shifting a hand from a gripping part.SOLUTION: A sensor data generation part 22 generates sensor data based on a contact detection signal obtained from a touch sensor 21 mounted to cover the gripping part of a steering wheel. A detection part 10a detects whether the driver grips the gripping part or not and an input operation to the touch sensor 21. When it is detected by the detection part 10a that the driver grips the holding part and it is detected that a specific input operation has been performed to the touch sensor 21, a control part 10 controls the operation target device according to the specific input operation. The control part 10 invalidates the control of the operation target device when the vehicle is in a specific condition.

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最終頁に続く

(54)【発明の名称】車両における操作対象装置の制御装置及び制御方法

(57)【特許請求の範囲】
【請求項１】
複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、
前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、
前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部と、
を備え、
前記制御部は、方向指示器が操作されたとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置。
【請求項２】
複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、

前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、
前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部と、
を備え、
前記制御部は、シフトレバーのシフト位置がリバースとなったとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置。

【請求項３】
前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の入力操作を検出する操作検出エリアとが設定されており、
前記検出部は、前記グリップ検出エリアから得られる接触検出信号に基づくセンサデータによって運転者が前記握持部を握っているか否かを検出し、前記操作検出エリアから得られる接触検出信号に基づくセンサデータによって前記特定の入力操作を検出する
ことを特徴とする請求項１または２に記載の車両における操作対象装置の制御装置。

【請求項４】
複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、
前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、
前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部と、
を備え、
前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の入力操作を検出する操作検出エリアとが設定されており、
前記検出部は、前記グリップ検出エリアから得られる接触検出信号に基づくセンサデータによって運転者が前記握持部を握っているか否かを検出し、前記操作検出エリアから得られる接触検出信号に基づくセンサデータによって前記特定の入力操作を検出し、
前記制御部は、車両が特定の状態にあるときに、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置。

【請求項５】
前記制御部は、前記特定の入力操作として、前記操作検出エリアに対して、前記握持部を前記ステアリングホイールの径方向に切断したときの断面における周方向に離間した２箇所を２つの指によって操作したパターンに応じて、前記操作対象装置を制御することを特徴とする請求項３または４に記載の車両における操作対象装置の制御装置。

【請求項６】
前記制御部は、さらに、前記ステアリングホイールの回転角度が所定の角度を超えたとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることを特徴とする請求項１～４のいずれか１項に記載の車両における操作対象装置の制御装置。

【請求項７】
前記タッチセンサは、運転者が左手で握る握持部の所定の範囲に装着された第１のタッチセンサと右手で握る握持部の所定の範囲に装着された第２のタッチセンサとを含み、

前記制御部は、前記特定の入力操作として、前記第１のタッチセンサに対する第１の入力操作と前記第２のタッチセンサに対する第２の入力操作との組み合わせによるパターンに応じて、前記操作対象装置を制御する

ことを特徴とする請求項１～６のいずれか１項に記載の車両における操作対象装置の制御装置。

【請求項８】

複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、

前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、

方向指示器が操作されたか否かを検出し、

車両が、方向指示器が操作された特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、車両が、方向指示器が操作された特定の状態にあることが検出された場合には、前記操作対象装置を制御を無効とする

ことを特徴とする車両における操作対象装置の制御方法。

【請求項９】

複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、

前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、

シフトレバーのシフト位置がリバースとなったか否かを検出し、

車両が、シフトレバーのシフト位置がリバースとなった特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、車両が、シフトレバーのシフト位置がリバースとなった特定の状態にあることが検出された場合には、前記操作対象装置を制御を無効とする

ことを特徴とする車両における操作対象装置の制御方法。

【請求項１０】

前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の操作を検出する操作検出エリアとが設定されており、

前記グリップ検出エリアに対する手のひらの接触によって、運転者が前記タッチセンサを握っていることを検出し、

前記操作検出エリアに対する指の接触によって、前記特定の入力操作が行われたことを検出する

ことを特徴とする請求項８または９に記載の車両における操作対象装置の制御方法。

【請求項１１】

複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、

前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、

車両が特定の状態にあるか否かを検出し、

車両が特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、

前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の操作を検出する操作検出エリアとが設定されており、

前記グリップ検出エリアに対する手のひらの接触によって、運転者が前記タッチセンサを握っていることを検出し、
前記操作検出エリアに対する指の接触によって、前記特定の入力操作が行われたことを検出する
ことを特徴とする車両における操作対象装置の制御方法。
【請求項１２】
前記特定の入力操作として、前記操作検出エリアに対して、前記握持部を前記ステアリングホイールの径方向に切断したときの断面における周方向に離間した２箇所を２つの指によって操作したパターンに応じて、前記操作対象装置を制御することを特徴とする請求項１０または１１に記載の車両における操作対象装置の制御方法。
【請求項１３】
前記ステアリングホイールの回転角度が所定の角度を超えたとき車両が特定の状態にあるにあるとして、前記操作対象装置の制御を無効とすることを特徴とする請求項８～１１のいずれか１項に記載の車両における操作対象装置の制御方法。
【請求項１４】
前記タッチセンサは、運転者が左手で握る握持部の所定の範囲に装着された第１のタッチセンサと右手で握る握持部の所定の範囲に装着された第２のタッチセンサとを含み、
前記特定の入力操作として、前記第１のタッチセンサに対する第１の入力操作と前記第２のタッチセンサに対する第２の入力操作との組み合わせによるパターンに応じて、前記操作対象装置を制御する
ことを特徴とする請求項８～１３のいずれか１項に記載の車両における操作対象装置の制御方法。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は、車両に搭載されているナビゲーション装置等の車載機器、または、変速機や方向指示器等の車両の動作を制御する車両動作制御装置を操作対象装置とし、操作対象装置を制御する制御装置及び制御方法に関する。
【背景技術】
【０００２】
車両に搭載されているナビゲーション装置等の車載機器を操作するための操作スイッチをステアリングホイールに配置した車両が普及している（特許文献１参照）。操作スイッチをステアリングホイールに配置すれば、運転者は車載機器を操作する際に車載機器まで手を伸ばす必要がないので、操作性が向上する。特許文献１に記載されているように、操作スイッチは、実際には、運転者が手で握る握持部であるステアリングホイールの円環状部ではなく、エアバッグが収納されているセンター部と円環状部との間を連結する連結部に配置されるのが通常である。従って、運転者は、操作スイッチを操作するために、握っている円環状部から手を離したり、手を大きくずらしたりする必要がある。特許文献２には、円環状部の背面や内側側面に操作スイッチを配置することが記載されている。
【先行技術文献】
【特許文献】
【０００３】
【特許文献１】特開２００７－１０６３５３号公報
【特許文献２】特開２００５－３４８１２３号公報
【特許文献３】特開２００８－１９５２２０号公報
【発明の概要】
【発明が解決しようとする課題】
【０００４】
特許文献２に記載の発明によれば、円環状部に操作スイッチを配置しているので、円環状部から手を離したり、手を大きくずらしたりすることなく、操作スイッチを操作するこ

とができる。しかしながら、特許文献２に記載されている操作スイッチは押しボタンによるキーや凹凸を設けたキーであり、この種のキーは運転者がステアリングホイールを操作する際の支障となる可能性がある。運転者が握る円環状部に大きな凹凸を設けることは好ましくない。また、円環状部に操作スイッチのような操作部を配置した場合、運転者が通常の運転のために円環状部を握っている場合のように、操作対象装置を操作しようとする意思がない場合に、不用意に操作対象装置が操作されないようにすることが求められる。さらに、車両の状態によっては誤操作を招く場合があり、誤操作を極力少なくすることが求められる。

【０００５】

本発明はこのような要望に対応するため、握持部から手を離したり、手を大きくずらしたりすることなく操作対象装置を操作することができ、運転者がステアリングホイールを操作する際に支障となる可能性を大幅に低減させることができる車両における操作対象装置の制御装置及び制御方法を提供することを目的とする。また、誤操作を大幅に低減させることができる車両における操作対象装置の制御装置及び制御方法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】

【０００６】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部とを備え、前記制御部は、方向指示器が操作されたとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置を提供する。

【０００７】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部とを備え、前記制御部は、シフトレバーのシフト位置がリバースとなったとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置を提供する。

【０００８】

上記の車両における操作対象装置の制御装置において、前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の入力操作を検出する操作検出エリアとが設定されており、前記検出部は、前記グリップ検出エリアから得られる接触検出信号に基づくセンサデータによって運転者が前記握持部を握っているか否かを検出し、前記操作検出エリアから得られる接触検出信号に基づくセンサデータによって前記特定の入力操作を検出することが好ましい。

【０００９】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両の

ステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサから得られる接触検出信号に基づいて、どの検出領域が触られているかを示す位置データを含むセンサデータを生成するセンサデータ生成部と、前記センサデータに基づいて、運転者が前記握持部を握っているか否か、及び、前記タッチセンサに対する入力操作を検出する検出部と、前記検出部によって運転者が前記握持部を握っていることが検出され、かつ、前記タッチセンサに対して特定の入力操作が行われたことが検出された場合に、前記特定の入力操作に応じて、前記タッチセンサによって操作する対象の操作対象装置を制御する制御部とを備え、前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の入力操作を検出する操作検出エリアとが設定されており、前記検出部は、前記グリップ検出エリアから得られる接触検出信号に基づくセンサデータによって運転者が前記握持部を握っているか否かを検出し、前記操作検出エリアから得られる接触検出信号に基づくセンサデータによって前記特定の入力操作を検出し、前記制御部は、車両が特定の状態にあるときに、前記操作対象装置の制御を無効とすることを特徴とする車両における操作対象装置の制御装置を提供する。

【００１０】

上記の車両における操作対象装置の制御装置において、前記制御部は、前記特定の入力操作として、前記操作検出エリアに対して、前記握持部を前記ステアリングホイールの径方向に切断したときの断面における周方向に離間した２箇所を２つの指によって操作したパターンに応じて、前記操作対象装置を制御することが好ましい。

上記の車両における操作対象装置の制御装置において、前記制御部は、さらに、前記ステアリングホイールの回転角度が所定の角度を超えたとき車両が特定の状態にあるとして、前記操作対象装置の制御を無効とすることが好ましい。

上記の車両における操作対象装置の制御装置において、前記タッチセンサは、運転者が左手で握る握持部の所定の範囲に装着された第１のタッチセンサと右手で握る握持部の所定の範囲に装着された第２のタッチセンサとを含み、前記制御部は、前記特定の入力操作として、前記第１のタッチセンサに対する第１の入力操作と前記第２のタッチセンサに対する第２の入力操作との組み合わせによるパターンに応じて、前記操作対象装置を制御することが好ましい。

【００１１】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、方向指示器が操作されたか否かを検出し、車両が、方向指示器が操作された特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、車両が、方向指示器が操作された特定の状態にあることが検出された場合には、前記操作対象装置を制御を無効とすることを特徴とする車両における操作対象装置の制御方法を提供する。

【００１２】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、シフトレバーのシフト位置がリバースとなったか否かを検出し、車両が、シフトレバーのシフト位置がリバースとなった特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、車両が、シフトレバーのシフト位置がリバースとなった特定の状態にあることが検出された場合には、前記操作対象装置を制御を無効と

することを特徴とする車両における操作対象装置の制御方法を提供する。

【００１３】

上記の車両における操作対象装置の制御方法において、前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の操作を検出する操作検出エリアとが設定されており、前記グリップ検出エリアに対する手のひらの接触によって、運転者が前記タッチセンサを握っていることを検出し、前記操作検出エリアに対する指の接触によって、前記特定の入力操作が行われたことを検出することが好ましい。

【００１４】

本発明は、上述した従来の技術の課題を解決するため、複数の検出領域を有し、車両のステアリングホイールにおける運転者が握る握持部の所定の範囲に、前記握持部を覆うように装着されたタッチセンサを運転者が握っているか否かを検出し、前記タッチセンサに対して特定の入力操作が行われたか否かを検出し、車両が特定の状態にあるか否かを検出し、車両が特定の状態にはないことが検出され、運転者が前記タッチセンサを握っていることが検出され、かつ、前記特定の入力操作が行われたことが検出された場合に、前記タッチセンサによって操作する対象の操作対象装置を制御し、前記タッチセンサには、前記複数の検出領域の一部を含み、運転者の手のひらの接触を検出するグリップ検出エリアと、前記複数の検出領域の他の一部を含み、指の接触による前記特定の操作を検出する操作検出エリアとが設定されており、前記グリップ検出エリアに対する手のひらの接触によって、運転者が前記タッチセンサを握っていることを検出し、前記操作検出エリアに対する指の接触によって、前記特定の入力操作が行われたことを検出することを特徴とする車両における操作対象装置の制御方法を提供する。

【００１５】

上記の車両における操作対象装置の制御方法において、前記特定の入力操作として、前記操作検出エリアに対して、前記握持部を前記ステアリングホイールの径方向に切断したときの断面における周方向に離間した２箇所を２つの指によって操作したパターンに応じて、前記操作対象装置を制御することが好ましい。

上記の車両における操作対象装置の制御方法において、前記ステアリングホイールの回転角度が所定の角度を超えたとき車両が特定の状態にあるにあるとして、前記操作対象装置の制御を無効とすることが好ましい。

上記の車両における操作対象装置の制御方法において、前記タッチセンサは、運転者が左手で握る握持部の所定の範囲に装着された第１のタッチセンサと右手で握る握持部の所定の範囲に装着された第２のタッチセンサとを含み、前記特定の入力操作として、前記第１のタッチセンサに対する第１の入力操作と前記第２のタッチセンサに対する第２の入力操作との組み合わせによるパターンに応じて、前記操作対象装置を制御することが好ましい。

【発明の効果】

【００１６】

本発明の車両における操作対象装置の制御装置及び制御方法によれば、握持部から手を離したり、手を大きくずらしたりすることなく操作対象装置を操作することができ、運転者がステアリングホイールを操作する際に支障となる可能性を大幅に低減させることができる。また、誤操作を大幅に低減させることができる。

【図面の簡単な説明】

【００１７】

【図１】本発明の車両における操作対象装置の制御装置の一実施形態を示すブロック図である。

【図２】一実施形態の操作対象装置の制御装置を備える車両の例を示す部分平面図である。

【図３】一実施形態におけるタッチセンサをステアリングホイールに装着する位置及び範囲の例を示す図である。

【図４】一実施形態におけるタッチセンサをステアリングホイールに装着する位置及び範囲の他の例を示す図である。
【図５】タッチセンサを変形ステアリングホイールに装着する例を示す図である。
【図６】ステアリングホイールにおけるタッチセンサの部分を握っている状態でセンサデータが得られる部分の例を示す部分斜視図である。
【図７】タッチセンサにおける断面周方向の座標を示す断面図である。
【図８】図６に示すタッチセンサを展開した状態を示す平面図である。
【図９】図８に示す各領域を均等の大きさに変換した状態を示す模式図である。
【図１０】ステアリングホイールにおけるタッチセンサの部分を握っていると判定するための要件の例を示す図である。
【図１１】タッチセンサに対する特定の入力操作の例を示す模式図である。
【図１２】タッチセンサに対する特定の入力操作の他の例を示す模式図である。
【図１３】タッチセンサに対する特定の入力操作のさらに他の例を示す模式図である。
【図１４】一実施形態の動作を説明するためのフローチャートである。
【図１５】ステアリングホイールの回転角度を説明するための図である。
【図１６】図１４のステップＳ４の具体的な処理の例を示すフローチャートである。
【図１７】タッチセンサを操作した際に色を変化させるための構成例を示す模式的な斜視図である。
【図１８】タッチセンサを操作した際に触覚を変化させるための構成例を示す模式的な斜視図である。
【図１９】ステアリングホイールの構成例を示す平面図である。
【発明を実施するための形態】
【００１８】
以下、本発明の車両における操作対象装置の制御装置及び制御方法の一実施形態について、添付図面を参照して説明する。図１，図２において、車載機器１００は、車両のダッシュボード内に装着されている。図１に示す例では、車載機器１００は、制御部１０，ナビゲーション処理部１１，オーディオ再生部１２，テレビジョン（ＴＶ）チューナ１３，映像信号処理部１４，映像表示部１５，音声信号処理部１６，表示素子１７，記憶部１８を備えている。制御部１０は検出部１０ａを含む。
【００１９】
ナビゲーション処理部１１は地図データを保持する記憶部とＧＰＳアンテナ等を有しており、制御部１０とナビゲーション処理部１１とが協同して経路案内を行う。オーディオ再生部１２は、制御部１０による制御に従って、例えばコンパクトディスク等の光ディスクや半導体メモリに記録されているオーディオ信号を再生する。ＴＶチューナ１３は、制御部１０による制御に従って、所定の放送局のＴＶ放送波信号を受信する。ナビゲーション処理部１１またはＴＶチューナ１３より出力された映像信号は、制御部１０を介して映像信号処理部１４に入力されて処理され、液晶パネル等の映像表示部１５に表示される。
【００２０】
ナビゲーション処理部１１，オーディオ再生部１２，ＴＶチューナ１３より出力された音声信号は、制御部１０を介して音声信号処理部１６に入力されて処理され、外部のスピーカ２０にて発音される。音声信号処理部１６は増幅部を含む。スピーカ２０は、車両のドアの内部等に設置されている。表示素子１７は例えば発光ダイオード（ＬＥＤ）であり、制御部１０による制御に従って、後述するタッチセンサ２１の接触状態に応じて点灯または消灯する。表示素子１７は、運転者から視認できるように、例えば車載機器１００の筐体に配置する。表示素子１７を車載機器１００から離して、車両のステアリングホイール２００の近傍に配置してもよい。記憶部１８は不揮発性のメモリである。
【００２１】
図２に示すように、操作部であるタッチセンサ２１は、ステアリングホイール２００の円環状部２００ｒに装着されている。円環状部２００ｒは、運転者が運転の際に握る部分である握持部である。図２に示す例では、タッチセンサ２１は、円環状部２００ｒにおけ

る左右それぞれの所定の角度範囲に装着されている。タッチセンサ２１は、複数箇所の接触を検出することができる、いわゆる多点検出（マルチタッチ）のタッチセンサである。タッチセンサ２１は、円環状部２００ｒの径方向の断面の周上に、３６０°の範囲で装着することが好ましい。３６０°未満の範囲であっても、実質的に円環状部２００ｒの断面の周のほぼ全体を覆っていればよい。

【００２２】

運転者は、円環状部２００ｒのタッチセンサ２１が装着された部分を握っている。図１において、タッチセンサ２１の出力はセンサデータ生成部２２に入力される。タッチセンサ２１を手で触ると、接触検出信号がセンサデータ生成部２２へと入力される。センサデータ生成部２２は、入力された接触検出信号に基づいて、タッチセンサ２１のどの位置から接触検出信号が得られたかを示す位置データを含むセンサデータを生成して制御部１０に供給する。タッチセンサ２１とセンサデータ生成部２２とを一体化してもよいし、センサデータ生成部２２を制御部１０内に設けてもよい。

【００２３】

タッチセンサ２１としては、例えば投影式静電容量（相互キャパシタンス）方式のタッチセンサを用いることができる。円環状部２００ｒに装着するタッチセンサ２１としては、一例として、ミクロ技術研究所が開発した可撓性を有するタッチパネルを採用することができる。この可撓性を有するタッチパネルは、センサ部を０．０２～０．０５ｍｍの板厚を有する超薄板ガラスとし、超薄板ガラスとＰＥＴ（ポリエチレンテレフタレート）フィルムとを貼り合わせた構造になっている。円環状部２００ｒにタッチセンサ２１を装着しても、タッチセンサ２１は手や指で知覚できるほどの凹凸を有さないので、運転者がステアリングホイール２００を操作する際に支障となることはほとんどない。

【００２４】

図２に破線にて示すように、タッチセンサ２１と車載機器１００とを結ぶ電線を、ステアリングホイール２００及びダッシュボードの内部を通して配線することが好ましい。

【００２５】

図１，図２において、ステアリング角センサ３１は、ステアリングホイール２００の回転角度を検出する。方向指示器センサ３２は、方向指示器３２０の操作を検出する。シフトレバーセンサ３３は、シフトレバー３３０によるシフト位置がどこにあるかを検出する。ステアリング角センサ３１，方向指示器センサ３２，シフトレバーセンサ３３の各検出信号は、車内通信部３４を介して制御部１０へと供給される。

【００２６】

図３を用いて、タッチセンサ２１をステアリングホイール２００の円環状部２００ｒに装着する位置及び範囲の例について説明する。なお、上、下、右、左とは、ステアリングホイール２００を回転させていない状態（車両が直進する状態）において、運転者の位置からステアリングホイール２００を見たときの上、下、右、左であるとする。図３（Ａ）は、円環状部２００ｒの全周にタッチセンサ２１を装着した例である。図３（Ｂ）は、図２と同様であり、円環状部２００ｒにおける上方で左右それぞれの所定の角度範囲にタッチセンサ２１を互いに離間させて装着した例である。図３（Ｃ）は、円環状部２００ｒにおける上方で右側のみの所定の角度範囲にタッチセンサ２１を装着した例である。

【００２７】

図３（Ｄ）は、円環状部２００ｒにおける下方で左右それぞれの所定の角度範囲にタッチセンサ２１を互いに離間させて装着した例である。図３（Ｅ）は、円環状部２００ｒにおける頂部を含む上方の比較的広い角度範囲にタッチセンサ２１を装着した例である。図３（Ｅ）は図３（Ｂ）における左右のタッチセンサ２１を連結したものに相当する。

【００２８】

図４は、図３（Ｂ）における左右のタッチセンサ２１を、上側のタッチセンサ２１ａと下側のタッチセンサ２１ｂとに分割した例である。図４の例では、上側のタッチセンサ２１ａは手の人差し指と親指による接触を検出し、下側のタッチセンサ２１ｂは主として手のひら，中指，薬指による接触を検出する。図５は、円形ではない変形ステアリングホイ

ール２０１にタッチセンサ２１を装着した例である。タッチセンサ２１は、変形ステアリングホイール２０１の左右の直線部２０１ｓに装着されている。運転者は握持部である直線部２０１ｓを握って運転し、タッチセンサ２１が手のひらや指による接触を検出する。

【００２９】

ここで、図２に示すように、タッチセンサ２１が円環状部２００ｒにおける上方で左右に装着されており、運転者がタッチセンサ２１の部分を握っている場合に、タッチセンサ２１によって手のひらや指の接触がどのように検出されるかについて説明する。図６は、図２の右側のタッチセンサ２１を運転者が握った場合に、手のひらと指が接触している範囲の例を示している。運転者が円環状部２００ｒを手で握る握り方、手の大きさは一様ではなく、図６は単なる例である。

【００３０】

図６に示す例では、ハッチングを付したＴｐで示す複数の検出領域Ｒが手のひらの接触を検出している部分であり、ハッチングを付したＴｔで示す複数の検出領域Ｒが親指の接触を検出している部分である。以下、手のひら接触検出部Ｔｐ、親指接触検出部Ｔｔと称することとする。図６では見えていない車両の進行方向側であるタッチセンサ２１の裏面側には、人差し指が接触する。

【００３１】

図６に示すように、タッチセンサ２１は手のひらや指の接触を検出する検出部分として複数の検出領域Ｒを有している。タッチセンサ２１の各検出領域Ｒには座標が設定されている。図６に示すように、円環状部２００ｒの周方向において、タッチセンサ２１の下端部に位置している検出領域Ｒを座標０とし、上端部に位置している検出領域Ｒまで１，２，…，３０，３１と周方向の座標を設定している。タッチセンサ２１における円環状部２００ｒの周方向の座標をＹ座標とする。

【００３２】

図７は、タッチセンサ２１を装着している部分で円環状部２００ｒの径方向に円環状部２００ｒを切断した断面図である。図７に示すように、円環状部２００ｒの断面において、例えば円環状部２００ｒの内径側に位置している検出領域Ｒを座標０とする。断面における周方向のそれぞれの検出領域Ｒに、円環状部２００ｒの内径側から正面側、正面側から外径側、外径側から裏面側、裏面側から内径側へと図７の反時計方向に１，２，…，２１，２２と座標を設定している。タッチセンサ２１における断面の周方向の座標をＸ座標とする。センサデータ生成部２２は、接触検出信号が得られた検出領域ＲのＸ座標，Ｙ座標によって運転者がタッチセンサ２１のどこを触っているかを示す位置データを得ることができる。

【００３３】

図６に示すタッチセンサ２１を展開すると、図８のようになる。図８に示すタッチセンサ２１の各領域を均等の大きさに変換した状態を模式的に示すと、図９のようになる。図８，図９においては、手のひら接触検出部Ｔｐと親指接触検出部Ｔｔに加えて、人差し指が接触している複数の検出領域Ｒである人差し指接触検出部Ｔｉも示している。なお、タッチセンサ２１に中指や薬指または小指が接触すれば、タッチセンサ２１はそれらの指の接触も検出する。本実施形態においては、運転者が、タッチセンサ２１上で特定の入力操作を行うのに好適な親指または人差し指を操作のための指として用いることとする。

【００３４】

親指または人差し指による入力操作の詳細については後に詳述することとする。制御部１０の検出部１０ａは、センサデータ生成部２２から出力されるセンサデータに基づいて、親指または人差し指によってタッチセンサ２１上で入力操作が行われたことを検出する。検出部１０ａは、センサデータ生成部２２から出力されるセンサデータに基づいて、円環状部２００ｒ（タッチセンサ２１）を握っていることも検出する。制御部１０は、タッチセンサ２１に対して行った特定の入力操作に応じて操作対象装置を制御する。

【００３５】

操作対象装置は一例として車載機器１００である。具体的には、制御部１０は、特定の

入力操作に応じて、ナビゲーション処理部１１における経路案内に関する制御を実行させたり、オーディオ再生部１２におけるオーディオ信号を再生または停止させたり、再生するトラック（楽曲）を進めたり戻したりすることができる。また、制御部１０は、特定の入力操作に応じて、ＴＶチューナ１３における受信チャンネルを切り換えたり、音声信号処理部１６の増幅部を制御して音量を減少または増加させたりすることができる。

【００３６】

操作対象装置の他の例は、車両の動作を制御する車両動作制御装置である。具体的には、制御部１０は、車内通信部３４を介して、変速機、方向指示器、エアーコンディショナのオン・オフ、エアーコンディショナの設定温度等を制御してもよい。なお、操作対象装置を車両動作制御装置とする場合には、センサデータ生成部２２から出力されるセンサデータを車両が有する制御部に入力して、車両動作制御装置を制御することが好ましい。操作対象装置を制御する制御部は、車載機器１００内の制御部１０であってもよいし、車両に備えられている車載機器１００外部の制御部であってもよい。

【００３７】

本実施形態によれば、運転者が握る円環状部２００ｒに極めて薄いタッチセンサ２１を装着して、タッチセンサ２１を操作することによって操作対象装置を操作するので、円環状部２００ｒから手を離したり、手を大きくずらしたりすることなく操作対象装置を操作することができる。また、タッチセンサ２１は円環状部２００ｒの表面上で凹凸がないため、運転者がステアリングホイール２００を操作する際に支障となる可能性はほとんどない。

【００３８】

ところで、運転者が通常の運転のために円環状部２００ｒを握っている場合のように、操作対象装置を操作しようとする意思がない場合に、不用意に操作対象装置が操作されないようにすることが必要となる。そこで、本実施形態においては、運転者が意図しない誤操作を回避するために、次のようにしている。

【００３９】

図８，図９に示すように、タッチセンサ２１上の複数の検出領域Ｒに、手のひらの接触を検出するためのグリップ検出エリアＡｒｇと、親指または人差し指による操作入力を有効として、操作入力を検出するための操作検出エリアＡｒｖと、グリップ検出エリアＡｒｇと操作検出エリアＡｒｖとの間の中間領域であり、操作入力を無効とする操作無効エリアＡｒivとを設定している。手のひら接触検出部Ｔｐはグリップ検出エリアＡｒｇ内に位置し、親指接触検出部Ｔｔ及び人差し指接触検出部Ｔｉは操作検出エリアＡｒｖ内に位置する。

【００４０】

操作無効エリアＡｒivは、グリップ検出エリアＡｒｇと操作検出エリアＡｒｖと同様に、手のひらまたは指の接触を検出する検出領域Ｒを有するものの、制御部１０（検出部１０ａ）またはセンサデータ生成部２２が操作無効エリアＡｒivからの入力操作を無効とするように処理することによって、操作無効エリアとすることができる。また、操作無効エリアＡｒivの範囲に検出領域Ｒを設けないようにタッチセンサ２１を構成することにより、操作無効エリアとしてもよい。この場合、図４に示す例と実質的に等価である。

【００４１】

運転者が通常の運転のために円環状部２００ｒを握っている場合には、手のひら接触検出部Ｔｐと親指接触検出部Ｔｔ及び人差し指接触検出部Ｔｉとは比較的近い位置となる。そこで、運転者が単に円環状部２００ｒを握っている場合と、操作対象装置を操作しようとしてタッチセンサ２１を触った場合とを的確に区別するために、本実施形態においては、操作無効エリアＡｒivを設けている。運転者は、操作対象装置を操作しようとする場合には、親指や人差し指を意図的に伸ばしてタッチセンサ２１を触って、後述する特定の入力操作を行うようにする。制御部１０は、操作検出エリアＡｒｖ内で後述する特定の入力操作が行われた場合に、入力操作に応じて操作対象装置を制御する。

【００４２】

運転者が運転のために円環状部２００ｒを握っていない状態で、操作検出エリアＡｒｖに不用意に触った場合に、操作対象装置が誤操作されることを回避することも必要である。そこで、本実施形態においては、検出部１０ａは、グリップ検出エリアＡｒｇで所定の面積以上の手のひら接触検出部Ｔｐが得られた場合に、円環状部２００ｒを握っていると判断する。制御部１０は、円環状部２００ｒを握っており、かつ、操作検出エリアＡｒｖ内で特定の操作が行われた場合に操作対象装置を制御するように構成している。円環状部２００ｒを握っていると判断する手のひら接触検出部Ｔｐの面積は、複数の運転者がステアリングホイール２００を通常の握り方で握った場合の面積を統計的に調べて、適宜に設定すればよい。

【００４３】

グリップ検出エリアＡｒｇにおける手のひら接触検出部Ｔｐの面積は、運転者が円環状部２００ｒを握っていると判定するための要件の一例であり、判定するための要件これに限定されるものではない。図１０は、タッチセンサ２１のグリップ検出エリアＡｒｇの部分で円環状部２００ｒを切断した断面を示している。検出部１０ａは、手のひら接触検出部Ｔｐの断面周方向の角度θが所定の角度以上のときに円環状部２００ｒを握っていると判断することができる。所定の角度は例えば１８０°である。

【００４４】

以上のように、本実施形態においては、運転者が円環状部２００ｒ（タッチセンサ２１）を握っているか否かを判定して、円環状部２００ｒを握っている場合のみタッチセンサ２１に対する操作入力を受け付けるようにしているので、操作検出エリアＡｒｖに不用意に触った場合の誤操作を回避することができる。本実施形態においては、好ましい構成として、操作検出エリアＡｒｖをグリップ検出エリアＡｒｇから所定の距離離間させた位置に設けているので、運転者が意図的にタッチセンサ２１に対して特定の入力操作を行っていることを的確に検出することができる。従って、誤操作を大幅に低減させることができる。

【００４５】

また、本実施形態においては、グリップ検出エリアＡｒｇにおける手のひら接触検出部Ｔｐの面積や断面周方向の角度θを、運転者が円環状部２００ｒを握っているか否かを判定する要件としているので、円環状部２００ｒを握っているか否かを的確に判定することができる。従って、運転者が円環状部２００ｒを握っていない状態で、操作検出エリアＡｒｖに不用意に触った場合の誤操作も回避することができる。

【００４６】

制御部１０は、検出部１０ａが、グリップ検出エリアＡｒｇからの接触検出信号に基づくセンサデータによって運転者が円環状部２００ｒ（タッチセンサ２１）を握っていることを検出した場合に、運転者に、操作検出エリアＡｒｖによる操作入力が可能であることを知らせるために、表示素子１７を点灯させる。運転者は、表示素子１７の点灯・消灯によって、タッチセンサ２１によって操作対象装置を操作することができるか否かを判断することができる。表示素子１７をステアリングホイール２００の近傍に配置する方が好ましい。

【００４７】

ところで、図３（Ａ）のように円環状部２００ｒの全周にタッチセンサ２１を装着したり、図３（Ｅ）のように比較的広い範囲にタッチセンサ２１を装着したりした場合には、運転者がタッチセンサ２１を握る位置は固定されない。そこで、図８及び図９で説明したグリップ検出エリアＡｒｇと操作検出エリアＡｒｖや、必要に応じて設ける操作無効エリアＡｒivの位置は、運転者がタッチセンサ２１を握った位置に応じて動的に設定する必要がある。

【００４８】

そこで、制御部１０は、グリップ検出エリアＡｒｇ等が未設定の状態でタッチセンサ２１が握られた場合には、手のひら接触検出部Ｔｐを含む領域をグリップ検出エリアＡｒｇに設定する。手のひら接触検出部Ｔｐを含むＹ座標の所定の範囲をグリップ検出エリアＡ

ｒｇとすればよい。前述のように、手のひら接触検出部Ｔｐは所定の面積以上となるので、タッチセンサ２１上の複数の検出領域Ｒにおいて所定の面積以上触られていることが検出された部分が手のひら接触検出部Ｔｐとなる。または、図１０で説明したように、タッチセンサ２１の部分で円環状部２００ｒを切断した断面周方向で、所定の角度以上触られていることが検出された部分が手のひら接触検出部Ｔｐとなる。

【００４９】

制御部１０は、グリップ検出エリアＡｒｇを設定したら、グリップ検出エリアＡｒｇよりも上側のＹ座標の所定の範囲を操作検出エリアＡｒｖと設定する。この場合、必要に応じて、グリップ検出エリアＡｒｇと隣接するＹ座標の所定の範囲を操作無効エリアＡｒｉｖとして設定し、グリップ検出エリアＡｒｇをグリップ検出エリアＡｒｇから離間させた位置とする。

【００５０】

次に、図１１～図１３を用いて、運転者が親指または人差し指を用いてタッチセンサ２１に対して行う特定の入力操作の例を説明する。図１１（Ａ）～（Ｅ）は、タッチセンサ２１の運転者と対向する正面側または裏面側である半分を模式的な平面で示している。図１１（Ａ）～（Ｅ）に示す操作は、正面側であれ親指で、裏面側であれば人差し指で行われることになる。図１１（Ａ）において、D_Rは、親指または人差し指をタッチセンサ２１（操作検出エリアＡｒｖ）上で右方向に滑らせる右方向ドラッグであり、D_Lは親指または人差し指を右方向に滑らせる左方向ドラッグである。D_Uは親指または人差し指を上方向に滑らせる上方向ドラッグであり、D_Dは親指または人差し指をした方向に滑らせる下方向ドラッグである。

【００５１】

図１１（Ａ）において、右方向ドラッグD_R，左方向ドラッグD_L，上方向ドラッグD_U，下方向ドラッグD_Dの代わりに、親指または人差し指でそれぞれの方向にタッチセンサ２１をはじくフリックとしてもよい。

【００５２】

図１１（Ｂ）は、親指または人差し指でタッチセンサ２１をたたくタップＴを示している。図１１（Ｃ）は、親指または人差し指でタッチセンサ２１上に円弧を描くようにドラッグする円弧ドラッグD_Cを示している。図１１（Ｄ）は、親指または人差し指でタッチセンサ２１上にジグザグ状にドラッグするジグザグドラッグD_Zを示している。図１１（Ｅ）は、親指または人差し指で記号を書くようにドラッグする記号入力ドラッグD_Sを示している。図１１（Ｅ）は記号として数字の３を描いた状態を示している。記号としては、認識が比較的容易な数字やアルファベットを用いることが好ましい。

【００５３】

図１２（Ａ）～（Ｄ）は、タッチセンサ２１を開いてタッチセンサ２１の正面側の半分である正面部２１ｆと裏面側の半分である裏面部２１ｒとを模式的な平面で示している。正面部２１ｆは、図８，図９に示すＸ座標の０～１１の部分であり、裏面部２１ｒは、Ｘ座標の１２～２２の部分である。図８，図９に示す例では、厳密には正面部２１ｆと裏面部２１ｒとは均等の面積にはならないが、図１２（Ａ）～（Ｄ）では正面部２１ｆと裏面部２１ｒとを同じ面積で示している。図１２（Ａ）～（Ｄ）は理解を容易にするため、裏面部２１ｒは、裏面部２１ｒを円環状部２００ｒの裏面側から見た状態ではなく、正面部２１ｆから裏面部２１ｒを透視した状態を示している。

【００５４】

図１２（Ａ）～（Ｄ）に示すように、正面部２１ｆに対する親指による入力操作と裏面部２１ｒに対する人差し指による入力操作とを組み合わせたパターンをタッチセンサ２１に対する特定の入力操作としてもよい。図１２（Ａ）は、正面部２１ｆで親指を右方向に滑らせる右方向ドラッグD_{TR}と、裏面部２１ｒで人差し指を右方向に滑らせる右方向ドラッグD_{IR}との双方を行う例である。親指及び人差し指の双方を円環状部２００ｒの内周側から外周側へとドラッグすることにより、図１２（Ａ）が実現される。親指と人差し指の双方を、図１２（Ａ）とは逆方向にドラッグするパターンとしてもよい。

【００５５】
図１２（Ｂ）は、正面部２１ｆで親指を左方向に滑らせる左方向ドラッグD_{TL}と、裏面部２１ｒで人差し指を右方向に滑らせる右方向ドラッグD_{IR}との双方を行う例である。親指を円環状部２００ｒの外周側から内周側へとドラッグし、人差し指を円環状部２００ｒの内周側から外周側へとドラッグすることにより、図１２（Ｂ）が実現される。図１２（Ｃ）は、正面部２１ｆで親指を右方向に滑らせる右方向ドラッグD_{TR}と、裏面部２１ｒで人差し指を左方向に滑らせる左方向ドラッグD_{IL}との双方を行う例である。親指を円環状部２００ｒの内周側から外周側へとドラッグし、人差し指を円環状部２００ｒの外周側から内周側へとドラッグすることにより、図１２（Ｃ）が実現される。
【００５６】
図１２（Ｄ）は、正面部２１ｆで親指を上方向に滑らせる上方向ドラッグD_{TU}と、裏面部２１ｒで人差し指を下方向に滑らせる下方向ドラッグD_{ID}との双方を行う例である。親指を下方向、人差し指を上方向にドラッグとするパターンとしてもよく、親指と人差し指の双方を上方向または下方向にドラッグするパターンとしてもよい。ここでは、正面部２１ｆに対する親指による入力操作と裏面部２１ｒに対する人差し指による入力操作とを組み合わせた種々のパターンを示したが、入力操作のしやすさを考慮して適宜選択すればよい。
【００５７】
図１２（Ａ）～（Ｄ）に示すように、親指による入力操作と人差し指による入力操作とを組み合わせたパターンを、操作対象装置を制御するための特定の入力操作とすれば、さらに大幅に誤操作を低減させることが可能となる。
【００５８】
さらには、図３（Ａ），（Ｂ），（Ｄ），（Ｅ）や図４，図５のように、左右の手でタッチセンサ２１（２１ａ，２１ｂ）を操作できる場合に、左右の手による操作を組み合わせたパターンを、操作対象装置を制御するための特定の入力操作とすることも可能である。図１３（Ａ）～（Ｄ）は、図３（Ｂ）における左側のタッチセンサ２１を左側タッチセンサ２１Ｌとし、右側のタッチセンサ２１を右側タッチセンサ２１Ｒとした場合の、左右の手による操作を組み合わせたパターンの例を示している。ここでは、親指によって操作する図１２の正面部２１ｆに相当する面を模式的な平面で示している。
【００５９】
図１３（Ａ）は、左側タッチセンサ２１Ｌに対して親指を左方向に滑らせる左方向ドラッグD_{TL}と、右側タッチセンサ２１Ｒに対して親指を右方向に滑らせる右方向ドラッグD_{TR}とを組み合わせたパターンである。図１３（Ｂ）は、左側タッチセンサ２１Ｌに対して親指を右方向に滑らせる右方向ドラッグD_{TR}と、右側タッチセンサ２１Ｒに対して親指を左方向に滑らせる左方向ドラッグD_{TL}とを組み合わせたパターンである。
【００６０】
図１３（Ｃ）は、左側タッチセンサ２１Ｌと右側タッチセンサ２１Ｒの双方に対して、親指を上方向に滑らせる上方向ドラッグD_{TU}を組み合わせたパターンである。図１３（Ｄ）は、左側タッチセンサ２１Ｌと右側タッチセンサ２１Ｒの双方に対して、親指を下方向に滑らせる下方向ドラッグD_{TD}を組み合わせたパターンである。
【００６１】
左右の手による入力操作を組み合わせたパターンを、操作対象装置を制御するための特定の入力操作とすれば、運転者は円環状部２００ｒを両手で握ることになるので、安全運転に寄与することが可能である。特に、図３（Ｂ）の例は、円環状部２００ｒを両手で握る最も適切な位置にタッチセンサ２１を装着しているので、安全運転に寄与する点で最も好ましい。両手で左右のタッチセンサ２１を握っている場合に入力操作を受け付けるようにしてもよい。片手がタッチセンサ２１から離れた場合に入力操作を受け付けない状態としてもよい。片手がタッチセンサ２１から離れた場合には入力操作を受け付ける状態を継続してもよい。片手のみの特定の入力操作を用いる場合であっても、両手で左右のタッチセンサ２１を握っている場合に入力操作を受け付けるようにすれば、安全運転に寄与する

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【００６２】

運転者が通常の運転のために円環状部２００ｒを握っていて、操作対象装置を操作しようとする意思がない場合に、偶然に、親指による入力操作と人差し指による入力操作とを組み合わせた特定のパターンや、左右の手による入力操作を組み合わせた特定のパターンになってしまう可能性は比較的低いと考えられる。そこで、親指による入力操作と人差し指による入力操作とを組み合わせた特定のパターンや、左右の手による入力操作を組み合わせた特定のパターンのみを用いる場合には、上述した誤操作を回避するための工夫の一部または全てを省略してもよい。勿論、左右の手による入力操作を組み合わせた特定のパターンのみを用いる場合であっても、上述した誤操作を回避するための工夫を併せて採用することが好ましい。

【００６３】

記憶部１８は、以上説明した特定の入力操作または特定の入力操作を組み合わせたパターンと、操作対象装置に対する制御の種別とを対応させたテーブルを記憶している。制御部１０は、記憶部１８に記憶されたテーブルに従って、タッチセンサ２１に入力された操作に応じて操作対象装置を制御する。記憶部１８を制御部１０内に設けてもよい。

【００６４】

図１４のフローチャートを用いて、本実施形態において制御部１０で実行される処理について改めて説明する。図１３において、制御部１０は、ステップＳ１にて、センサデータ生成部２２から出力されるセンサデータを取得する。制御部１０は、ステップＳ２にて、検出部１０ａによる検出出力に基づいて、円環状部２００ｒが握られているか否かを判定する。円環状部２００ｒが握られていると判定されれば（YES）、制御部１０は、ステップＳ３に処理を移し、円環状部２００ｒが握られていると判定されなければ（NO）、制御部１０は、ステップＳ１に処理を戻す。

【００６５】

制御部１０は、ステップＳ３にて、検出部１０ａによる検出出力に基づいて、入力操作があったか否かを判定する。入力操作があったと判定されれば（YES）、制御部１０は、ステップＳ４に処理を移し、操作入力があったと判定されなければ（NO）、制御部１０は、ステップＳ１に処理を戻す。制御部１０は、ステップＳ４にて、ステップＳ３における入力操作によって操作対象装置に対する操作を許可するか否かを判定する。操作を許可すると判定されれば（YES）、制御部１０は、ステップＳ５に処理を移し、操作を許可すると判定されなければ（NO）、制御部１０は、ステップＳ１に処理を戻す。

【００６６】

上述のように、制御部１０は、操作検出エリアＡｒｖ内で特定の入力操作がなされた場合に操作対象装置に対する操作を許可し、操作無効エリアＡｒiv内で特定の入力操作がなされたとしても操作対象装置に対する操作を許可しない。また、制御部１０は、操作検出エリアＡｒｖ内で何らかの入力操作がなされたとしても、上述した特定の入力操作でない場合は操作対象装置に対する操作を許可せず、特定の入力操作がなされた場合のみ操作対象装置に対する操作を許可する。

【００６７】

制御部１０は、ステップＳ５にて、入力操作に基づいた操作を確定し、ステップＳ６にて、操作対象装置に対して、確定した操作に応じた制御を実行して、ステップＳ１に処理を戻す。

【００６８】

また、ステップＳ４では、車両が特定の状態にあるときに、操作対象装置に対する制御を許可しないようにする（即ち、無効にする）ことが好ましい。制御部１０には、操作対象装置に対する制御を許可するか否かを判断するためのステアリングホイール２００の回転角度が設定されている。図１５に示すように、ステアリングホイール２００を回転させていない状態を回転角度０°とし、例えば右方向に回転させたときをプラス、左方向に回転させたときをマイナスとして、一例として回転角度±３０°の範囲でタッチセンサ２１

に対する入力操作を有効として許可し、回転角度が±３０°を超えたらタッチセンサ２１に対する入力操作を無効として不許可とする。

【００６９】

回転角度が±３０°を超えた場合には、車両は右折または左折をしていたり、コーナリング走行していたりする特定の状態である。このような特定の状態で操作対象装置を制御しようとすれば誤操作が発生する可能性が高い。言い換えれば、このような特定の状態における操作入力は、ユーザの意図していない操作入力である可能性が高い。また安全性の上でも好ましくない。そこで、本実施形態では、車両が特定の状態にあるときには、操作対象装置に対する制御を無効とする。

【００７０】

前述のように、制御部１０にはステアリング角センサ３１によって検出されたステアリングホイール２００の回転角度が入力される。制御部１０は、ステアリング角センサ３１によって検出されたステアリングホイール２００の回転角度に応じて、タッチセンサ２１に対する入力操作を有効とする状態と無効とする状態とを切り換える。制御部１０には方向指示器センサ３２からの検出信号も入力される。そこで、制御部１０は、方向指示器センサ３２からの検出信号によって方向指示器３２０が操作された場合に、タッチセンサ２１に対する入力操作を無効としてもよい。方向指示器３２０が操作された場合は、ステアリングホイール２００が所定の回転角度を超えて回転される特定の状態になるとみなすことができる。なお、方向指示器３２０が右折または左折の合図以外の操作を兼用している場合があるが、ここでの方向指示器３２０の操作とは右折または左折の合図を行う操作である。

【００７１】

さらに、車両を後退させている最中にタッチセンサ２１に対して特定の入力操作を行って操作対象装置を制御することは好ましくない。誤操作が発生する可能性が高く、安全性の上でも好ましくない。そこで、制御部１０は、シフトレバーセンサ３３からの検出信号によって、シフトレバー３３０のシフト位置がリバースとなった場合にも、タッチセンサ２１に対する入力操作を無効とすることが好ましい。ステアリングホイール２００の回転角度が例えば±３０°の所定角度を超えた場合、または、方向指示器３２０が操作された場合に加えて、シフトレバー３３０のシフト位置がリバースとなった場合に操作対象装置に対する制御を無効とすることが好ましいが、一方のみとしてもよい。

【００７２】

なお、操作対象装置に対する制御を無効にするとは、仮に上述した特定の入力操作がなされたとしても特定の入力操作を無効として操作対象装置に対する制御を不許可とすることであってもよく、制御部１０に対してセンサデータ生成部２２から何らかのセンサデータが入力されても、制御部１０がセンサデータを無効することであってもよい。結果として、操作対象装置に対する制御を無効とすればよい。

【００７３】

図１６のフローチャートを用いて、図１４のステップＳ４の具体的な処理の例を説明する。図１６において、制御部１０は、ステップＳ４１にて、シフトレバー３３０のシフト位置がリバースであるか否かを判定する。シフト位置がリバースであれば（YES）、制御部１０は、ステップＳ４５にて、ステップＳ３での入力操作を不許可として、図１４のステップＳ１に移行させる。シフト位置がリバースでなければ（NO）、制御部１０は、ステップＳ４２にて、方向指示器３２０が操作されたか否かを判定する。方向指示器３２０が操作されたら（YES）、制御部１０は、ステップＳ４５にて、ステップＳ３での入力操作を不許可として、図１４のステップＳ１に移行させる。

【００７４】

方向指示器３２０が操作されなかったら（NO）、制御部１０は、ステップＳ４３にて、ステアリングホイール２００の回転角度が所定角度を超えたか否かを判定する。ステアリングホイール２００の回転角度が所定角度を超えたら（YES）、制御部１０は、ステップＳ４５にて、ステップＳ３での入力操作を不許可として、図１４のステップＳ１に移行さ

せる。ステアリングホイール２００の回転角度が所定角度を超えていなかったら（NO）、制御部１０は、ステップＳ４４にて、操作検出エリアＡｒｖ内で特定の入力操作がなされたか否かを判定する。特定の入力操作がなされなかったら（NO）、制御部１０は、ステップＳ４５にて、ステップＳ３での入力操作を不許可として、図１４のステップＳ１に移行させる。ステップＳ４５にて、入力操作を不許可とすれば、操作対象装置に対する制御が無効となる。特定の入力操作がなされたら（YES）、制御部１０は、ステップＳ４６にて、ステップＳ３での入力操作を許可して、図１４のステップＳ５に移行させる。

【００７５】

図１６に示す例では、ステップＳ４１，Ｓ４２，Ｓ４３の全てを設けたが、これらのステップの内の１つまたは２つのみとしてもよい。また、ステップＳ４１，Ｓ４２，Ｓ４３の全てまたはこれらのステップの内の２つを設ける場合、順番は任意である。なお、ここではシフトレバー３３０と称したが、車両の直進と後退の切り換え、変速機の変速比を変える操作部の形状は任意であり、フロアシフト，コラムシフト，パドルシフト等のいずれでもよい。これらは全てシフトレバーに含まれる。

【００７６】

以上のように、車両が右折，左折，コーナリング走行，後退等の特定の状態にあるときに、操作対象装置に対する制御を無効とすれば、運転者はこれらの特定の状態のときにタッチセンサ２１に対する入力操作を行わない。従って、安全性の向上に寄与する。

【００７７】

本実施形態による動作をまとめると、次の通りである。検出部１０ａ（第１の検出部）は、ステアリングホイール２００，２０１における運転者が握る握持部（円環状部２００ｒまたは直線部２０１ｓ）に装着されたタッチセンサ２１における第１のエリアが触られている状態であることを検出する。第１のエリアの例は、グリップ検出エリアＡｒｇである。検出部１０ａ（第２の検出部）は、第１のエリアが触られている状態で、タッチセンサ２１における第１のエリアよりも上側に位置する第２のエリアに対して特定の入力操作がなされたことを検出する。第２のエリアの例は、操作検出エリアＡｒｖである。運転時、親指または人差し指は手のひらよりも上方に位置するので、第１のエリアよりも上側を第２のエリアとすればよい。そして、第１のエリアが触られている状態であり、特定の入力操作がなされたら、タッチセンサ２１によって操作する対象の操作対象装置を特定の入力操作に応じて制御する。

【００７８】

上側に位置するエリアとは、ステアリングホイール２００を回転させていない状態で運転者が握持部を握った状態で、第１のエリアよりも上側に位置するエリアである。第１のエリアが所定の面積以上触られていることを検出した場合に、第１のエリアが触られている状態であるとすることが好ましい。

【００７９】

また、別の観点では、次の通りである。検出部１０ａ（第１の検出部）は、ステアリングホイール２００，２０１における運転者が握る握持部（円環状部２００ｒまたは直線部２０１ｓ）の所定の範囲に、握持部を覆うように装着されたタッチセンサ２１が、タッチセンサ２１上の第１のエリアにおいて、握持部をステアリングホイール２００，２０１の径方向に切断したときの断面における周方向の所定角度以上触られている状態であることを検出する。検出部１０ａ（第２の検出部）は、第１のエリアが所定角度以上触られている状態で、タッチセンサ２１における第１のエリアとは異なる第２のエリアに対して特定の入力操作がなされたことを検出する。第１のエリアが前記所定角度以上触られている状態であり、特定の入力操作がなされたら、タッチセンサ２１によって操作する対象の操作対象装置を特定の入力操作に応じて制御する。

【００８０】

第２のエリアは、第１のエリアよりも上側に位置するエリアであることが好ましい。上側に位置するエリアとは、ステアリングホイール２００を回転させていない状態で運転者が握持部を握った状態で、第１のエリアよりも上側に位置するエリアである。

【００８１】
図１７及び図１８は、タッチセンサ２１を操作したことを運転者に効果的に知らせるための構成例を示している。図１７及び図１８は、図９と同様、タッチセンサ２１を展開して矩形状に変換した模式図である。図１７は、タッチセンサ２１の下面側に発色物質を含む色変化シート４１を設けた例である。タッチセンサ２１に透明導電膜を用いることにより、運転者は、タッチセンサ２１を介して、タッチセンサ２１の下面に配置されている色変化シート４１の色を見ることができる。制御部１０による制御によって、タッチセンサ２１を触った部分の色変化シート４１の色を変化させることにより、運転者はタッチセンサ２１を操作したことを認識することができる。
【００８２】
図１８は、タッチセンサ２１の上面側に触覚（手触り）を変化させる触覚フィードバックシート４２を設けた例である。触覚フィードバックシート４２としては、例えば、フィンランドのSenseg社が開発した“E-Sense”と称されるシートを採用することができる。このシートは、フィルムを帯電させることで触覚のフィードバックを実現するものである。タッチセンサ２１の上面側に触覚フィードバックシート４２を設けても、タッチセンサ２１は指等の接触を検出することが可能である。触覚フィードバックシート４２を介してタッチセンサ２１を操作した場合に、制御部１０による制御によって、触覚フィードバックシート４２の触覚を変化させることにより、運転者はタッチセンサ２１を操作したことを認識することができる。
【００８３】
次に、図１９を用いてステアリングホイールの構成例について説明する。図１９に示すステアリングホイール２１０は、操作対象装置に対する制御信号をステアリングホイール２１０から出力させるように構成したものである。図１９において、図１，図２と同一部分には同一符号を付し、その説明を適宜省略する。図１９に示すように、ステアリングホイール２１０は、例えば円環状部２００ｒ以外の部分に、図１のセンサデータ生成部２２と同様のセンダデータ生成部２３と、制御部１０と同様の制御部２４を備えている。制御部２４は、検出部１０ａと同様の検出部２４ａと、制御信号発生部２４ｂを有する。
【００８４】
ステアリングホイール２１０を車両に装着した場合、制御信号発生部２４ｂは、タッチセンサ２１に対する特定の入力操作に応じて、操作対象装置を制御するための制御信号を発生する。制御信号発生部２４ｂより出力された制御信号はケーブル２５を介して出力端子２６へと出力される。出力端子２６を操作対象装置に接続すれば、制御信号によって操作対象装置を制御することが可能となる。特定の入力操作の例は図１１～図１３と同様である。制御信号発生部２４ｂが制御信号を発生する要件も上述と同様である。
【００８５】
本発明は以上説明した本実施形態に限定されるものではなく、本発明の要旨を逸脱しない範囲において種々変更可能である。タッチセンサ２１を、面ファスナを用いて円環状部２００ｒに着脱自在に装着するようにしてもよい。円環状部２００ｒを握持部としたが、握持部は必ずしも円環状でなくてもよい。
【００８６】
タッチセンサ２１は１枚のシートによって構成する必要はなく、複数のタッチセンサの片によってタッチセンサ２１を構成してもよい。複数のタッチセンサの片によってタッチセンサ２１を構成すれば、一つ一つのタッチセンサの片の形状を簡単な形にすることができるため、タッチセンサを生産する際に有利である。なお、複数のタッチセンサの片によってタッチセンサ２１を構成する場合、必ずしもタッチセンサの片を隙間なく配置しなくてもよい。本実施形態のタッチパネル２１は、握持部を覆うように装着されているが、本実施形態における、握持部を覆うように装着されているということは、複数のタッチセンサの片からなるタッチセンサ２１が、タッチセンサの片と片との間に隙間がある状態で、握持部を覆うように装着されていることも含むものとする。
【００８７】

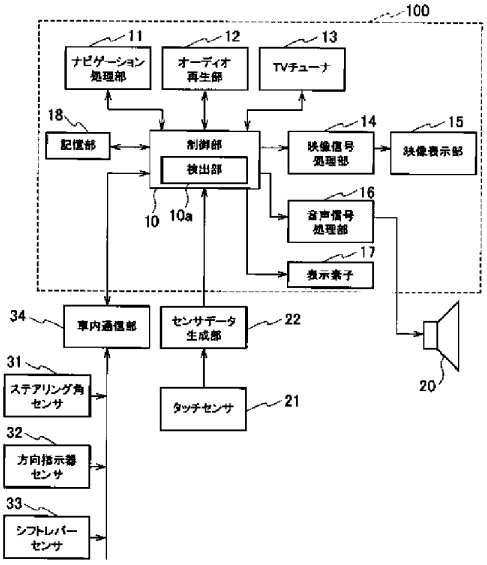
さらには、タッチセンサ２１を設ける範囲を、運転者が運転時に握る握持部（円環状部２００ｒまたは直線部２０１ｓ）に限定せず、例えばエアバッグ等が収納されるセンター部と円環状部２００ｒとの間を連結する連結部の表面まで広げてもよい。連結部は、図２においては、図2に示す状態で左右の手の間に位置する部分であり、図１９においては、センサデータ生成部２３及び制御部２４が設けられている部分である。このようにタッチセンサ２１を連結部の表面まで広げて、連結部における握持部に近い位置に操作検出エリアＡｒｖを設定してもよい。握持部に近い位置であれば、運転者が運転時に握持部から手を離したり、手を大きくずらしたりすることなく操作対象装置を操作することができる。よって、タッチセンサ２１を連結部の表面まで広げた構成としても、運転者がステアリングホイール２００，２０１，２１０を操作する際に支障となる可能性はほとんどない。

【符号の説明】

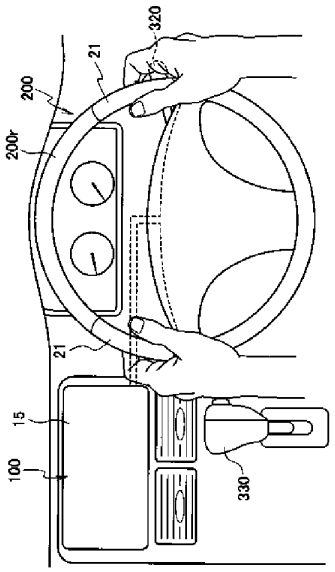
【００８８】

１０，２４　制御部
１０ａ，２４ａ　検出部
１１　ナビゲーション処理部
１２　オーディオ再生部
１３　テレビジョンチューナ
１４　映像信号処理部
１５　映像表示部
１６　音声信号処理部
１７　表示素子
１８　記憶部
２０　スピーカ
２１　タッチセンサ
２２，２３　センサデータ生成部
２４ｂ　制御信号発生部
２５　ケーブル
２６　出力端子
３１　ステアリング角センサ
３２　方向指示器センサ
３３　シフトレバーセンサ
３４　車内通信部
２００，２０１，２１０　ステアリングホイール
２００ｒ　円環状部（握持部）
２０１ｓ　直線部（握持部）

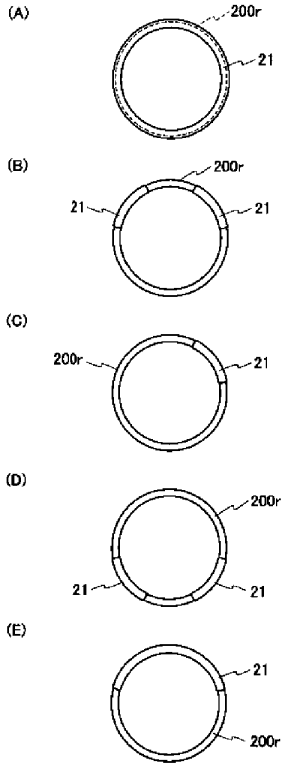
【図１】


100
11
ナビゲーション処理部
12
オーディオ再生部
13
TVチューナ
18
記憶部
制御部
検出部
10
10a
14
映像信号処理部
15
映像表示部
16
音声信号処理部
17
表示素子
20
34
車内通信部
センサデータ生成部
22
31
ステアリング角センサ
タッチセンサ
21
32
方向指示器センサ
33
シフトレバーセンサ

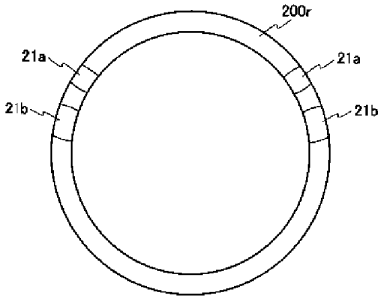
【図２】


320
21
200
200r
21
15
100
330

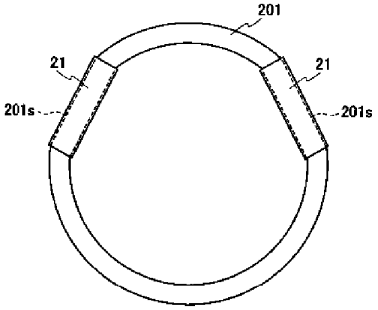
【図３】


(A)
200r
21
(B)
200r
21
21
(C)
200r
21
(D)
200r
21
21
(E)
21
200r

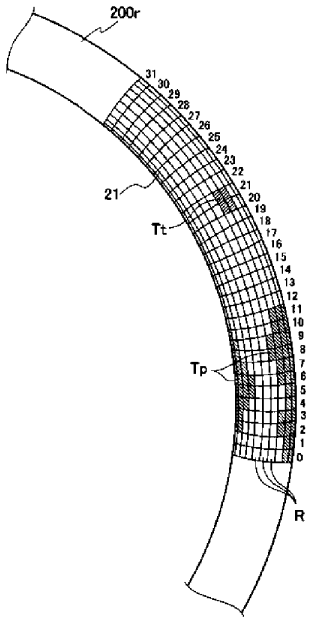
【図４】


200r
21a
21a
21b
21b

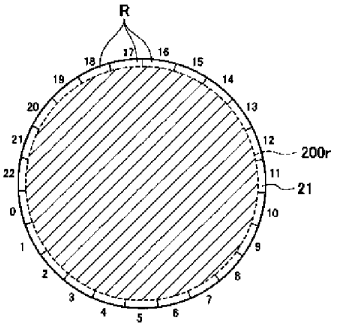
【図５】


201
21
21
201s
201s

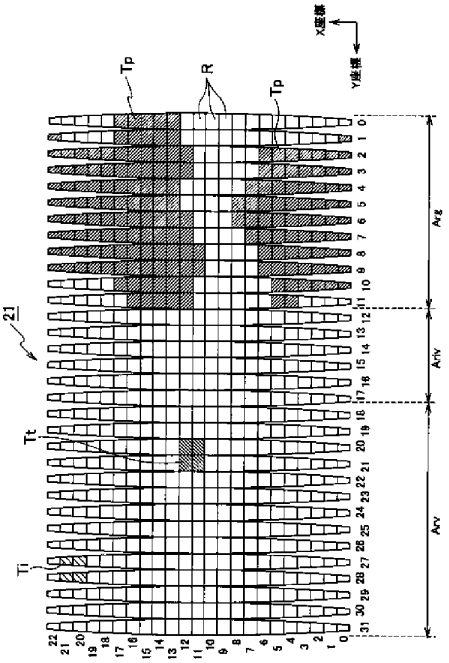
【図６】


200r
21
Tt
Tp
R

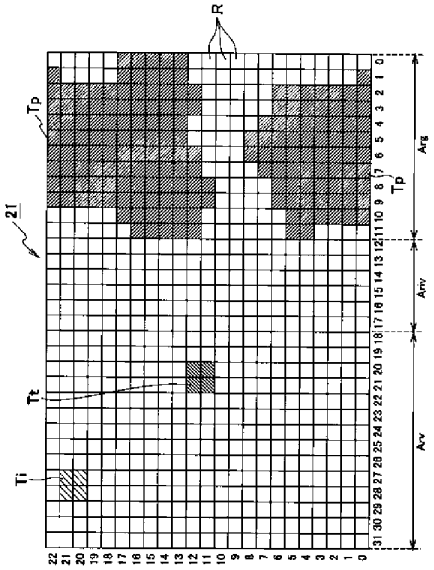
【図７】


R
200r
21

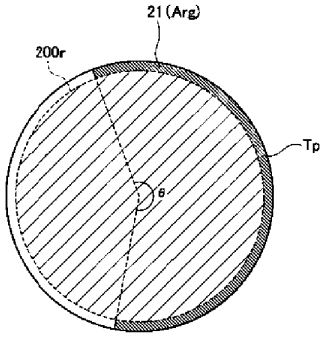
【図８】


X座標
Y座標
Tp
R
Tp
21
Tt
Ti
Arg
Arv
Arv

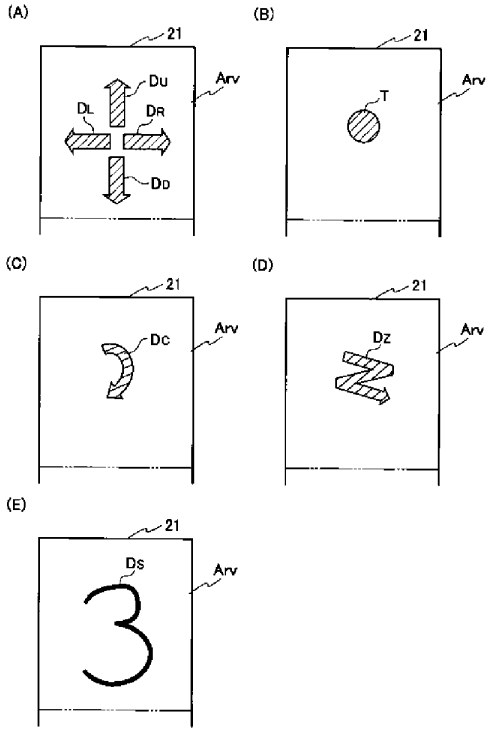
【図９】


R
Tp
21
Tt
Ti
Tp
Arg
Arv
Arv

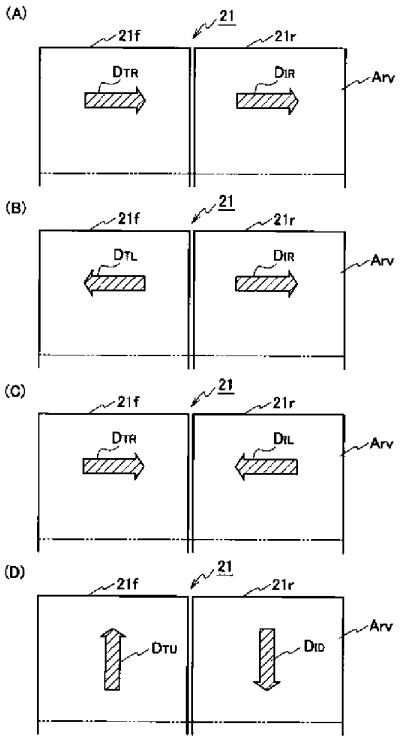
【図１０】



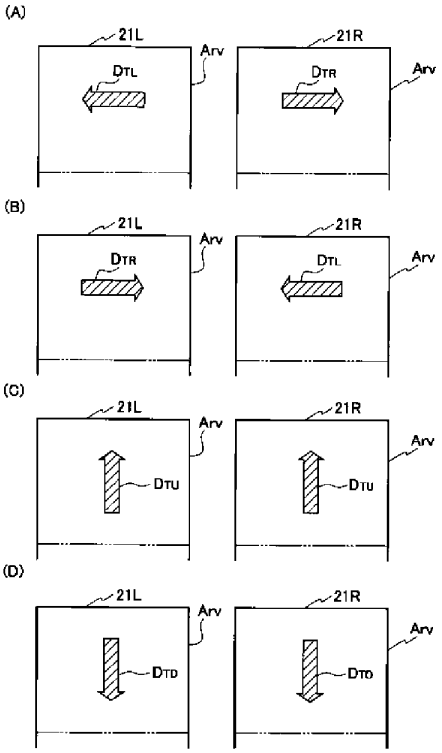
【図１１】



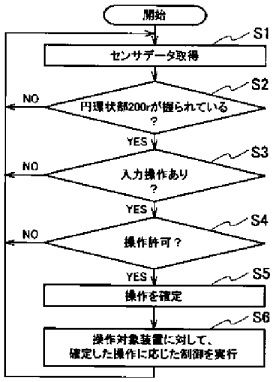
【図１２】



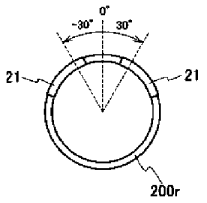
【図１３】



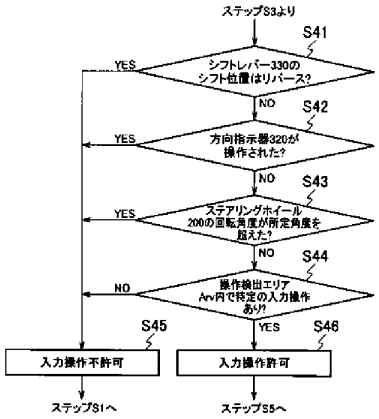
【図１４】



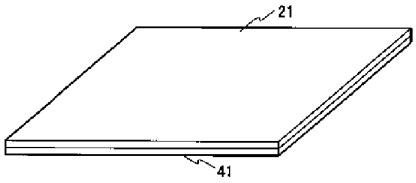
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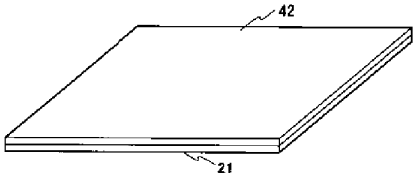
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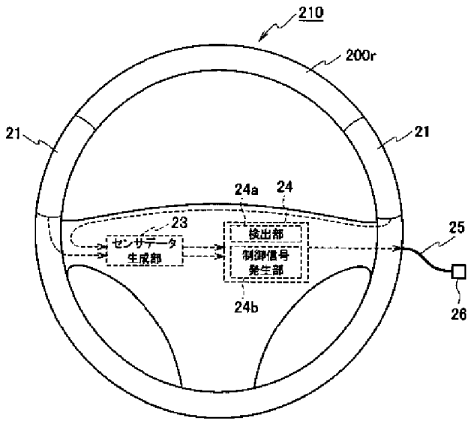
【図１７】



【図１８】



【図１９】



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CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING

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A closed blood sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The valve is a stopcock-like device that includes a rotating valve member and attached control handle with clear visible and tactile indicators for the mode of operation. The rotating valve member has a number of internal and circumferential channels for connecting or disconnecting select ports in the core of the valve. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room. The valve may also incorporate a blunt cannula sampling site therewithin.

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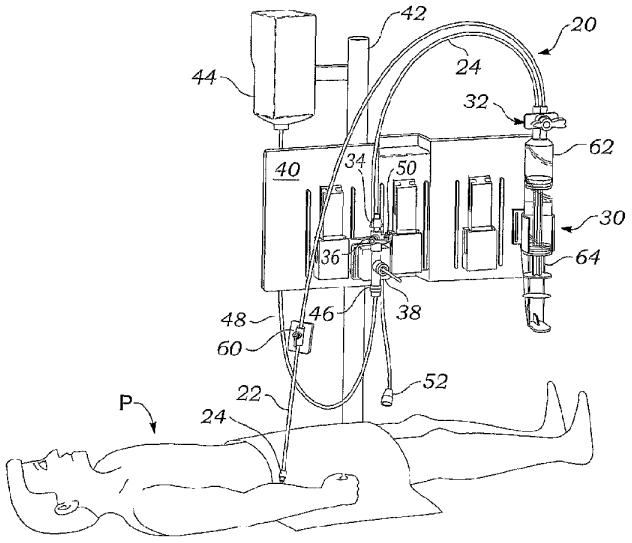
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(54) Title: CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING



(57) Abstract: A closed blood sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The valve is a stopcock-like device that includes a rotating valve member and attached control handle with clear visible and tactile indicators for the mode of operation. The rotating valve member has a number of internal and circumferential channels for connecting or disconnecting select ports in the core of the valve. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room. The valve may also incorporate a blunt cannula sampling site therewithin.

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CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING

Field of the Invention

[0001] The present invention relates to blood sampling systems and, in particular, to closed blood sampling systems with a clearing reservoir and pressure monitoring.

Background of the Invention

[0002] In a hospital setting there is always the need to monitor patient health through the evaluation of blood chemistry profile. The simplest method employed in the hospital is to use a syringe carrying a sharpened cannula at one end and insert that cannula into a vein or artery to extract a blood sample from the patient. Patients that are in the critical care units or the operating room sometimes require as many as twelve samples a day. Such frequent sampling injections potentially expose the patient to airborne bacteria and viruses which can enter the bloodstream through the opening made by the sharpened cannula.

[0003] One way to obtain a blood sample is to draw the blood from a catheter that is already inserted in the patient, either in a central venous line, such as one placed in the right atrium, or in an arterial line. Typically, existing injection sites for arterial or venous drug infusion or pressure monitoring lines are used to take periodic blood samples from the patient. Conventional mechanisms for drawing blood from the lines used for infusion or pressure monitoring utilize a plurality of stopcock mechanisms that preclude flow from the infusion fluid supply or from the pressure column drip supply, while allowing blood to flow from the patient into a collecting syringe connected to a proximal port formed in one of the stopcocks. Typically, a blunt cannula through a slit septum is used to remove the danger of sticking the nurse or clinician, in a so-called "needle-less" system.

[0004] Most early systems required a two-step operation where a first sample of fluid, generally about 5ml in volume for intensive care environments was withdrawn into the sampling syringe and discarded. This first sample potentially included some of the infusion fluid and thus would be an unreliable blood chemistry measurement sample. After the initial sample had been discharged, the second sample was pure blood from the artery or vein and was typically re-infused to the patient.

[0005] In response to the drawbacks associated with earlier two-step sampling systems, closed systems were developed as described in U.S. Patent No. 4,673,386 to Gordon, and more recently in U.S. Patent No. 5,961,472 to Swendson, which are expressly incorporated by reference herein. Commercial closed systems such as the Edwards VAMP® and VAMP Plus® Venous Arterial blood Management Protection systems of Edwards Lifesciences in Irvine, CA feature a reservoir in the tubing line from the patient that can draw fluid past a sampling port. The clearing volume is held in the in-line reservoir, and not set-aside in a syringe for re-infusion later. The sampling systems are often used in conjunction with a pressure monitor having a transducer continually or periodically sensing pressure within the sampling line except during the draw of a blood sample.

[0006] The VAMP Plus® system conveniently utilizes a reservoir with one-handed operability, and includes a line from the patient into and out of the reservoir and to a proximal source of flushing fluid and a pressure transducer. (The standard directional nomenclature is that proximal is toward the clinician, or away from the patient, and distal is toward the patient). A stopcock valve at the reservoir controls the mode of operation. Prior to drawing a blood sample, the reservoir plunger is latched closed, though a reservoir gap allows a continuous drip of IV flushing fluid through an inlet port to an outlet port. A pressure transducer in the line proximal to the reservoir senses fluid pressure within the line and conveys the signal to a monitor. One exemplary pressure transducer used with both the VAMP® and

VAMP Plus® systems is the Edwards TruWave® Disposable Pressure Transducer.

[0007] When a blood sample is to be taken, the flow of flushing or infusion fluid is halted by turning the handle of the reservoir stopcock valve. The nurse or clinician then withdraws an amount of fluid into the reservoir chamber and distal line sufficient to pull pure blood past one or more fluid sampling sites. After full retraction of the plunger, the stopcock valve closes off the reservoir from the patient and a sample of blood is taken at one or the other sampling sites. Subsequently, the clinician manipulates the stopcock valve so that the volume within the reservoir can be reinfused back into the patient by depressing the plunger, and the flushing drip and pressure monitoring resumes.

[0008] In the closed blood sampling/pressure monitoring systems described above, the pressure transducer typically includes a diaphragm exposed to the in-line fluid on one side and has a device for measuring deflection of the diaphragm on the other. Such pressure lines typically make use of relatively stiff tubing primed with a suitable physiological fluid such as saline or 5% dextrose solution as a pressure column. For adults, a bag pressurized with air surrounds the fluid supply bag to maintain a constant pressure differential in the line urging fluid toward the patient through a restrictor orifice. The slow drip of physiological fluid flushes the line to prevent clotting. Some transducers such as the TruWave® Disposable Pressure Transducer include a flush device that also can be used for sending transient pressure waves through the line. A Snap-Tab™ device of the TruWave® is a rubber tab which when pulled and then released sends a square wave through the pressure column to check the inherent frequency response of the entire system, which includes the tubing and any components attached thereto, such as the sampling ports and reservoir. Proper system frequency response is necessary for reliable blood pressure measurements. In general, a more accurate signal may be obtained with a shorter sampling line and fewer

components so that the transducer is closer to the patient and there is less delay between the generation and receipt of the blood pressure signal, and less interference. However the limited amount of space available or the location of the anesthesiologist during a surgical procedure often necessitates a relatively long tubing line which degrades the signal. Furthermore, minimum functionality of the system requires various components such as sampling sites be included.

[0009] In view of the foregoing, there is a need for a blood sampling system used in conjunction with a pressure transducer that produces more accurate pressure readings.

Summary of the Invention

[0010] The present invention provides a fluid sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The control valve further permits complete flushing of the system with no dead spaces. Additionally, control valve desirably incorporates a sampling port therein capable of isolating the sampling port from the clearance reservoir. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room.

[0011] In accordance with a first embodiment of the invention, a medical system for fluid sampling and pressure monitoring of a fluid system of a patient is provided. The system includes a conduit line with a proximal segment adapted to be supplied with a physiological fluid (e.g., saline) and a distal segment adapted to be in communication with a fluid system of a patient. A control valve has a manifold defining an interior chamber. The manifold has a proximal port fluidly connected to the proximal segment, a distal port fluidly connected to the distal segment, and a reservoir port,

wherein each of the manifold ports opens to the interior chamber. A system further includes a fluid sampling port and pressure transducer connected to the conduit line for sensing the pressure of the fluid therein. A reservoir fluidly communicates with the reservoir port of the control valve manifold. The control valve further includes a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports. The valve member is movable into at least two positions:

a first position that provides open fluid communication from the proximal segment to the patient through the control valve so as to eliminate any dead spaces therein, wherein reduced pressure within the reservoir pulls fluid from the distal segment through the control valve and into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port, and

a second position that provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member to the distal segment while bypassing the reservoir, such that the pressure of fluid within the conduit line exclusive of the reservoir can be sensed by the pressure transducer.

[0012] Desirably, the valve member also has a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

[0013] In a preferred embodiment the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, wherein mating features on the valve member core and manifold provide tactile feedback and positive positioning of the core in both first and second positions. Alternatively, or in addition, coordinated visible features on the control handle and manifold provide symbolic indicators of both first and second positions of the valve member.

[0014] The sampling port may be formed within the control valve or along the distal segment of the conduit line. If within the control valve, the sampling port may be formed within the valve member and communicates with a sampling cavity formed internally within the valve member open to at least one of the channels. Alternatively, the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the interior chamber of the manifold. Furthermore, the system may include a second sampling port having a sampling cavity positioned along the distal segment of the conduit line.

[0015] In accordance with one embodiment, the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold, the core having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core. The internal channel desirably opens to the exterior surface of the core at two separated locations spaced from the external channel.

[0016] System further may include means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position. Desirably, the reservoir has an inlet open to an outlet port of the control valve manifold and an outlet open to an inlet port of the control valve manifold. In this embodiment, the first position of the valve member provides open fluid communication between the control valve flow passages through the inlet and outlet of the reservoir to flush a chamber of the reservoir.

[0017] A second embodiment of the present invention comprises a medical system for fluid sampling of a fluid system of a patient. The system encompasses a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient. A control valve connects between the proximal segment and the distal segment of the conduit line. A

fluid sampling port defines a flow path therethrough whose opposite ends open to internal channels in the control valve. A reservoir fluidly communicates with a reservoir port of the control valve manifold. The control valve further includes a valve member movable into at least three positions:

a first position that provides open fluid communication from the proximal segment through the control valve to the distal segment,

a second position that provides open fluid communication from the proximal segment to the distal segment while bypassing the reservoir and sampling port, and

a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

[0018] Desirably, the control valve further includes a manifold defining an interior chamber. The manifold has a proximal port fluidly connected to the proximal segment of the conduit line, a distal port fluidly connected to the distal segment, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber. The valve member also comprises a core movable within the interior chamber of the manifold and having channels therein that selectively communicate with the manifold ports. The reservoir has an inlet open to the manifold outlet port and an outlet open to the manifold inlet port. In this embodiment:

the first position provides open fluid communication from the proximal segment to the proximal port and the outlet port of the control valve, through the inlet and outlet of the reservoir, to the inlet port and the distal port of the control valve to the distal segment,

the second position provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member core to the distal segment while bypassing the reservoir and sampling port, and

the third position provides open fluid communication from the distal segment to distal port and one of the channels of the valve member core, and to the sampling port.

[0019] The valve member core may have an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core. Desirably, the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

[0020] Another aspect of the invention is a method of taking samples and measuring the pressure of a fluid system of a patient. The method provides a fluid sampling system with a conduit line and a reservoir connected thereto between a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient. A control valve interposed between the reservoir and the conduit line has a movable valve member with a control handle, the valve member movable into at least a first position and a second position. A pressure transducer connects to the conduit line for sensing the pressure of the fluid therein, and a fluid sampling port is provided in the sampling system.

[0021] The method includes selecting the first position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve and the reservoir, and creating a reduced pressure within the reservoir such that fluid flows from the distal segment through the control valve into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port. The method further includes selecting the second position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve while bypassing the reservoir, and monitoring the pressure sensed by the pressure transducer. Desirably, the valve member has a third position, and the method includes selecting the third position of the valve

member to provide open fluid communication from the distal segment to the sampling port but prevent communication between the sampling port and both the reservoir and the proximal segment, and sampling fluid from the conduit line through the sampling port.

[0022] In a preferred embodiment, the fluid system of the patient is the blood system, and the method further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position. In this instance, the method including the steps of:

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient; then

creating a reduced pressure within reservoir and collecting sufficient fluid therein such that blood flows past the sampling port; then

selecting the third position of the valve member; then

sampling blood from the conduit line through the sampling port; then

creating an elevated pressure within the reservoir to expel blood therefrom into the distal segment of the conduit line; then

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient and flushes the reservoir of blood; and then

selecting the second position of the valve member and monitoring the pressure sensed by the pressure transducer.

[0023] Preferably, the control valve has a manifold defining an interior chamber within which the valve member rotates, and further including mating features on the valve member and manifold that provide tactile feedback and positive positioning of the core in both first and second positions, the method of selecting the first and second positions further including rotating the valve member until the tactile feedback is sensed. Or, the control valve includes

visible features that provide symbolic indicators of the first and second positions of the control handle, the method of selecting the first and second positions further includes interpreting the symbolic indicators to determine the placement of the control handle corresponding to the first and second positions.

[0024] Another useful aspect of the present invention is a medical system for fluid sampling of a fluid system of a patient. The sampling system includes a conduit line with a proximal end adapted to be supplied with a physiological fluid and a distal end adapted to be in communication with a fluid system of a patient. A pressure transducer connects to the conduit line for sensing the pressure of the fluid therein, and a fluid sampling port is provided having a sampling cavity. A control valve interposes between the conduit line and the sampling port and has a manifold defining an interior chamber. The manifold further includes a proximal port fluidly connected to the conduit line, a distal port fluidly connected to the conduit line, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber. The control valve also has a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least three positions:

a first position that provides open fluid communication from the conduit line to the proximal port and the outlet port of the control valve to the sampling cavity, and to the inlet port and the distal port of the control valve to the conduit line,

a second position that provides open fluid communication from the conduit line to the proximal port and through at least one channel in the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal end of the conduit line through the control valve to the sampling port but prevents communication between the sampling port and the proximal end of the conduit line.

[0025] A further understanding of the nature and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings in which like parts bear like reference numerals.

Brief Description of the Drawings

[0026] Features and advantages of the present invention will become appreciated as the same become better understood with reference to the specification, claims, and appended drawings wherein:

[0027] Fig. 1 illustrates a typical hospital room setup of a fluid sampling system of the present invention incorporating a reservoir, the sampling port, and a pressure transducer within a conduit line to a patient;

[0028] Figure 2 is a perspective view of a reservoir of the fluid sampling system in Figure 1 having an attached control valve of the present invention;

[0029] Figures 3A-3C are several orthogonal views of one end of the reservoir showing the control valve;

[0030] Figure 4 is a close-up perspective view of the control valve on the end of the reservoir having a central sampling port in a rotatable valve member;

[0031] Figure 5 is an exploded perspective view of the control valve;

[0032] Figures 6-11 are various external and sectional views of the rotatable valve member used in the control valve shown in Figures 4 and 5;

[0033] Figures 12-15 are various external and sectional views of a manifold of the control valve of Figures 4 and 5;

[0034] Figures 16 and 17 are axial sectional views of the control valve of the present invention taken along lines 16-16 and 17-17, respectively, of Figure 4;

[0035] Figures 18A-18C are axial sectional views of the control valve taken along line 18-18 of Figure 4 showing the positions of interior fluid flow channels for different positions of the valve member;

[0036] Figures 19A-19C are views similar to Figures 18A-18C of the interior fluid flow channels for the three different positions of the control valve showing selective interconnections between the various manifold ports;

[0037] Figures 20A-20E are various external and sectional views of an alternative control valve of the present invention with a different arrangement of internal flow paths and a central sampling port;

[0038] Figures 21A-21E are various external and sectional views of an alternative control valve with a different arrangement of internal flow paths and a luer-style central sampling port;

[0039] Figures 22A-22E are various external and sectional views of an alternative control valve with a sampling port extending from the side of a manifold;

[0040] Figures 23A-23E are various external views of a luer-style valved sampling port;

[0041] Figure 24 is an axial sectional view of the valved sampling port of Figures 23A-23E; and

[0042] Figures 25A-25E are various external and sectional views of a further alternative valved sampling port with the sampling port extending from the side of a manifold.

Detailed Description of the Preferred Embodiments

[0043] The present invention provides an improved closed blood sampling system in conjunction with pressure monitor. As mentioned above, continuous or periodic blood pressure monitoring is a common and extremely

useful tool in the intensive care or operating room. However, it should be mentioned that the apparatuses and methods described herein could be utilized in conjunction with any fluid system of a patient which would benefit from pressure monitoring. For instance, intracranial pressures could be monitored and cerebrospinal fluid samples taken by placing the system described herein in fluid communication with an intraventricular catheter. Therefore, the appended claims cover the sampling and monitoring of any fluid system within a patient unless otherwise specified.

[0044] The present invention comprises an improved, closed, one-handed fluid sampling system especially useful for sampling blood in the operating room or critical care unit (CCU). The overall functioning of the system is similar to those in the prior art, in particular the VAMP Plus® Venous Arterial blood Management Protection system available from Edwards Lifesciences of Irvine, CA. Furthermore, the blood sampling function is desirably combined with a pressure transducer and monitoring hardware. The term "closed fluid sampling system" should be understood to include both systems that have a dedicated reservoir (i.e., one that remains connected) and that utilize a removable reservoir (or syringe) that gains access to the fluid column through a port. As explained above, dedicated reservoirs are preferred because of their enhanced sterility, but the feature of the present invention that isolates the reservoir from the fluid pressure column may also be useful with removable reservoirs.

[0045] Figure 1 illustrates an exemplary blood sampling system 20 of the present invention in the environment of a typical set up in a hospital room and connected to a patient P. The blood sampling system 20 comprises a conduit line having a distal segment 22 toward the patient and a proximal segment 24. The conduit line is primarily medical grade pressure tubing. The distal segment 22 may terminate in a male luer connector 26 for attaching to a female luer connector (not shown) of an injection site, or other conduit leading to the patient. A reservoir 30 connects to the conduit line via a control valve

32 interposed between the distal segment 22 proximal segment 24. The control valve 32 externally resembles a stopcock and controls fluid flow between the conduit line and the reservoir 30.

[0046] The proximal segment 24 extends from the control valve 32 and terminates in a female luer connector 34 attached to a stopcock 36 of a pressure transducer 38. The reservoir 30 and pressure transducer 38 removably mount to a bracket 40 which, in turn, may be secured to a conventional pole support 42 with the reservoir in a vertical orientation.

[0047] As mentioned above, the blood sampling system 20 forms a portion of a pressure monitoring system, and the fluid pressure transducer 36 may be a TruWave™ Disposable Pressure Transducer available from Edwards Lifesciences of Irvine, CA. A supply of flush solution 44 connects to a flush port 46 of the transducer 38 via tubing 48. Typically for adults, the flush solution 44 comprises a bag of physiological fluid such as saline surrounded by a pressurized sleeve that squeezes the fluid and forces it through the tubing 48. In addition, an infusion fluid supply (not shown) may be provided in communication with an infusion port 50 of the stopcock 36. The pressure transducer 38 is thus placed in fluid communication with the arterial or venous system of the patient through the conduit line, and preferably includes a cable and plug 52 to connect to a suitable display monitor (not shown). Though the pressure transducer 38 is shown positioned within the proximal segment 24, it could also be located in the distal segment 22.

[0048] The sampling system 20 further comprises a fluid sampling site 60 that desirably defines a Z-shaped flow passage adjacent a pre-slit septum (not numbered). With this configuration, a minimal amount of flush volume is needed to clear the line after sampling. The septum preferably comprises an elastomeric disc which accepts a blunt cannula and reseals after each sample is drawn, reducing the potential for contamination and eliminating the danger of needle sticks. Such sampling site is described in U.S. Patent No. 5,135,489 to Jepson, et al., which is hereby expressly incorporated by reference.

[0049] Figure 2 better illustrates one embodiment of a blood sampling reservoir 30 of the present invention removed from the bracket 40. The reservoir 30 desirably includes a syringe-type variable volume chamber 62, though other reservoirs that have constant volume chambers or other receptacles for receiving fluid may be used. Preferably, the reservoir 30 is of a type that includes a constantly open flow channel through the variable volume chamber 62 for passage of flushing fluid therethrough. A particularly useful such reservoir 30 is the Edwards VAMP Plus® system mentioned above.

[0050] In one mode of operation of the system 20, a reduced pressure is created within the variable volume chamber 62 by withdrawing the plunger 64 such that a fluid sample from the distal segment 22 is drawn into the chamber. The chamber 62 has a sufficient volume, typically 12 ml, to draw blood from the patient P passed the sampling site 60. The clinician can then take a sample of undiluted blood from the site 60. Subsequently, the blood and other fluids drawn into the reservoir 30 during the sampling operation are re-infused by depressing the plunger 64. It should be noted that the pressure transducer 38 may include a flow restrictor or flow control means to prevent flushed solution from going proximally through the sensor rather than back to the patient. For instance, the stopcock 36 may be used to close off the fluid path through the pressure transducer 38 prior to re-infusing the reservoir clearance volume.

[0051] The entire sampling system 20 is thus closed as the "priming" volume that ensures a pure sample of blood reaches the sampling site 60 remains within the system 20 and is reinfused into the patient. It will be understood by those skilled in the art that the syringe-type reservoir 30 shown in Figures 1-2 is only exemplary and other configurations may be designed to adequately provide the variable volume chamber.

[0052] With reference now to Figures 3A-3C and 4-5, the proximate relationship between the reservoir 30 and the control valve 32 will be described. Desirably, the reservoir 30 and control valve 32 are molded plastic

pieces that are rigidly mounted together such as with adhesive or ultrasonic welding. However, the reservoir 30 simply needs to be in proximity with the control valve 32 such that they are connected by two fluid flow paths. For convention, the ordinary flow path of the whole system as seen in Figure 1 is from proximal to distal, or from the fluid bag 44 to the patient P. With reference back to Figure 2, the saline or other physiological fluid flows into the reservoir 30 and control valve 32 combination through the proximal segment 24 of the conduit line and flows out of the distal segment 22. In this regard, therefore, the reservoir 30 has an inlet that receives saline from an outlet port of the control valve 32, and also an outlet through which saline flows to an inlet port of the control valve. These internal flow paths and channels will become clearer below, and as mentioned are desirably molded into the mating sections of the reservoir 30 and control valve 32. It is entirely feasible, however, to separate these two components with short lengths of tubing.

[0053] The control valve 32 as best seen in Figures 4-5 comprises a manifold 70 that receives a movable valve member 72. In the exemplary embodiment, the manifold 70 defines a cylindrical interior chamber 74 sized to rotatably receive a generally cylindrical core 76 of the valve member 72. A control handle 78 extends externally from the chamber 74 and provides leverage for rotating the core 76 within the chamber. The interior chamber 74 is shown oriented 90° from the axis of the reservoir 30, although other arrangements are possible.

[0054] Figures 4 and 5 further illustrate an exemplary fluid sampling port 84 provided in an outer portion of the control handle 78. The fluid sampling 44 may take a variety of forms, but as illustrated includes an elastomeric slit septum 86 captured by a cap 88 over a sampling cavity 90 within the valve member 72. The assembly seen in Figure 4 provides access for a blunt cannula through the slit septum 86 to withdraw fluid from within the sampling cavity 90. The sampling site 84 is located along the center line

of the rotating valve member 72, although as will be explained below, other locations for a sampling site within the control valve are contemplated.

[0055] Figures 4 and 5 also illustrate exemplary indicators for the various rotational positions of the valve member 72 within the manifold 70. More specifically, the preferred form of the invention includes both tactile and visual indicators to help reduce clinician errors, speed up and clarify the process. The visual indicators include an arrow-shaped control handle 78 with a pointed end 92 that registers with one of three symbols 94a, 94b, 94c raised and/or printed on a faceplate 96 of the control valve 32. The valve member 72 may be rotated to one of the three positions with the pointed end 92 registering with one of the three symbols 94a, 94b, 94c. The indicator plate 96 shows the three position indicators 94 at the 0°, 90°, and 180° locations relative to a 0° horizontal reference line to the right (3:00). The 90° angular separation between the positions of the valve member 72 facilitates selection of one of three modes. An arc-shaped lip 98 projecting from an outer end of the interior chamber body desirably interferes with a small tooth 99 (see Fig. 6A) on the valve member 72 to prevent its rotation into the fourth, unmarked quadrant. The meaning of the symbols 94a, 94b, 94c will become apparent below. 91 psuedo inlet/outlet port, good flushing

[0056] In addition to visual indicators, the control valve 32 also desirably provides tactile feedback to the operator when the valve member 72 is in one of the three discrete positions. There are a number of ways to indicate tactilely the proper positioning of a rotating body within another, but the means used in the present context also preferably provide positive positioning of the valve member 72 within the interior chamber 74. For example, a small rib or bump 100 extending inward from the chamber 74 or lip 78 may be sized in position to register with small grooves or depressions 102 formed in the valve member core 76. These mating features are preferably sized large enough for the male portion to fit within the female portion and nominally restrain motion of the valve member 72, but small

enough to allow the user to relatively easily overcome their engagement and further rotate the valve member. As the engaging pieces are molded plastic, and the assembly is designed to be used once and disposed of, small rounded bumps engaging equal sized depressions are an effective short-term tactile indicator. It should be understood that the bumps and depressions could be provided on the parts as shown, or on the opposite elements in a reverse configuration. Moreover, these physical mating features desirably emit a small click when engaging, which provides a third, aural indicator.

[0057] Figures 6A-6E and 7-11 provide details of the exemplary valve member 72 having the central sampling port 84 therein. With reference to Figure 6A, the core 76 has a generally cylindrical exterior that slightly narrows away from the control handle 78 and is interrupted at a lower end by a trough 110 bordered by two shoulders 112. A pair of channels 114, 116 through the interior of the core 76 open to the core exterior at two locations separated circumferentially by almost 90° but in a common radial plane (as used herein, "radial" is relative to the rotational axis of the valve member 72). Looking at the reverse orientation of Figure 6E, the core 76 further features an arc-shaped groove or channel 120 that extends around the circumference of the core in a radial plane, preferably the same plane as that of the openings of the channels 114, 116. Figure 9 is a radial sectional view through that common plane and illustrates the relative positions and orientations of the channels 114, 116, 120.

[0058] The generally cylindrical portion of the core 76 is sized to closely fit within the interior chamber 74 of the manifold 70 (see Figure 5) such that the valve member 72 can rotate within the manifold but there is no unintended fluid leakage between the various ports and channels. The openings of the channels 14, 16 and the circumferential channel 120 lying in a common radial plane provide the only avenue for fluid passage around or through the valve member 72 when it is closely fit within the interior chamber 74. It should be understood that alternative configurations are possible with,

for example, the openings to the channels 114, 116 and circumferential channel 120 being spaced apart axially with respect to one or the others.

[0059] Figure 7 is an axial cross-sectional view through the valve member 72 that illustrates the inner components of the sampling port 84. Namely, the cap 88 restrains the elastomeric slit septum 86 over the sampling cavity 90. Figure 8 illustrates the sampling cavity 90 along a different axial plane that passes directly between a pair of axially-oriented channels 130, 132 seen in Figure 7 that communicate, respectively, with the radial channels 114, 116. Figure 8 further illustrates the generally semi-circular cross-section of the circumferential channel 120. With reference again to Figure 9, it should therefore be apparent that the radial channels 114, 116 are in constant fluid communication with each other via the respective connecting channels 130, 132 opening into the common sampling cavity 90. As will be explained below, these bifurcated channels through the valve member 72 function to permit blood or other body fluid into the sampling cavity 90, and also effectively flush the sampling cavity 90 in between samples. An axial extension 134 of the wall separating the connecting channels 130, 132 continues into close proximity with the slit septum 86. The extension 134 creates a pseudo inlet/outlet to the sampling cavity 90 such that a flow of flushing fluid therethrough is directed all the way to the slit septum 86 before turning the corner and continuing through the valve member 72. The extension 134 therefore enhances the efficacy of the flushing step and helps eliminate dead zones within the simply cavity 90 that might otherwise be a source of blood coagulation and contamination.

[0060] Structural details of the manifold 70 are seen in Figures 12-15. Specifically, the manifold 70 features a plurality of ports that opened into the interior chamber 74. A distal port 140 and a proximal port 142 extend upward from the chamber 74 in the orientation where the reservoir 30 plunger points downward. These ports 140, 142 are shown respectively connected to the distal segment 22 and proximal segment 24 of the conduit line in Figures 1

and 2. Therefore these ports 140, 142 represent the two diverging segments of the conduit line, the former extending toward the patient and the latter to the pressure transducer 38 and saline drip.

[0061] On the opposite side of the chamber 74, a manifold outlet port 144 leads to an inlet 146 to the reservoir variable volume chamber 62. An outlet 148 of the reservoir 30 leads directly into a manifold inlet port 150. The distal and proximal ports 140, 142 and outlet and inlet ports 144, 150 all open directly to the interior chamber 74 of the manifold 70. Note that one possible configuration is a reservoir connected through the control valve 32 using only a single reservoir port as opposed to inlet and outlet ports. For example, a syringe-type removable reservoir may be connected to a single port of the control valve 32. In such a system, the benefit of isolating the reservoir remains although the flush mode of operation will not pass through the reservoir. The term "reservoir port" therefore includes one or both of the outlet and inlet ports 144, 150.

[0062] Figures 13-14 show the manifold 70 having relatively long outlet and inlet ports 144, 150 leading to and from the reservoir 30 to provide some clearance for rotation of the valve member 72. Desirably, the manifold 70 is a single molded piece that is rigidly secured to the end of the reservoir 30. However, the manifold 70 could be a combination of more than one piece, and could be connected to the reservoir 30 through short tubes.

[0063] Figures 15A and 15B show the gradual taper of the interior chamber 74 at the narrow end of the chamber 74, a circular rib 160 projects inward for engaging and retaining the valve member 72, as will be explained next.

[0064] Figures 16 and 17 illustrate in cross-section the coupling of the valve member 72 within the manifold 70. Specifically, the gradual tapers of both closely match and provide an effective fluid seal at the point that the inward rib 160 of the manifold passes over the first shoulder 112 of the valve member 72 and resides within the trough 110. A cavity 162 in the narrow end

of the valve member 72 permits inward flexing of the shoulder 112 such that it can be forced passed the rib 160. Interference between the outwardly-sprung shoulder 112 and rib 160 effectively locks the valve member 72 within the manifold 70 and ensures good fluid sealing around the various ports and openings. Figure 16 shows the alignment of the proximal port 142 with the circumferential groove 120 two valve member 72. Likewise, the radial channel 114 also lies in the same plane. It is worth mentioning again at this stage that the coplanar nature of all of the ports and openings is an efficient and relatively straightforward design, but more complex fluid pathways between the rotating valve member 72 and manifold 70 could be designed to perform the same function. For example, one or more of the internal channels could be curvilinear, or there could be more than one circumferential surface channel.

[0065] Now with reference to Figures 18A-18C and 19A-1C, the fluid flow paths for the three positions of the valve member 72 will be explained.

[0066] The reader will recall from the description of the system of Figure 1 that there is a physiological fluid flush drip, preferably pressurized. When such flush is needed, the clinician rotates the valve member 72 to the downward position, as indicated by the arrow F/C in Figure 18A. This corresponds to a "Flush/Clear" mode of operation, and is symbolically indicated by the symbol 94a of three divergent flow paths in Figure 5, meaning all fluid communications are open. When pressure monitoring is desirable, the clinician rotates the valve member 72 to the left position, as indicated by the arrow M in Figure 18B. This corresponds to a "Monitoring" mode of operation, and is symbolically indicated by the symbol 94b of a pressure wave in Figure 5. Finally, when the clinician requires a fluid sample, he/she rotates the valve member 72 to the right position, as indicated by the arrow S in Figure 18C. This corresponds to a "Sampling" mode of operation, and is symbolically indicated by the symbol 94C of a drop of fluid in Figure 5. As mentioned above, the symbolic indicators 94a, 94b, and 94c are desirably

supplemented by the clear directional nature of the arrow-shaped control handle 78, and by tactile and audible feedback measures, to help avoid error.

[0067] Figures 18A-18C further illustrate the change in rotational orientation of the valve member 72 within the internal chamber of the manifold 70, in particular through the radial plane passing through the flow channels that open to the exterior of the valve member core 76. The same illustrations of the flow channels in the three positions are shown more clearly in Figures 19A-19C with relevant labels and fluid flows indicated. The two sets of diagrams further indicate the four manifold ports 140, 142, 144, and 150.

[0068] In the F/C position of the valve member 72 of Figures 18A and 19A, a slow drip of flushing fluid travels from the supply of flush solution 44 (Figure 1) through the proximal segment 24 (Figure 2) to the manifold proximal port 142, through the circumferential channel 120 and the outlet port 144. As indicated by the flow arrows in Figure 19A, the drip continues through the inlet 146 and outlet 148 of the reservoir 30 passing through the variable volume chamber 62. The fluid then passes through the inlet port 150 into the radial channel 114, and along the axial channel 130 into the sampling reservoir 90 (see Figure 7), and back through the parallel axial channel 132 into the other radial channel 132. Finally, the fluid exits the valve member 72 into the manifold distal port 140 and from there continues through the distal segment 22 of the conduit line to the patient.

[0069] In the F/C position of the valve member 72, all of the internal flow paths within the reservoir 30 and control valve 32 are open to form a single continuous flushing pathway. This desirably permits any blood or other bodily fluid to be completely flushed from within the system 20, leaving no dead spots for bubbles to form or blood to coagulate. This "pocket-less" fluid pathway through the system in conjunction with the ability to isolate components that degrade the pressure signal is extremely useful. Furthermore, the control valve 32 is desirably made of transparent or frosted plastic that

permits the user to visualize blood flow therethrough, thus insuring blood as been completely flushed out of the system after a sample is taken.

[0070] The F/C position also enables a clearing volume to be pulled into the reservoir 30. Specifically, a reduced pressure within the variable volume chamber 62 pulls fluid from the distal segment 22 into the reservoir 30 in a reverse flow from that shown in Fig. 19A. The volume of the chamber 62 is sufficient to draw blood from the patient past the sampling port 84 (sampling cavity 90), that is, through the internal channels of the valve member 72. A flow restrictor or control valve at the pressure transducer 38 toward the proximal segment 24 ensures that the reservoir 30 fills with fluid from the distal segment 22. That is, there is greater resistance to flow into the reservoir from the proximal segment 24 as compared to the distal segment 22.

[0071] Before a sample is taken, however, the control handle 78 must be rotated into the third S position shown in Figures 18C and 19C. In this position, the channels of the valve member 72 provide open fluid communication only from the distal port 140 to the radial channel 114 as shown, and from there to the sampling cavity 90 (Figure 7). A fluid sample is taken from the port 84 using a blunt cannula or other sampling device.

[0072] Pressure monitoring occurs with the valve member 72 in the second M position shown in Figures 18B and 19B. In that position, the pressure transducer 38 (or DPT, Disposable Pressure Transducer), is in fluid communication with the patient directly though the circumferential channel 120, bypassing the reservoir 30 and sampling port 84. This feature of the control valve 32 isolates the elastomeric elements of the reservoir 30 and sampling port 84, as well as the associated channels leading thereto, from the fluid pressure column. The fluid pressure column therefore extends directly from the patient through the distal segment 22, making a U-turn in the circumferential channel 120 to the proximal segment 24. Bypassing the reservoir 30, and in particular the elastomeric seal of the plunger 64, and the sampling port 84 (elastomeric septum 86), greatly improves the signals

received by the pressure transducer 38. A distal sampling port 60 in the distal segment 22 may be of a conventional type which includes an elastomeric septum that would affect the pressure signal, or that sampling port may also be isolated from the pressure column as will be described below. One benefit of improving the pressure response of the system by isolating the various functional elements is that the entire conduit line can be lengthened to move the reservoir 30 farther away from the patient. In conventional blood sampling systems, where the elastomeric components remain in contact with the pressure column, the maximum length of the conduit line from the reservoir to the patient is about __ cm. By isolating just the reservoir 30 as indicated above, the conduit line can be lengthened to about __cm. [Mark, please fill in these distances]

[0073] It is important to understand that the principles of the control valve 32 described above are applicable to other configurations of fluid sampling systems. In the exemplary system described above, a sampling port 84 is incorporated centrally in the rotating valve member 72 of the control valve 32, which is connected or adjacent to the reservoir 30. The control valve 32 isolates both the reservoir and the sampling port in the sampling mode. However, the sampling port in the control valve may connect through the manifold 70 instead of the valve member 72. Also, the exemplary valve member has three positions 90° apart from each other, but the arrangement of the channels within the valve member and manifold may be altered to change the amount of the valve member rotates in each position. Furthermore, the principles of isolating the elastomeric elements of the reservoir and sampling port can be transferred to a stand-along sampling port in the conduit line. Examples of each of these alternatives will be described below, and it should be clear that these are representative of numerous other alternatives.

[0074] Figures 20A-20E illustrate an alternative control valve 170 of the present invention adjacent a reservoir 30 with a modified arrangement of internal flow paths than the exemplary embodiment described above. The

control valve 170 is similar to the first embodiment in that a housing or manifold 172 connects to the reservoir 30 and rotatably receives therein a valve member 174. Furthermore, the valve member 174 carries a central sampling port 176, which is illustrated as a slit septum-type but could be any number of kinds of sampling ports. Figure 20B shows a control handle 178 of the valve member 174 oriented with its pointed and 180 down into the right at about a 45° angle. The indicator plate 182 shows the three position indicators at the 45°, 90°, and 180° locations relative to a horizontal reference line to the right at 0°. This is a departure from the 90° separation between the valve member positions in the first embodiment.

[0075] The control handle 178 in Figure 20B is in the "S" or sampling position. The internal flow channels defined within the valve member 174 in the radial plane of the ports of the manifold 172 are illustrated in Figure 20E. Comparing this view with a similar view shown in Figure 18C, the reader will discern the slightly different orientations of the internal channels within the valve member 174. By rotating the valve member 174 clockwise another 45°, the control valve 170 will be placed in the F/C mode wherein all of the internal flow paths are in series so that the system can be flushed. Rotating the valve member 174 a further 90° into the M position isolates both the reservoir 30 and the sampling port 176 from the attached conduit line for undegraded pressure monitoring. Although the relative spacing between the S position and the F/C position is only 45°, in contrast with 90° in the first embodiment, the flow channels are modified to prevent cross-talk or pressure perturbations transmitted to the proximal segment and pressure transducer when switching positions. Furthermore, the channels are arranged so that there is greater separation between the internal channels in the sampling mode.

[0076] Figures 21A-21E show another alternative control valve 190 similar to the valve 170 of Figure 20A-20E, but with a luer-style central sampling port. Specifically, the control valve 190 includes the modified internal flow paths such that the three operating positions of a control handle

192 seen in Figure 21B are other than 90° apart. More particularly, the cross-section of Figure 21E is the same as that of Figure 20E. Also, the control valve 190 includes a sampling port 194 provided in the center of a rotatable valve member 196. In contrast to the embodiments of Figures 20A-20E, however, the sampling port 194 includes a luer-style connector 198, best seen in Figure 21C. The male luer-style connector 198 mates with a female luer connector on a sampling syringe (not shown). Because of the typically larger sizes of the blunt cannulas in such sampling syringes, the septum 200 of the sampling port 194 is highly compliant, or at least more compliant than the slit septum 86 used in the sampling port 84 described above. The ability to isolate the luer-style sampling port 194 using the control valve 190 is therefore highly desirable as it greatly improves the quality of the pressure signal received by the pressure transducer by removing the compliance of the septum 200 from the pressure column.

[0077] Figures 22A-22E illustrates a control valve 210 that, as before, may be associated with or connected to a reservoir 30, but includes an alternative fluid sampling port 212. Specifically, the fluid sampling port 212 comprises a side port from a control valve manifold 214 rather than being formed centrally in a rotatable valve member 216. The sampling port 212 is shown in cross-section in Figure 22E which reveals an elastomeric septum 220 captured by a cap 222 over a sampling cavity 224. A pair of flow channels 226, 228 open into the sampling cavity 224. The opposite ends of the flow channels 226, 228 opened to an interior chamber of the control valve manifold 214. In this sense, the sampling port 212 communicates with internal channels in the control valve 210 via a through flow path defined by the channels 226, 228.

[0078] Figure 22E also shows six openings to the internal channel of the manifold 214, two of which lead to the sampling port channels 226, 228. Another two openings lead to proximal and distal ports 230, 232 that connect to the proximal and distal conduit line segments. Finally, two more openings

lead respectively to the inlet and outlet of the reservoir 30. The valve member 216 includes circumferential channels that selectively communicate with these 6 ports depending on the rotational position of a handle 234. As with the earlier embodiments, there are 3 positions of flush, monitor, and sample. In the monitor position, the control valve 210 isolates both the reservoir 30 and sampling port 212 from the conduit line for a more accurate pressure signal. Also, the valve 210 prevents flow from the proximal conduit line segment in the sampling mode. This embodiment illustrates the alternative of having the sampling port connected with the control valve manifold as opposed to the rotating valve member. ;

Figures 23A-23E are various views of a luer-style valved sampling station 250 which can be incorporated into a pressure monitoring line in conjunction with a reservoir or independently. The valved sampling station 250 includes a housing or manifold 252 that defines therewithin an internal chamber 254 as seen in Figure 24 with which a pair of ports 256, 258 communicate. The downstream port 256 may be connected to the patient, while an upstream port 258 is connected to a pressure transducer (not shown), in like manner as the manifold ports 140, 142 seen in Figure 12. Additionally, a loop-shaped channel 260 formed in the manifold 252 has opposite ends that open to the internal chamber 254. A valve member 262 rotates within the internal chamber 254. The valve member 262 has the same configuration has the valve member 196 shown in Figures 21A-21E. That is, the internal flow channels are the same and the valve member 262 carries a central luer-type sampling port 264.

[0079] With reference to Figure 23B, the manifold 252 includes an indicator plate 266 on which are provided the familiar three operational mode symbols of sampling, flush, and pressure monitoring. A control handle 268 is used to rotate the valve member 262 into the three operational positions. The reader will recognize that the three positions have the same spacing as the positions for the control valve 190 in Figures 21A-21E. Indeed, the valved

sampling station 250 functions analogously to the control valve 190 in that in the pressure monitoring position of the control handle 268, the central sampling port 264 is isolated from the ports 256, 258, and thus the attached conduit line and pressure column. The sole difference between the valved sampling station 250 and the control valve 190 is the substitution of the loop-shaped channel 260 for the clearance reservoir. The channel 260 is important in that a flow of fluid passes through it and through all of the internal channels of the valved sampling station 250 when the control handle 268 is in the flush position, seen in Figure 23B. Again, the valved sampling station 250 can be used in a conduit line of a pressure monitoring system where a clearance volume of fluid is pulled past the sampling port using a reservoir as described above, or other such clearing device.

[0080] Finally, Figures 25A-25E illustrate a further alternative valved sampling station 280 with a sampling port 282 extending from one side of a manifold 284. The manifold 284 is configured in a T-shape with a pair of ports 286, 288 that open to an internal chamber projecting outward at 90° with respect to one another, and with respect to the sampling port 282. The valve member 290 rotates within the internal chamber. As seen in Figure 25E, the valve member 290 includes two circumferential channels 292, 294 that selectively communicate with the ports 286, 288, and with two ports 296, 298 leading to and from the sampling port 282. As in the valved sampling station 250 of Figures 23-24, the valve member 290 rotates into three positions corresponding to flush, sampling, and pressure monitoring. The ports 286, 288 attach to proximal and distal segments of a conduit line in a manner described above. In the pressure monitoring mode, the sampling station 280 excludes the sampling port 282 from the conduit line. This embodiment is similar to the immediately preceding sampling station 250, but illustrates a sampling port 282 that connects directly to the manifold 284 rather than to the rotating valve member 290. Furthermore, the sampling port 282 has a slit

septum 299 for receiving a blunt cannula (not shown), but a luer-type sampling port could also be used.

[0081] While the invention has been described in its preferred embodiments, it is to be understood that the words which have been used are words of description and not of limitation. Therefore, changes may be made within the appended claims without departing from the true scope of the invention.

WHAT IS CLAIMED IS:

1. A medical system for fluid sampling and pressure monitoring of a fluid system of a patient, comprising:

a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

a control valve with a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the proximal segment, a distal port fluidly connected to the distal segment, and a reservoir port, wherein each of the manifold ports opens to the interior chamber,

a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

a fluid sampling port in the medical system;

a reservoir in fluid communication with the reservoir port of the control valve manifold;

the control valve further including a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least two positions:

a first position that provides open fluid communication from the proximal segment to the patient through the control valve so as to eliminate any dead spaces therein, wherein reduced pressure within the reservoir pulls fluid from the distal segment through the control valve and into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port, and

a second position that provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member to the

distal segment while bypassing the reservoir, such that the pressure of fluid within the conduit line exclusive of the reservoir can be sensed by the pressure transducer.

2. The system of claim 1, wherein the valve member has a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

3. The system of claim 1, wherein the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, and further including mating features on the valve member core and manifold that provide tactile feedback and positive positioning of the core in both first and second positions.

4. The system of claim 1, wherein the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, further including coordinated visible features on the control handle and manifold that provide symbolic indicators of both first and second positions of the valve member.

5. The system of claim 1, wherein the sampling port is formed within the control valve.

6. The system of claim 5, wherein the sampling port is formed within the valve member and communicates with a sampling cavity formed internally within the valve member open to at least one of the channels.

7. The system of claim 5, wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the interior chamber of the manifold.

8. The system of claim 5, further including a second sampling port having a sampling cavity positioned along the distal segment of the conduit line.

9. The system of claim 8, further including a second control valve interposed between the second sampling port and the distal segment and having a valve member movable into at least three positions:

a first position that provides open fluid communication from the conduit line through the control valve to the sampling cavity and back to the conduit line,

a second position that provides open fluid communication from the conduit line through the valve member and back to the conduit line while bypassing the second sampling port, such that the pressure of fluid within the conduit line exclusive of the second sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal segment through the control valve to the second sampling port but prevents communication between the second sampling port and the conduit line proximal from the second sampling port.

10. The system of claim 1, wherein the sampling port is positioned along the distal segment of the conduit line.

11. The system of claim 10, further including a second control valve interposed between the sampling port and the distal segment and having a valve member movable into at least three positions:

a first position that provides open fluid communication from the conduit line through the control valve to the sampling cavity and back to the conduit line,

a second position that provides open fluid communication from the conduit line through the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal segment through the control valve to the sampling port but prevents communication between the sampling port and the conduit line proximal from the sampling port.

12. The system of claim 1, wherein the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold, the core having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

13. The system of claim 12, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

14. The system of claim 1, further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position.

15. The system of claim 1, wherein the reservoir has an inlet open to an outlet port of the control valve manifold and an outlet open to an inlet port of the control valve manifold, and wherein the first position of the valve member provides open fluid communication between the control valve flow passages through the inlet and outlet of the reservoir to flush a chamber of the reservoir.

16. A medical system for fluid sampling of a fluid system of a patient, comprising:

a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

a control valve connected between the proximal segment and the distal segment of the conduit line;

a fluid sampling port having a flow path therethrough whose opposite ends open to internal channels in the control valve;

a reservoir in fluid communication with a reservoir port of the control valve manifold;

the control valve further including a valve member movable into at least three positions:

a first position that provides open fluid communication from the proximal segment through the control valve to the distal segment,

a second position that provides open fluid communication from the proximal segment to the distal segment while bypassing the reservoir and sampling port, and

a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

17. The system of claim 16, wherein:

the control valve further includes a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the proximal segment of the conduit line, a distal port fluidly connected to the distal segment, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber, and wherein the valve member comprises a core movable within the interior chamber of the manifold and having channels therein that selectively communicate with the manifold ports, and the reservoir has an inlet open to the manifold outlet port and an outlet open to the manifold inlet port, and wherein:

the first position provides open fluid communication from the proximal segment to the proximal port and the outlet port of the control valve, through the inlet and outlet of the reservoir, to the inlet port and the distal port of the control valve to the distal segment,

the second position provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member core to the distal segment while bypassing the reservoir and sampling port, and

the third position provides open fluid communication from the distal segment to distal port and one of the channels of the valve member core, and to the sampling port.

18. The system of claim 17, wherein the valve member core has an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

19. The system of claim 18, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

20. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber in which the valve member moves, and wherein the sampling port is formed within the valve member and includes a sampling cavity open to channels within the valve member that communicate with the manifold interior chamber.

21. The system of claim 20, wherein the valve member comprises a cylindrical core rotatable within the manifold interior chamber, and wherein the fluid sampling port opens in a control handle of the valve member and is centered along the axis of rotation of the valve member core.

22. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber in which the valve member moves, and wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the manifold interior chamber.

23. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber and the valve member comprises a core movable within the interior chamber of the manifold, and further including mating features on the valve member core and manifold that

provide tactile feedback and positive positioning of the core in all three positions of the valve member.

24. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber and the valve member comprises a movable within the interior chamber of the manifold and a control handle external to the manifold, and further including coordinated visible features on the control handle and manifold that provide symbolic indicators of all three positions of the valve member.

25. A method of taking samples and measuring the pressure of a fluid system of a patient, comprising:

providing a fluid sampling system with a conduit line and a reservoir connected thereto between a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

interposing a control valve between the reservoir and the conduit line having a movable valve member with a control handle, the valve member movable into at least a first position and a second position;

providing a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

providing a fluid sampling port in the sampling system;

selecting the first position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve and the reservoir, and creating a reduced pressure within the reservoir such that fluid flows from the distal segment through the control valve into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port; and

selecting the second position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve while bypassing the reservoir, and monitoring the pressure sensed by the pressure transducer.

26. The method of claim 25, wherein the valve member has a third position, and the method includes selecting the third position of the valve member to provide open fluid communication from the distal segment to the sampling port but prevent communication between the sampling port and both the reservoir and the proximal segment, and sampling fluid from the conduit line through the sampling port.

27. The method of claim 26, wherein the fluid system of the patient is the blood system, and further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position, the method including the steps of:

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient; then

creating a reduced pressure within reservoir and collecting sufficient fluid therein such that blood flows past the sampling port; then

selecting the third position of the valve member; then

sampling blood from the conduit line through the sampling port; then

creating an elevated pressure within the reservoir to expel blood therefrom into the distal segment of the conduit line; then

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient and flushes the reservoir of blood; and then

selecting the second position of the valve member and monitoring the pressure sensed by the pressure transducer.

28. The method of claim 25, wherein the control valve has a manifold defining an interior chamber within which the valve member rotates, and further including mating features on the valve member and manifold that provide tactile feedback and positive positioning of the core in both first and second positions, the method of selecting the first and second positions further including rotating the valve member until the tactile feedback is sensed.

29. The method of claim 25, wherein the control valve includes visible features that provide symbolic indicators of the first and second positions of the control handle, the method of selecting the first and second positions further includes interpreting the symbolic indicators to determine the placement of the control handle corresponding to the first and second positions.

30. A medical system for fluid sampling of a fluid system of a patient, comprising:

a conduit line with a proximal end adapted to be supplied with a physiological fluid and a distal end adapted to be in communication with a fluid system of a patient;

a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

a fluid sampling port having a sampling cavity;

a control valve interposed between the conduit line and the sampling port and having a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the conduit line, a distal port fluidly connected to the conduit line, an outlet port, and an

inlet port, wherein each of the manifold ports opens to the interior chamber,

the control valve further including a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least three positions:

a first position that provides open fluid communication from the conduit line to the proximal port and the outlet port of the control valve to the sampling cavity, and to the inlet port and the distal port of the control valve to the conduit line,

a second position that provides open fluid communication from the conduit line to the proximal port and through at least one channel in the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal end of the conduit line through the control valve to the sampling port but prevents communication between the sampling port and the proximal end of the conduit line.

31. The system of claim 30, wherein the valve member comprises a core movable within the interior chamber of the manifold and having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

32. The system of claim 31, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

33. The system of claim 30, wherein the sampling port is formed within the valve member and includes a sampling cavity open to the valve member channels.

34. The system of claim 33, wherein the valve member comprises a cylindrical core rotatable within the manifold interior chamber, and wherein the fluid sampling port opens in a control handle of the valve member and is centered along the axis of rotation of the valve member core.

35. The system of claim 30, wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the manifold interior chamber.

36. The system of claim 30, wherein the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold.

37. The system of claim 36, further including mating features on the valve member core and manifold that provide tactile feedback and positive positioning of the core in all three positions of the valve member.

38. The system of claim 36, further including coordinated visible features on the control handle and manifold that provide symbolic indicators of all three positions of the valve member.

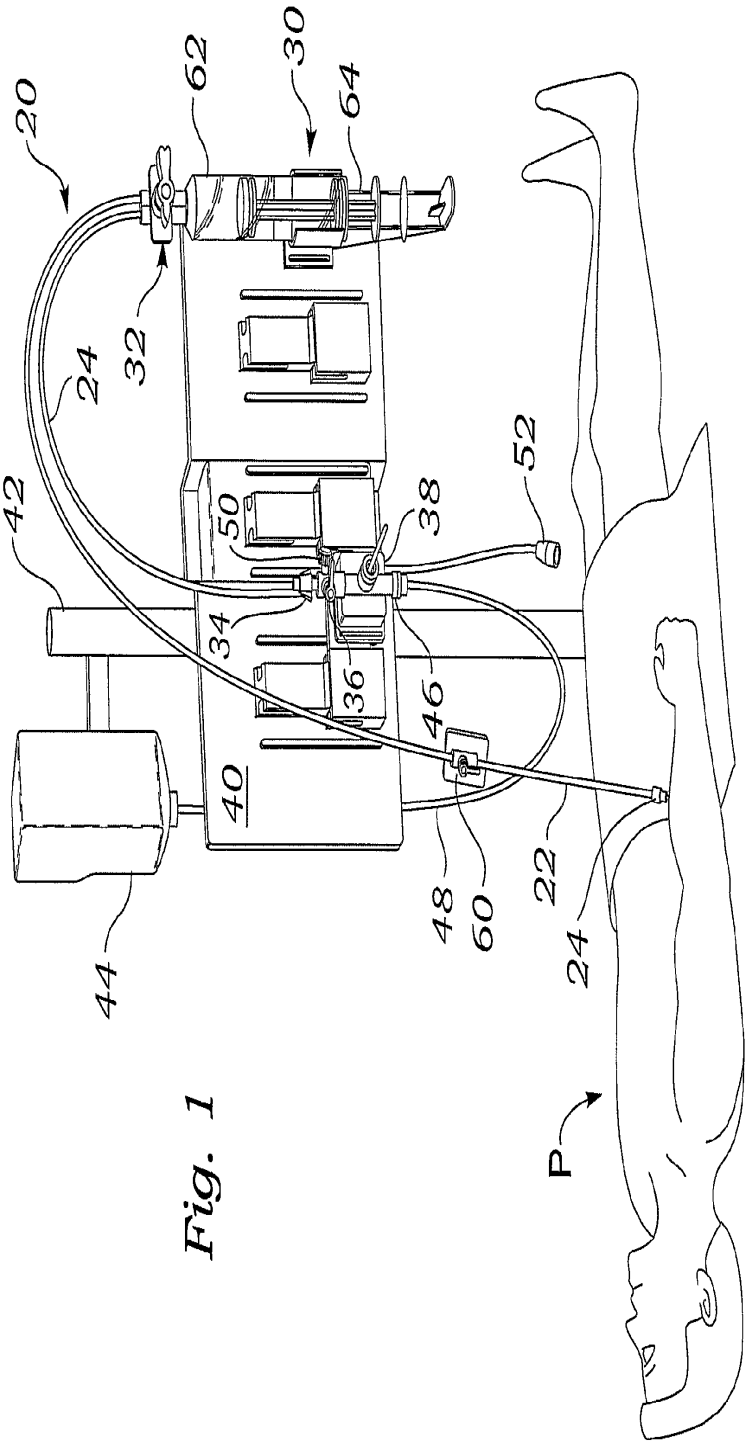


Fig. 1

Fig. 2

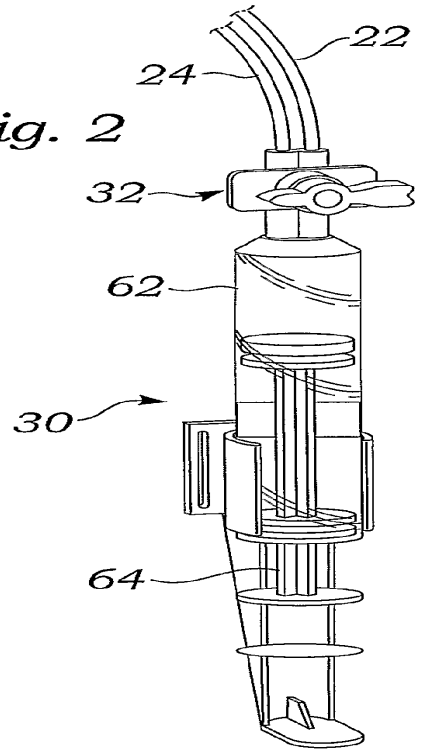


Fig. 3

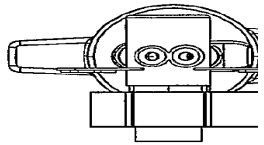


Fig. 3B

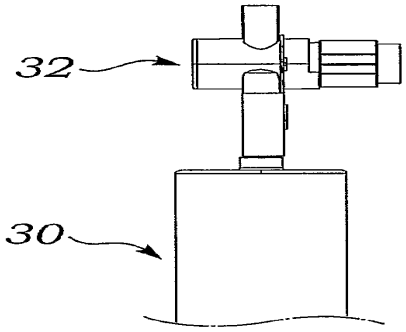
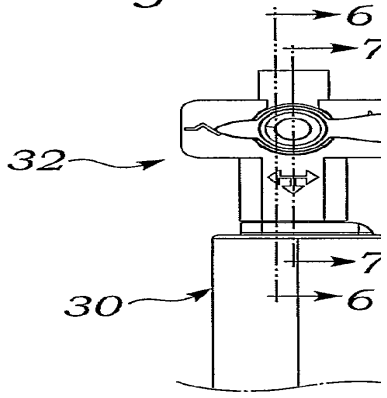


Fig. 3A



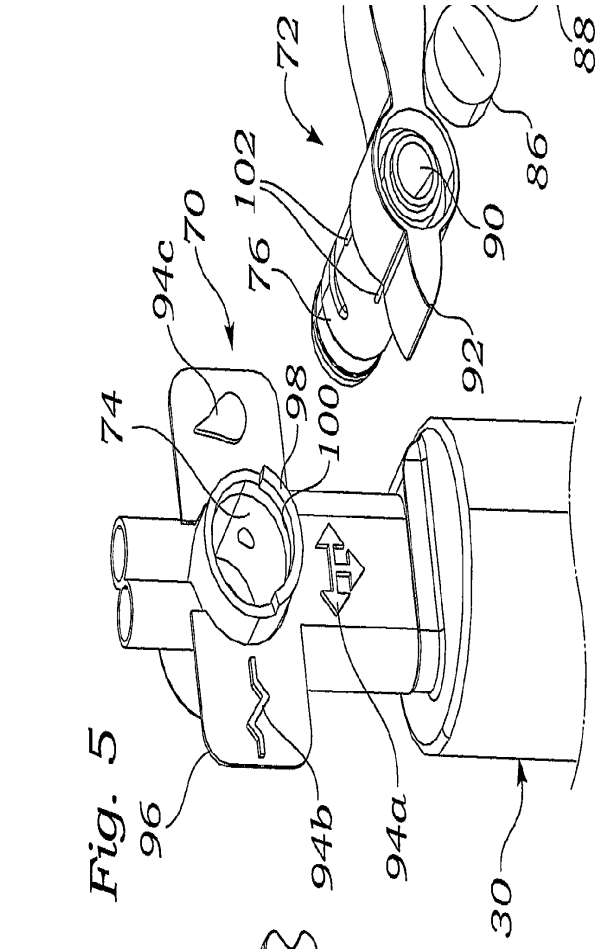

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94c
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74
98
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96
94b
94a
30

Fig. 5

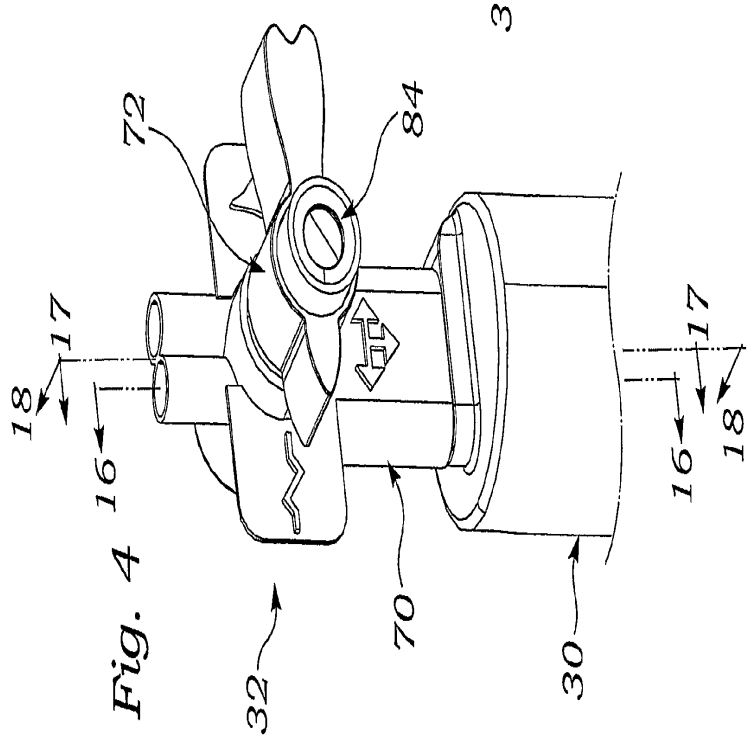

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30

Fig. 4

Fig.6B

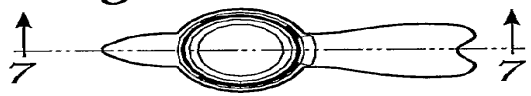


Fig.6D

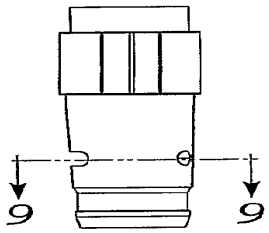


Fig.6A

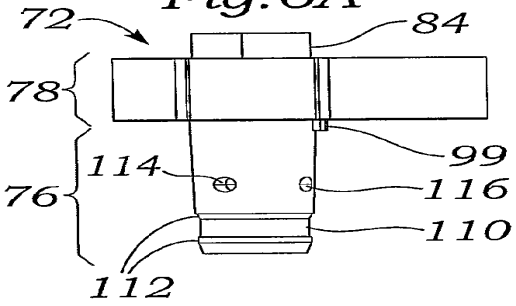


Fig.7

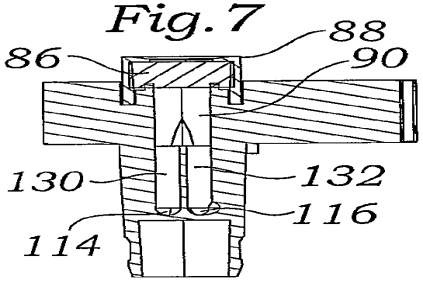


Fig.6

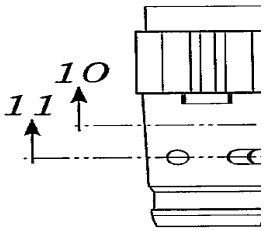


Fig.9



Fig.6E

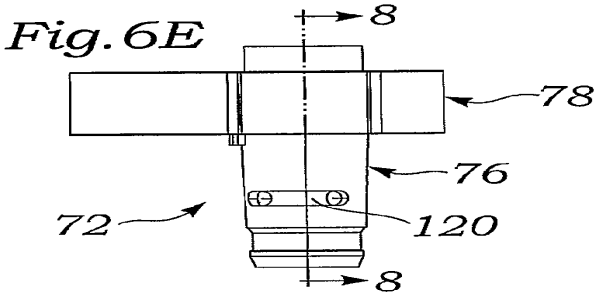


Fig.8

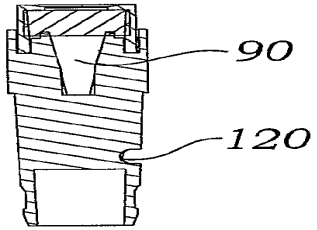


Fig.10

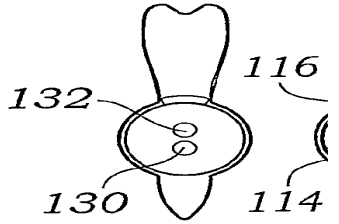


Fig. 12

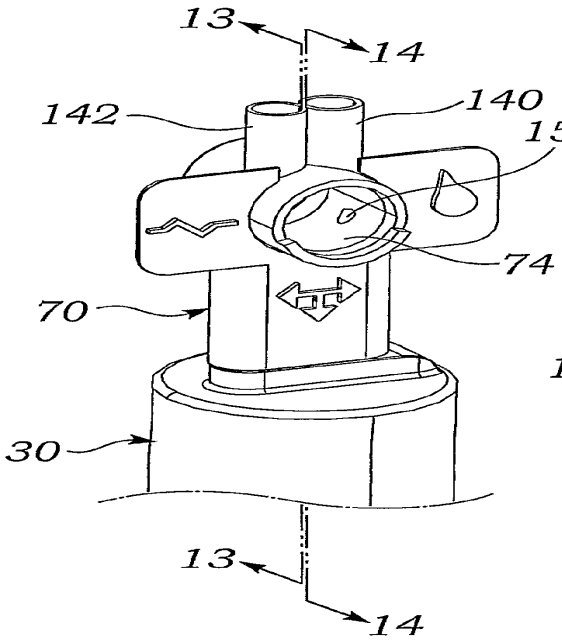


Fig. 13

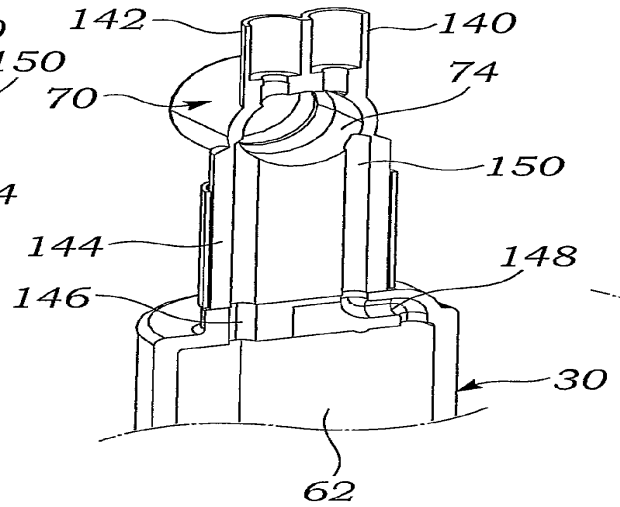


Fig. 14

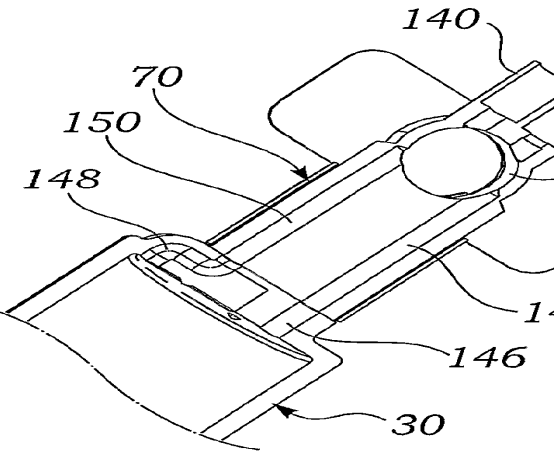


Fig. 15B

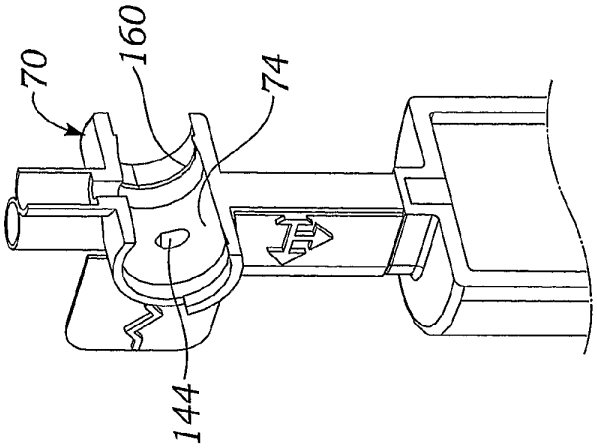


Fig. 15A

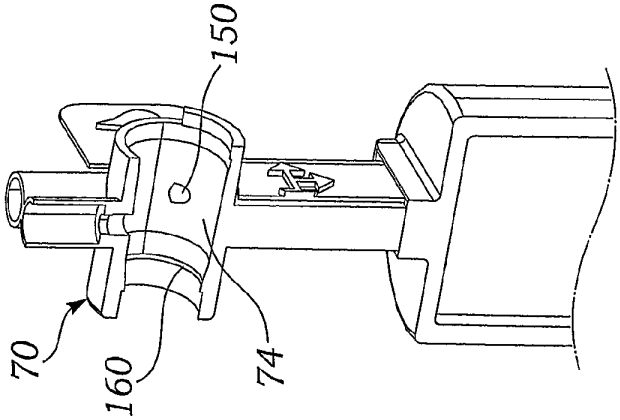


Fig. 17

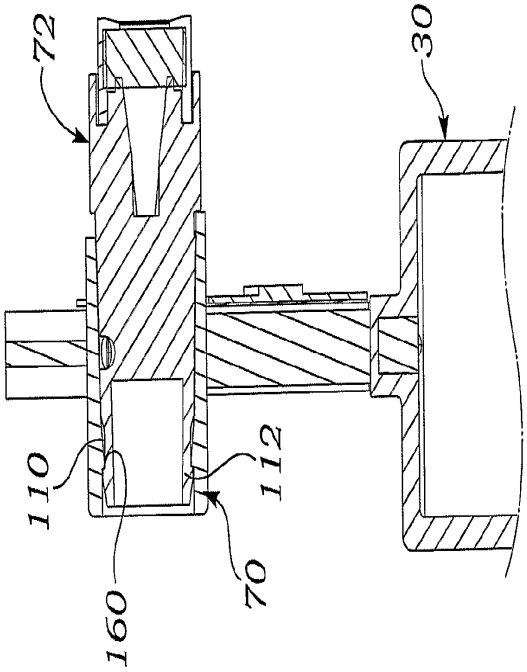


Fig. 16

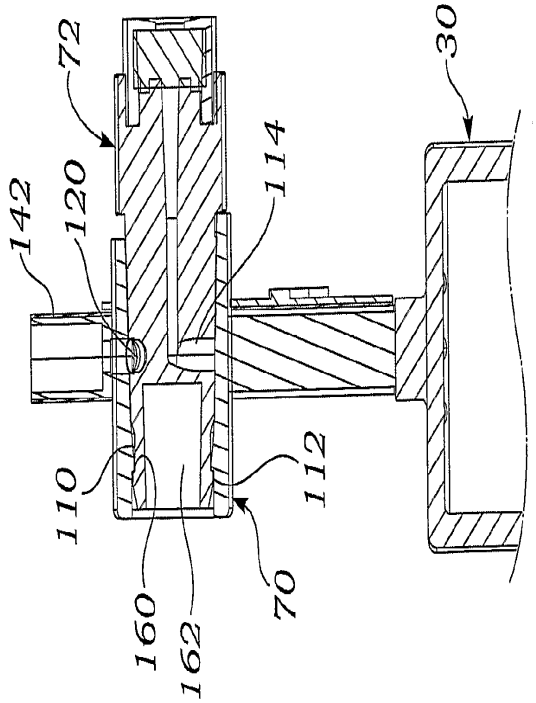


Fig. 18A

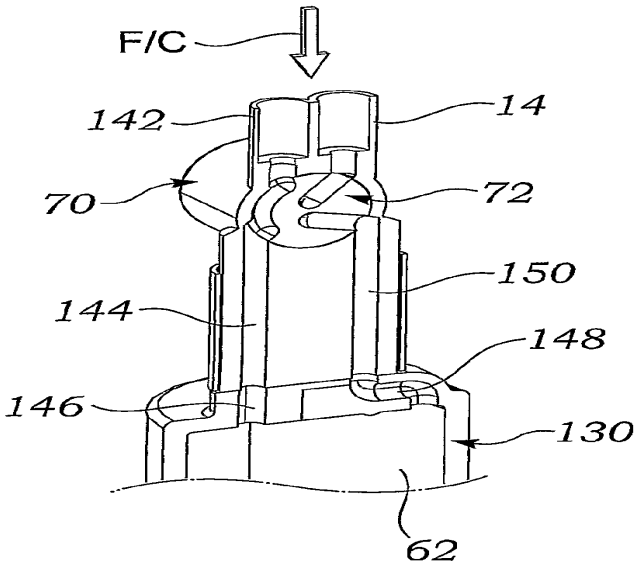


Fig. 18B

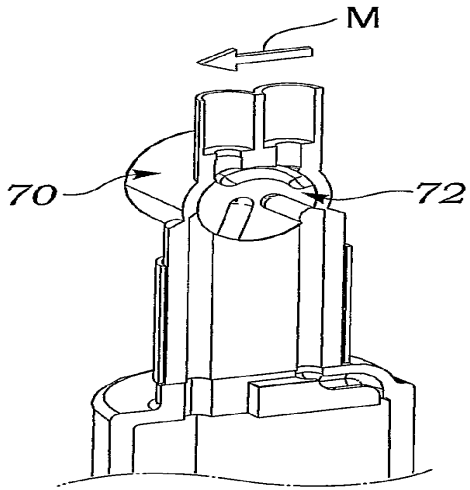


Fig. 18

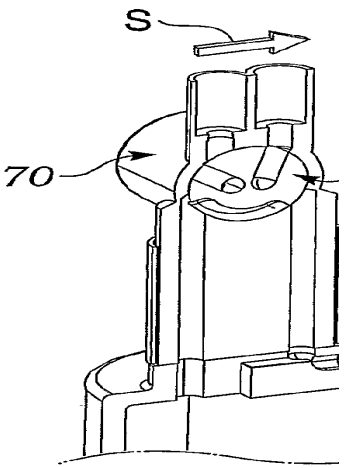


Fig. 19A

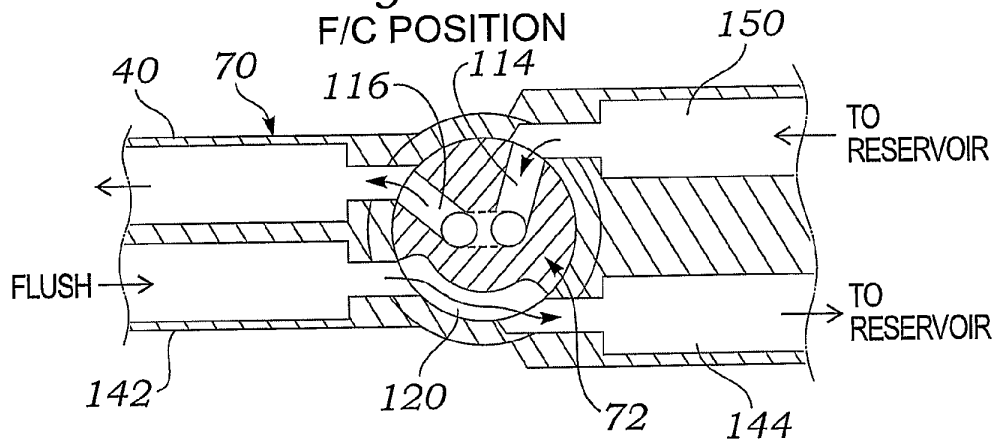


Fig. 19B

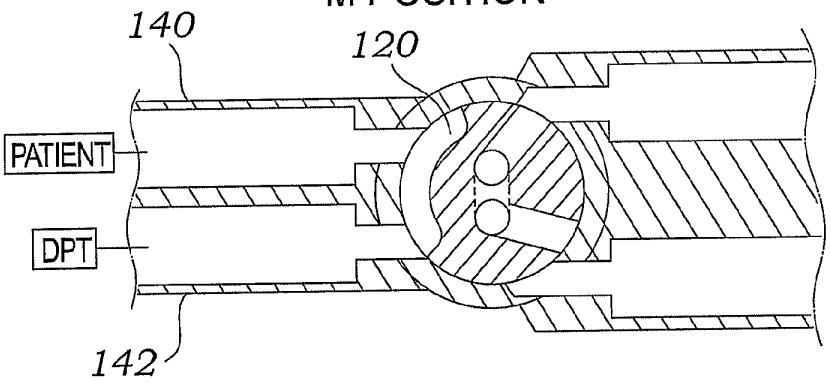


Fig. 19C

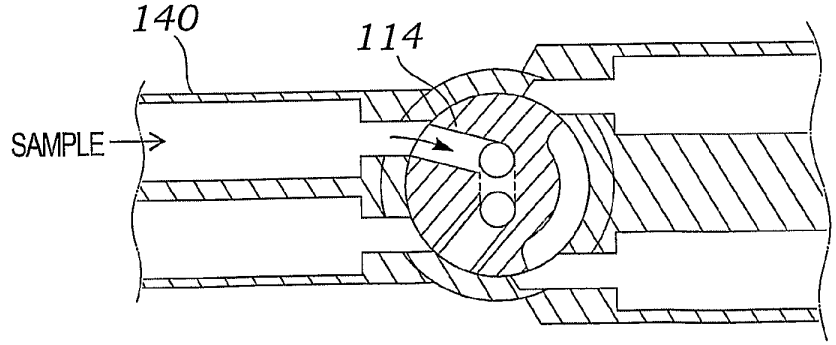


Fig.20D

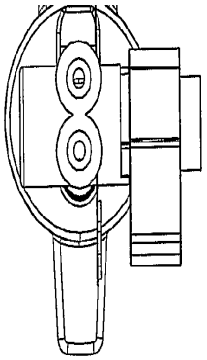


Fig.20B

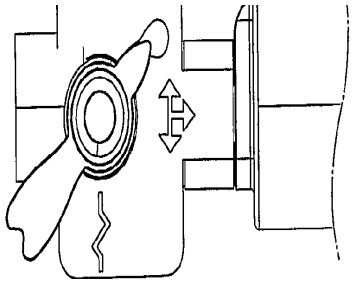


Fig.20C

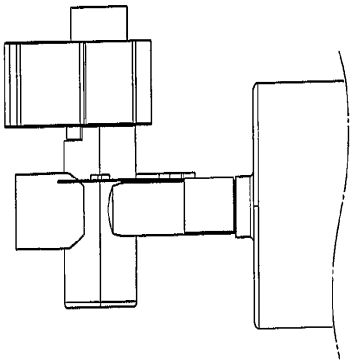


Fig.20A

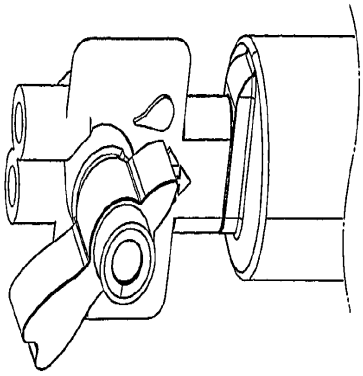


Fig.21A

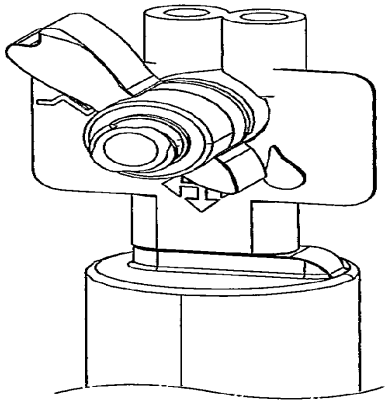


Fig.21L

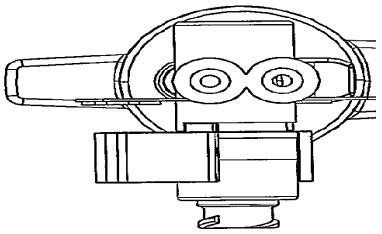


Fig.21C

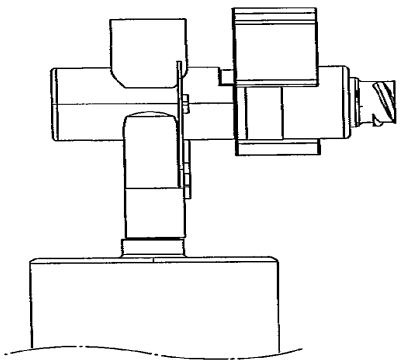


Fig.21B

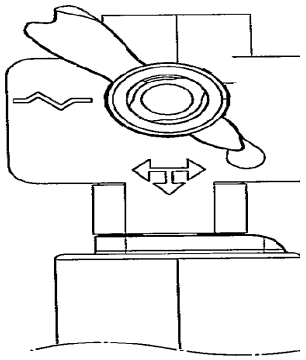


Fig.22A

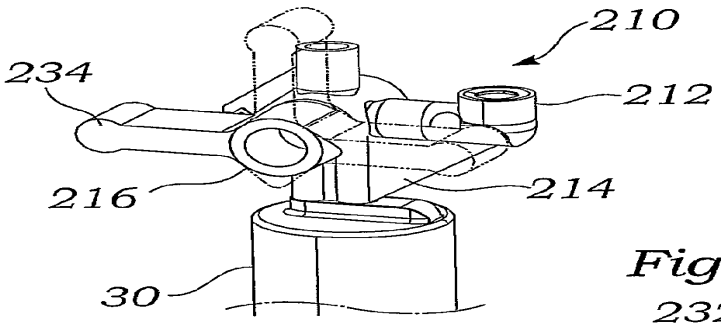


Fig.22

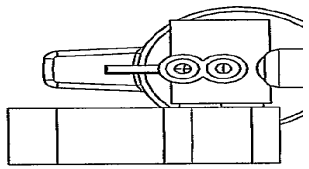


Fig.22E

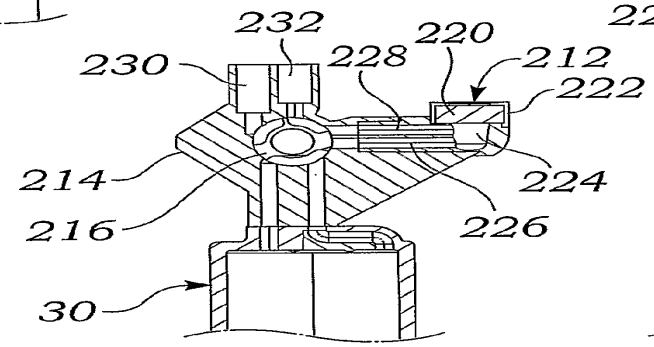


Fig.22C

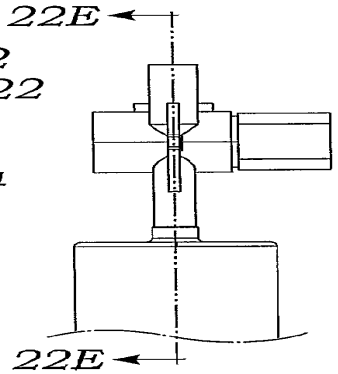


Fig.22

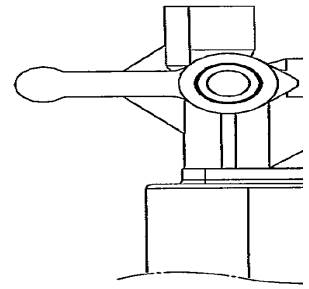


Fig.24D

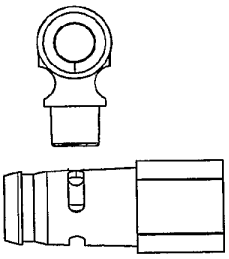


Fig.24B

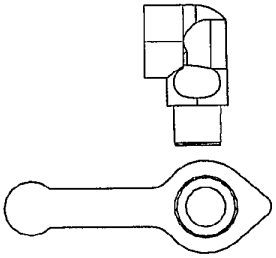


Fig.24A

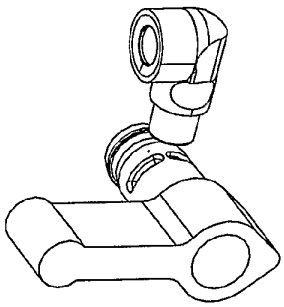


Fig.24C

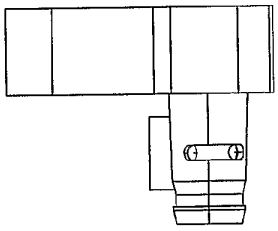


Fig.25D

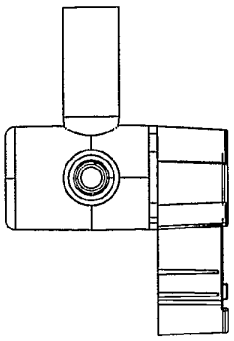


Fig.25B

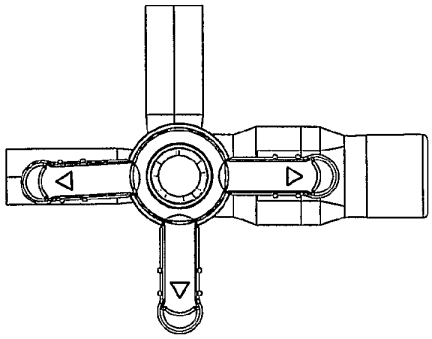


Fig.25C

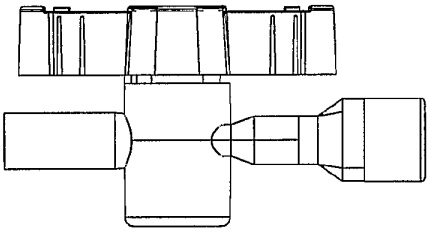
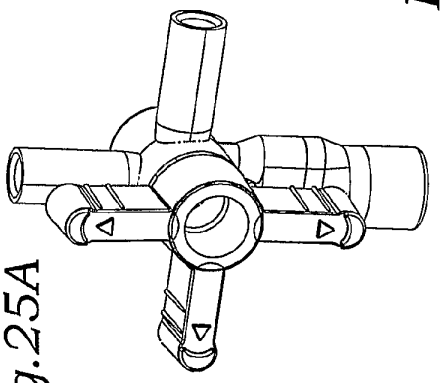


Fig.25A



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/035832

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 643 218 A (LYNN LAWRENCE A [US] ET AL) 1 July 1997 (1997-07-01) column 13, line 42 - column 14, line 57	1-24, 30-38
A	US 5 961 472 A (SWENDSON DAVID L [US] ET AL) 5 October 1999 (1999-10-05) cited in the application column 12, line 31 - column 14, line 64	1-24, 30-38
A	EP 0 376 603 A (MEDEX INC [US]) 4 July 1990 (1990-07-04) column 3, line 53 - column 4, line 58	1-24, 30-38

☐ 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

"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
5 December 2006	27/12/2006

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	Manschot, Jan

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/035832

Box 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. [X] Claims Nos.: 25-29
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

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 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:

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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/035832

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5643218 A	01-07-1997	US 5743886 A	28-04-1998
US 5961472 A	05-10-1999	AT 309743 T	15-12-2005
		AU 732501 B2	26-04-2001
		AU 9508798 A	23-04-1999
		BR 9812532 A	25-07-2000
		CA 2304146 A1	08-04-1999
		CN 1278710 A	03-01-2001
		DE 69832399 D1	22-12-2005
		DE 69832399 T2	14-06-2006
		EP 1017317 A1	12-07-2000
		ES 2256960 T3	16-07-2006
		JP 3421320 B2	30-06-2003
		JP 2001517522 T	09-10-2001
		WO 9916354 A1	08-04-1999
		US 6224561 B1	01-05-2001
EP 0376603 A	04-07-1990	CA 2005042 A1	22-06-1990
		DK 653189 A	23-06-1990
		US 5002066 A	26-03-1991

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

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WUESTHOFF & WUESTHOFF
Patentanwälte PartG mbB
06. Nov. 2018
RECEIVED

Application No.	Ref.	Date
16 747 682.9 - 1132	EPA-142 451	31.10.2018
Applicant: KURIN, INC.		

Basis 28.02./gedr.
WL 06.12.18 ✓
WV 28.01.19 ✓ voll 103

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 insofar 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
EPO Form 2001 11.16TRI

Schultz, Ottmar
Primary Examiner
For the Examining Division

Enclosure(s): 1 page/s reasons (Form 2906)

Registered letter
EPO Form 2001 11.16 TRI

The examination is being carried out on the **following application documents**

Description, Pages

1-33 as published

Claims, Numbers

1-20 as published

Drawings, Sheets

1/50-50/50 as published

+++++

An International Preliminary Report on Patentability has already been drawn up for the present application in accordance with the PCT. The deficiencies mentioned in that report give rise to objections under the corresponding provisions of the EPC.

+++++

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 50828-501001WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2016/043709	International filing date *(day/month/year)* 22 July 2016 (22.07.2016)	Priority date *(day/month/year)* 24 July 2015 (24.07.2015)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant KURIN, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	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 Article 35(2) with regard to novelty, inventive step or 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

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 30 January 2018 (30.01.2018)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Lingfei Bai e-mail: pct.team2@wipo.int

Form PCT/IB/373 (January 2004)

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.

+++++

Vox Sanguinis (2002) **83**, 13–16
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ORIGINAL PAPER

Diversion of first blood volume results in a reduction of bacterial contamination for whole-blood collections

D. de Korte,[1] J. H. Marcelis,[2] A. J. Verhoeven[1] and A. M. Soeterboek[2]

[1]*CLB, Sanquin Blood Supply Foundation, Amsterdam, the Netherlands*

[2]*Blood bank De Meierij, Sanquin Blood Supply Foundation, Amsterdam, the Netherlands*

Vox Sanguinis

Background and Objectives In a previous study we established a reliable setpoint for the prevalence of bacteria in whole blood. In the present study we investigated the possible preventive effect, of diversion of the first 10 ml of a blood donation, on the bacterial contamination rate.

Materials and Methods To divert the first 10 ml of a whole-blood donation, we used a special five-bag system equipped with a Composampler® device. After venepuncture, the first 10 ml of a donation was sampled into a vacutainer tube. This was followed by the collection of the whole-blood unit. The extra bag allowed direct sampling of the final donation in a closed system for BacT/Alert. Whole-blood samples were taken after storage (2–14 h at 20 °C) and subsequent mixing. BacT/Alert culture bottles were incubated until positive, or for 7 days if negative. Confirmation and identification of positive cultures was performed according to internationally recognized standard reference methods.

Results The prevalence of bacteria in whole blood, as determined by using standard collection techniques, was 0·35% (95% confidence interval 0·27–0·44%, $n = 18\,257$). After diversion of the first 10 ml this value was significantly lower: 0·21% ($P < 0·05$, 95% confidence interval 0·12–0·35%, $n = 7087$). Most strikingly, a reduction in the frequency of staphylococcal species was observed ($P < 0·02$, reduction from 0·14 to 0·03%).

Conclusions Diversion of the first 10 ml of blood was shown to contribute significantly to a reduction in the prevalence of superficial skin bacteria in whole-blood units. In our opinion, blood collection systems should be adapted to use the first 10–30 ml of a whole-blood donation for testing purposes.

Received: 15 November 2001, revised 1 March 2002, accepted 2 March 2002

Key words: bacteria, collection, diversion, reduction, whole blood.

Introduction

Since the implementation of programmes for reducing the contamination of the blood supply by blood-borne viruses, transfusion-transmitted bacterial infections (TTBI) have become one of the major hazards of blood transfusion. Sazama [1] estimated that 10% of blood transfusion-associated deaths are caused by bacterial contamination of the transfused product.

In the last decade, increased attention has been given to the prevention of possible systematic contamination during the collection (i.e. by disinfection) and preparation stages (i.e. closed systems, by the use of sterile-docking devices, etc.) of blood components. Reliable data on the frequency of bacterial contamination of donated whole blood, used for component preparation, is needed in order to validate the occurrence of systemic contamination, or to evaluate measures taken to decrease contamination. Recently, we showed that 0·34% of whole blood units were contaminated with bacteria [2]. That

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KUR-MAG-DE003803

study compromised a number of units tested, resulting in a narrow 95% confidence interval (CI) of 0·27–0·44%.

Because the majority of bacteria involved in TTBI are skin organisms, it is probable that contamination is introduced during venepuncture. Investigators have speculated that a skin-plug is punched out by the needle during phlebotomy [3,4]. Therefore, one of the suggested measures to reduce the bacterial contamination of whole-blood collections is diversion of the first volume of whole blood collected [4]. Olthuis *et al.* [5] were the first to show that for apheresis collections, the first 10 ml had a higher rate of bacterial contamination than the next two aliquots of 10 ml. Recently, Wagner *et al.* [6] showed the effectiveness of the diversion approach in an *in vitro* model system. Bruneau *et al.* [7] showed that the first aliquot (15-ml) of whole blood collected has a higher contamination rate than the second aliquot, without testing the final whole-blood unit collected.

We investigated, under routine blood bank conditions, whether diversion of the first 8–10 ml of whole blood from the primary collection container reduced the degree of bacterial contamination in the final whole-blood collection.

Materials and methods

Blood collection

Whole blood (500 ± 50 ml) was collected under standardized blood bank conditions in four-bag Compoflex CPD/SAGM systems (Fresenius Hemocare, NPBI International, Emmer-Compascuum, the Netherlands), with an additional fifth bag. These blood-collection systems were designed and validated [2] for use in this particular study (see Fig. 1). They allow both diversion of the whole blood (by Composampler) and sampling in a closed system, with the only aseptic handling being the transfer (in a laminar airflow cabinet) of a sample from the final donation to anaerobic and aerobic culture bottles (BacT/Alert; Organon Teknika, Boxtel, the Netherlands).

At all different collection sites of the De Meierij and CLB Sanquin Blood Banks, standardized methods for disinfection (double-swab method with isopropyl alcohol swabs), blood collection and storage were used. After venepuncture, an EDTA-vacutainer tube (nominal volume 10 ml; Becton-Dickinson, Franklin Lakes, NJ) was filled via the Composampler device (the mean collected volume was 9·8 ml with ≈ 1 ml of anticoagulant derived from the tube between the needle and the Composampler), followed by filling of the primary collection bag utilizing a clamp on the line before the Composampler. The only difference between the Blood Banks was the storage time on butane-diol cooling plates [8] (Fresenius Hemocare/NPBI International) between collection and sampling for BacT/Alert (2–3 h in Group A; De Meierij Blood Bank, and overnight in Group B; CLB Blood Bank). Butane-diol cooling plates were used to rapidly cool down the blood to 20 °C (within 2 h) and to hold the blood at this temperature during subsequent storage [8].

Automated microbe-detection system

Sampling was performed as described previously [2]. Both aerobic and anaerobic culture bottles were inoculated with a 10-ml sample of whole blood under aseptic conditions in a laminar airflow cabinet, using the integrated sampling

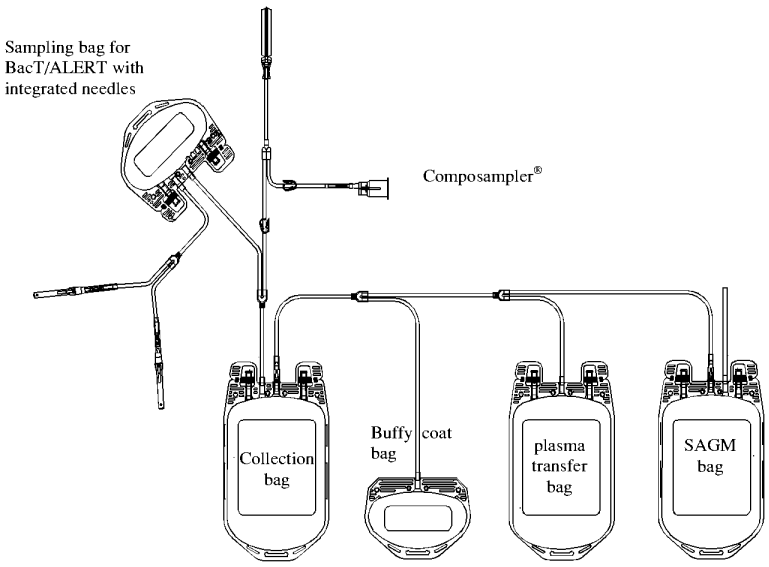


Fig. 1 Special five-bag Compoflex® blood-collection system, consisting of a conventional four-bag system with an additional BacT/ALERT sampling bag (the fifth bag) containing integrated transfer needles and equipped with a Composampler® to allow vacutainer sampling.

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needle of the extra sampling bag. Culture bottles were incubated at 35 °C in the BacT/Alert® system (an automated microbial detection system, based on the colorimetric detection of CO_2 [9]) until flagged positive, or for 7 days if negative. Subculture and identification of positive flagged bottles was performed as described previously [2].

Statistical analysis

Statistical analysis was performed using the computer program INSTAT 2·03 (GraphPad Software, San Diego, CA). The difference in proportions between the two groups was analysed using a one-sided χ^2-test (one-sided because of the hypothesis that diversion would lower the contamination rate). *P*-values of < 0·05 were considered significant. Confidence intervals (CI) were calculated according to Fleiss [10].

Results

Degree of bacterial contamination

In group A (sampling within 3 h after collection of whole blood), a total of 3405 units was collected and tested by using the BacT/ALERT® system. Out of these 3405 units, seven were culture positive, i.e. 0·21% (95% CI: 0·09–0·44%). In group B (sampling after overnight storage) in total 3682 units were collected and tested. In this group eight units were culture positive, i.e. 0·22% (95% CI: 0·10–0·45%). No significant difference was found between the two test groups (χ^2-test, $P = 0·48$). Combining these results, in total 7087 units of whole blood were tested (Table 1), with a bacterial contamination rate of 0·21% (95% CI: 0·12–0·35%). Using our standard collection method without diversion of the first 10 ml of sample, the prevalence was 0·35% (18 257 units tested [2]), which is significantly different (χ^2-test, one-sided because of the hypothesis that diversion would reduce the contamination rate; $P = 0·044$). Except for the diversion step, the collection procedures were similar for both studies. Furthermore, the distribution over the year of the collections for both studies was similar (to avoid seasonal effects).

Table 1 Summarized results of both studies

	Diversion of the first 10 ml	Standard, whole-blood collections [2]
Donations tested	*n* = 7087	*n* = 18 257
Positive cultures	*n* = 15	*n* = 63
Contamination rate[a]	0·21%	0·35%
95% CI of rate[b]	0·12–0·35%	0·27–0·44%

[a]Significant difference, $P < 0·05$ (χ^2-test; one-sided).
[b]Difference between the rates, (95% CI): 0·133 (–0·02 to 0·29).

Table 2 Differentiation of positive samples

	Diversion of the first 10 ml	Standard, whole-blood collections [2]
Resident skin flora		
Staphylococcus[a,b]	2 (0·03)	25 (0·14)
Propionibacterium[c]	10 (0·14)	27 (0·15)
Micrococcus	0	1 (0·01)
Diphteroids, *Corynebacterium* spp	0	5 (0·03)
Transient skin flora		
Bacillus	0	3 (0·02)
Gemella morbillorum	1 (0·01)	0
Klebsiella pneumoniae	1 (0·01)	0
(Upper) Gastrointestinal flora		
Streptococcus bovis	1 (0·01)	0
Peptostreptococcus	0	1 (0·01)
Not identified[d]	0	1 (0·01)

Values are expressed as absolute numbers per series (% prevalence).
[a]Coagulase-negative isolates, i.e. no occurrence of *Staphylococcus aureus*. Isolates were mainly *Staphylococcus epidermidis*.
[b]Significant difference, $P = 0·015$.
[c]Mainly *Propionibacterium acnes*.
[d]Growth curve in the BacT/ALERT was suggestive for *Propionibacterium*.
Resident skin flora: bacteria normally living on the skin. Transient skin flora: bacteria normally present in the air, but transient on skin. Gastrointestinal flora: bacteria normally present in the (upper) gastrointestinal system.

Identification of positive samples

Table 2 shows the bacterial species isolated from the subcultures derived from the BacT/ALERT® bottles that were flagged as positive. When the first 10 ml of blood was diverted, the majority of bacteria cultured were *Propionibacterium* spp, i.e. common skin flora. One isolate of *Streptococcus bovis* was found; this bacterial species is not normally part of the resident skin flora and therefore may have been transient skin flora that was not removed during the pre-bleed hygiene procedures. An examination of the donor from whom an isolate of *Klebsiella pneumoniae* was recovered revealed that the donor had no clinical signs of infection, and no blood products from this donation were used for transfusion. Culture results from both the red cell concentrate and the plasma from this donation were negative. Six months later a whole-blood sample from this donor was found to be culture negative.

The rate of contamination with *Staphylococcus* spp was significantly lower in the series tested after diversion of the first 10 ml of the blood donation ($P = 0·015$), whereas the contamination rate for *Propionibacterium* spp was similar (Table 2). Contamination rates for diphteroids and *Bacillus* spp were lower after diversion of the first 10 ml of the blood donation, but not significantly so.

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Discussion

In this study, under routine blood bank conditions diversion of the first 10 ml of whole blood was shown to significantly reduce the rates of bacterial contamination of final whole-blood units. Although previous studies by Wagner *et al.* [6] (using an *in vitro* model system) and Bruneau *et al.* [7] (with culture of diverted samples), strongly suggested that diversion of an initial blood sample would be effective in reducing skin contaminants in the collected unit, our study is the first to prove this for whole-blood collections.

A rather unexpected finding was the specific reduction of contamination with *Staphylococcus* spp upon diversion of the first 10 ml of sample, whereas contamination with *Propionibacterium* spp was similar, regardless of whether or not the first 10 ml of sample was diverted. A possible explanation for this might be that venepuncture, rather than coring skin plugs (which are transferred into the diverted volume, and include both superficial and intrinsic bacteria), results in skin flaps that do not become transferred into the diverted volume. Superficial skin bacteria such as *Staphylococcus* spp might be rinsed from the skin flaps by the initial diverted volume, whereas bacteria such as *Propionibacterium* spp (which colonize the deeper skin layer, the sebaceous glands and hair roots) are eluted from the flap during prolonged flow and thus are still able to enter the collected unit.

Compared to *Staphylococcus* spp, *Propionibacterium* spp are slow growing, yielding a positive signal in the BacT/Alert between 5 and 6 days after culture. Because culture in the BacT/Alert is carried out under optimal conditions with respect to medium composition and temperature, it is probable that *Propionibacterium* will rarely reach critical levels in platelet concentrates during the standard storage time of 5 days. Based on the findings of the present study, the effect of diversion on the actual frequency of (stored) erythrocyte and platelet concentrates containing sufficient bacteria to cause health problems might be greater than expected.

It is unknown whether the origin of the *Strep. bovis* and *K. pneumoniae* contaminants was the upper gastrointestinal tract of the donor, as these bacteria can easily be part of transient skin flora not removed from either the donor or phlebotomist during the pre-bleed hygiene procedures.

To prevent waste of collected whole blood, the initial diverted volume could be used for test purposes and, based on the results of Wagner *et al.* [6] and Bruneau *et al.* [7], a volume larger than 10 ml (current tests need ≈ 25 ml) could only be beneficial in terms of the final contamination rate. However, our diversion system cannot easily be used to fill several tubes without affecting the integrity of the closed system, because the Composampler membrane is no longer intact after its first use. Therefore, as long as clotting of the test sample is prevented, the collection system used by Bruneau *et al.* [7] might be an alternative.

Using whole blood as a source material for platelet components, the theoretical prevalence of bacteria in pooled platelet concentrates, composed of five single-donor units, would still be considerable (≈ 1%), despite the reduced contamination rate of whole blood. Therefore, in addition to diversion of the first volume during blood collection, all platelet concentrates should be tested for bacterial contamination in order to increase the safety of the blood supply.

In conclusion, the rate of bacterial contaminants in whole-blood units could be reduced by diversion of the first 8–10 ml of collected volume, especially with respect to contamination with *Staphylococcus* spp, commonly considered to be superficial skin flora.

Acknowledgements

This study was supported by Organon Teknika (Boxtel, the Netherlands) and Fresenius HemoCare/NPBI International (Emmer-Compascuum, the Netherlands). The authors would also like to thank all donors, donor assistants and technicians involved in this study.

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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
KURIN4PCT		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 20/23617	19 March 2020 (19.03.2020)	13 March 2020 (13.03.2020)
Applicant KURIN, 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 2 sheets.

☐ 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:

☒ 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**,

☒ 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.

☐ 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. 35

☐ 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.

Pending processing

Form PCT/ISA/210 (first sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/23617

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61B 5/15, A61B 5/153, A61B 5/154, A61B 5/157 (2020.01)

CPC - A61B 5/15003, A61B 5/150213, A61B 5/150251, A61B 5/150992, A61B 5/150206, A61B 5/150221, A61B 5/150946

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	US 2018/0177445 A1 (Kurin, Inc.) 28 June 2018 (28.06.2018), entire document	1-4, 10-12, 18 --- 5-9, 13-17, 19-20
Y	US 4,349,035 A (Thomas et al.) 14 September 1982 (14.09.1982), entire document	5-6, 8-9, 13-14, 16-17, 19-20
Y	US 5,401,262 A (Karwoski et al.) 28 March 1995 (28.03.1995), entire document	5, 7, 13, 15
A	US 2018/0271425 A1 (Kurin, Inc.) 27 September 2018 (27.09.2018), entire document	1-20
A	US 2018/0353117 A1 (Magnolia Medical Technologies, Inc.) 13 December 2018 (13.12.2018), entire document	1-20

Document being processed

☐ 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
07 JUNE 2020	19 JUN 2020
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 Lee Young 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

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	19 JUN 2020

Applicant's or agent's file reference	FOR FURTHER ACTION
KURIN4PCT	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 20/23617	19 March 2020 (19.03.2020)	13 March 2020 (13.03.2020)

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

IPC - A61B 5/15, A61B 5/153, A61B 5/154, A61B 5/157 (2020.01)

CPC - A61B 5/15003, A61B 5/150213, A61B 5/150251, A61B 5/150992, A61B 5/150206, A61B 5/150221, A61B 5/150946

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	07 JUNE 2020	Lee Young PCT Help Desk Telephone No. 571-272-4300

Form PCT/ISA/237 (cover sheet) (revised January 2019)

Unofficial Processing

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

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:

Pending processing

Form PCT/ISA/237 (Box No. I) (revised January 2019)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

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	5-9, 13-20	YES
	Claims	1-4, 10-12	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 1-4 and 10-12 lack novelty under PCT Article 33(2) as being anticipated by US 2018/0177445 A1 to Kurin, Inc. (hereinafter Kurin).

Regarding claim 1, Kurin teaches a blood sequestration device (see fig. 30A-G; para [0156]) comprising; an inlet path (fig. 30A see inlet path 3002; para [0156]); an outlet path (fig. 30A see outlet path 3004; para [0158]); a sequestration chamber (fig. 30A see sequestration chamber 3008; para [0160]) connected with the inlet path by a junction (fig. 30A see junction 3007; para [0160]; see fig. 17A-B) and being configured to receive a first portion of blood through the inlet path (para [0160]; para [0163]-[0164]), the sequestration chamber having a vent that allows air to be displaced by the first portion of blood (fig. 30A-D see vent 3010; para [0161]; para [0163]-[0165]), the junction being configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber (intended use - see para [0160] "the diverter junction 3007 is configured such that the flow out of the inlet port 3002 is preferentially directed toward the sequestration chamber 3008" - since the junction is configured to direct flow away from the inlet port, it is thereby considered capable of inhibiting a return to the inlet path of any of the first portion of blood received by the sequestration chamber; see para[0156], [0160]-[0161], [0061],[0067]); and a sampling channel connected between the inlet path and the outlet path (fig. 30A see sampling channel 3006; para [0159]-[0160]), the sampling channel being configured to convey subsequent amounts of blood between the inlet path and the outlet path after the first amount of blood is received by the sequestration chamber (para [0160]-[0170]).

Regarding claim 2, Kurin teaches the blood sequestration device in accordance with claim 1, wherein the junction is angled from the inlet path toward the sequestration chamber (fig. 30A; fig. 17A see junction 3007 is angled from the inlet path to the sequestration chamber; para [0160]) .

Regarding claim 3, Kurin teaches the blood sequestration device in accordance with claim 1, wherein the junction has a cross-sectional area that is smaller than a cross-sectional area of the inlet path (fig. 30A; fig. 17A see junction 3007 has a cross-sectional area closest to the inlet path that is smaller than a cross-sectional area of the inlet path below where it meets the junction; para [0160]).

Regarding claim 4, Kurin teaches the blood sequestration device in accordance with claim 1, wherein the junction has a cross-sectional area that is larger than a cross-sectional area of the inlet path (fig. 30A; fig. 17A see junction 3007 has a cross-sectional area near the sequestration chamber 3008 that is larger than a cross-sectional area of the inlet path where the inlet path opens to the junction; para [0160]; para [0163] junction cross-sectional area widens towards the sequestration chamber to direct blood).

Regarding claim 10, Kurin teaches the blood sequestration device in accordance with claim 1, wherein the vent includes two or more vent apertures (para [0161] vent 3010 comprises air permeable blood barrier 3012 as previously described; para [0060] air permeable blood barrier may comprise a mesh, a mesh inherently comprises two or more vent apertures).

Regarding claim 11, Kurin teaches a blood sequestration device (see fig. 30A-G; para [0156]) comprising; a housing (fig. 30A see housing 3001; para [0161]) having in inlet port (fig. 30A see inlet path 3002 has port opening in housing 3001; para [0156; para [0161]) and an outlet port (fig. 30A see outlet path 3004 has outlet opening in housing 3001; para [0159]; para [0161]), the housing containing: an inlet path connected to the inlet port (fig. 30A see inlet path 3002; para [0156]); an outlet path connected with the outlet port (fig. 30A see outlet path 3004; para [0158]); a sequestration chamber (fig. 30A see sequestration chamber 3008; para [0160]) connected with the inlet path by a junction (fig. 30A see junction 3007; para [0160]; see fig. 17A-B) and being configured to receive a first amount of blood through the inlet path (para [0160]; para [0163]-[0164]), the sequestration chamber having a vent that allows air to be displaced by the first portion of blood (fig. 30A see vent 3010; para [0161]; para [0163]-[0165]), the vent further being further configured to close upon the sequestration chamber being filled with the first portion of blood (para [0161] vent 3010 comprises air permeable blood barrier 3012 as previously described; para [0060]; para [0160]-[0170]), the junction being configured to inhibit a return of the first portion of blood out of the sequestration chamber (intended use - see para [0160] "the diverter junction 3007 is configured such that the flow out of the inlet port 3002 is preferentially directed toward the sequestration chamber 3008" - since the junction is configured to direct flow away from the inlet port, is is thereby considered capable of inhibiting a return to the inlet path of any of the first portion of blood received by the sequestration chamber; see also para[0156],[0160]-[0161],[0061],[0067]); and a sampling channel connected between the inlet path and the outlet path (fig. 30A see sampling channel 3006; para [0159]-[0160]), the sampling channel being configured to convey subsequent amounts of blood between the inlet path and the outlet path after the first portion of blood is received by the sequestration chamber (para [0160]-[0170]).

-*-Continued in Supplemental Box-*-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

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:

Regarding claim 18, the claim language is confusing and lacks clarity. Specifically, the recitation "the patient needle and the sample needle", lack proper antecedent basis. In order to give meaning to this claim and to give proper antecedent basis, based on the specification (para [0063]), this recitation has been interpreted as the following: "and a blood sequestration device connected along the blood sampling pathway between a patient needle and a sample needle, wherein the venipunture apparatus includes the patient needle and the reservoir includes the sample needle".

Pending processing

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
-*-Box V.2 - Citations and Explanations-*-

Regarding claim 12, Kurin teaches the blood sequestration device in accordance with claim 11, wherein the vent further comprises a closure mechanism that inhibits air from reentering the sequestration chamber after it has been displaced (para [0161] vent 3010 comprises air permeable blood barrier 3012 as previously described; para [0060]).

Claim 18 lacks an inventive step under PCT Article 33(3) as being obvious over Kurin.

Regarding claim 18, Kurin teaches a blood sample optimization system (fig. 30A-G; para [0156]) comprising: a blood sampling system (para [0156]) comprising: a venipuncture apparatus configured for venipuncture of a patient to access a sample of blood of a patient (para [0156] inlet port 3002 with opening connects to patient needle, needle is a suitable venipuncture apparatus); a blood sampling pathway connected with the venipuncture apparatus for conveying the sample of blood (fig. 30A see system 3000 comprises blood sampling pathway from inlet 3002 to outlet 3004 through sampling channel 3006; para [0156]); and a reservoir (fig. 30A see reservoir 3004; para [0158]); and a blood sequestration device connected along the blood sampling pathway between a patient needle and the reservoir (see fig. 30A-G; para [0156]), wherein the venipunture apparatus includes the patient needle (para [0156] inlet port 3002 with opening connects to patient needle), the blood sequestration device comprising: an inlet path connected with the patient needle (fig. 30A see inlet path 3002; para [0156]); an outlet path connected with the reservoir (fig. 30A see outlet path through outlet reservoir 3004; para [0158]); a sequestration chamber (fig. 30A see sequestration chamber 3008; para [0160]) connected with the inlet path by a junction (fig. 30A see junction 3007; para [0160]; see fig. 17A-B) and being configured to receive a first portion of blood through the inlet path (para [0160]; para [0163]-[0164]), the sequestration chamber having a vent that allows air to be displaced by the first portion of blood (fig. 30A see vent 3010; para [0161]; para [0163]-[0165]), the junction being configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber (intended use - see para [0160] "the diverter junction 3007 is configured such that the flow out of the inlet port 3002 is preferentially directed toward the sequestration chamber 3008" - since the junction is configured to direct flow away from the inlet port, is is thereby considered capable of inhibiting a return to the inlet path of any of the first portion of blood received by the sequestration chamber; see para[0156], [0160]-[0161], [0061],[0067]); and a sampling channel connected between the inlet path and the outlet path (fig. 30A see sampling channel 3006; para [0159]-[0160]), the sampling channel being configured to convey subsequent amounts of blood between the inlet path and the outlet path after the first amount of blood is received by the sequestration chamber (para [0160]-[0170]); but Kurin does not explicitly teach wherein the reservoir is configured for receiving an evacuated blood collection tube to collect and contain at subsequent portion of the sample of blood, nor wherein reservoir and connected outlet path comprise a sample needle. However, in another embodiment, Kurin teaches a sample needle at an outlet path of a blood sample collection device facilitates connection to an evacuated blood collection tube to collect and contain at subsequent portion of the sample of blood (fig. 1 see sample needle 5; para [0065]; see fig. 7). Combining embodiments is within the ordinary skill of a person within the art. Accordingly, it would have been obvious to a person having ordinary skill in the art to have provided a sample needle such that the reservoir is configured for receiving an evacuated blood collection tube to collect and contain at subsequent portion of the sample of blood in order to provide blood collection means with the blood sampling device.

Claims 5-6, 8-9, 13-14, 16-17 and 19-20 lack an inventive step under PCT Article 33(3) as being obvious over Kurin in view of US 4,349,035 A to Thomas et al. (hereinafter Thomas).

Regarding claim 5, Kurin teaches the blood sequestration device in accordance with claim 1, but does not explicitly teach wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber. However, in similar art, Thomas teaches a blood collection device (see fig. 1; column 4, ln 20-24) comprising an inlet path (fig. 5 see cannula 19; column 4, ln 23-38) and a chamber connected by a junction (fig. 4-5 see junction 22 leads to chamber 21; column 4, ln 23-38). Kurin further teaches wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber (fig. 4-5 see junction 22 comprises one-way valve to prevent backflow; column 4, ln 32-38). Passive structures for preventing backflow are well known in the art for improved blood collection by preventing contaminated blood from returning to a patient. Accordingly, it would have been obvious to a person having ordinary skill in the art to have included a passive structure as taught by Thomas in the device taught by Kurin in order to prevent return flow to the patient for improved blood sampling.

Regarding claim 6, Kurin in view of Thomas teaches the blood sequestration device in accordance with claim 5, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a conical baffle having a tapered end directed toward the sequestration chamber (see Thomas fig. 4-5 passive structure tapers to a point towards chamber, thus restricting flow; see column 5, ln 13 -17).

Regarding claim 8, Kurin in view of Thomas teach the blood sequestration device in accordance with claim 5, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a divider wall extending across a cross-section of the junction (see Thomas fig. 4-5 divider wall 25; column 6, ln 7-13).

-*-Continued in next Supplemental Box-*-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
-*-Supplemental Box - Box V.2 - Citations and Explanations-*-

Regarding claim 9, Kurin in view of Thomas teach the blood sequestration device in accordance with claim 5, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a flow director extending from an inner surface of the junction (see Thomas fig. 4-5 valve 22 is a flow director; column 4, ln 23-38; column 5, ln 13-17), the flow director being configured to control a flow of blood (see Thomas column 4, ln 23-28 flow director valve 22 controls flow by directing into chamber 21 and preventing backflow).

Regarding claim 13, Kurin teaches the blood sequestration device in accordance with claim 11, but does not explicitly teach wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber. However, in similar art, Thomas teaches a blood collection device (see fig. 1; column 4, ln 20-24) comprising an inlet path (fig. 5 see cannula 19; column 4, ln 23-38) and a chamber connected by a junction (fig. 4-5 see junction 22 leads to chamber 21; column 4, ln 23-38). Kurin further teaches wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber (fig. 4-5 see junction 22 comprises one-way valve to prevent backflow; column 4, ln 32-38). Passive structures for preventing backflow are well known in the art for improved blood collection by preventing contaminated blood from returning to a patient. Accordingly, it would have been obvious to a person having ordinary skill in the art to have included a passive structure as taught by Thomas in the device taught by Kurin in order to prevent return flow to the patient for improved blood sampling.

Regarding claim 14, Kurin in view of Thomas teach the blood sequestration device in accordance with claim 13, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a conical baffle having a tapered end directed toward the sequestration chamber (see Thomas fig. 4-5 passive structure tapers to a point towards chamber, thus restricting flow; see column 5, ln 13 -17).

Regarding claim 16 Kurin in view of Thomas teach the blood sequestration device in accordance with claim 13, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a divider wall extending across a cross-section of the junction. (see Thomas fig. 4-5 divider wall 25; column 6, ln 7-13).

Regarding claim 17 Kurin in view of Thomas teach the blood sequestration device in accordance with claim 13, and Kurin modified by Thomas further teaches wherein the one or more passive structures include a flow director extending from an inner surface of the junction (see Thomas fig. 4-5 valve 22 is a flow director; column 4, ln 23-38; column 5, ln 13-17), the flow director being configured to control a flow of blood (see Thomas column 4, ln 23-28 flow director valve 22 controls flow by directing into chamber 21 and preventing backflow).

Regarding claim 19, Kurin teaches the blood sample optimization system in accordance with claim 18, but does not explicitly teach wherein the junction of the blood sequestration device includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber. However, in similar art, Thomas teaches a blood collection device (see fig. 1; column 4, ln 20-24) comprising an inlet path (fig. 5 see cannula 19; column 4, ln 23-38) and a chamber connected by a junction (fig. 4-5 see junction 22 leads to chamber 21; column 4, ln 23-38). Kurin further teaches wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber (fig. 4-5 see junction 22 comprises one-way valve to prevent backflow; column 4, ln 32-38). Passive structures for preventing backflow are well known in the art for improved blood collection by preventing contaminated blood from returning to a patient. Accordingly, it would have been obvious to a person having ordinary skill in the art to have included a passive structure as taught by Thomas in the device taught by Kurin in order to prevent return flow to the patient for improved blood sampling.

Regarding claim 20, Kurin in view of Thomas teach the blood sample optimization system in accordance with claim 19, and Kurin modified by Thomas further teaches wherein the one or more passive structures includes a wall extending from an inner surface of the junction to control a flow of the first portion of blood (see Thomas fig. 4-5 divider wall 25; column 6, ln 7-13).

-*-Continued in next Supplemental Box-*-

Pending (Continued)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 20/23617

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
-*-Supplemental Box - Box V.2 - Citations and Explanations-*-

Claim 5, 7 and 13, 15 lack an inventive step under PCT Article 33(3) as being obvious over Kurin in view of US 5,401,262 A to Karwoski et al. (hereinafter Karwoski).

Regarding claim 5, Kurin teaches the blood sequestration device in accordance with claim 1, but does not explicitly teach wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber. However, in similar art, Karwoski teaches a blood collection device (see fig. 1; column 4, ln 20-40). Karwoski further teaches wherein a pathway of the blood collection devices includes one or more passive structures configured to inhibit a return to an inlet path of any of a sample of blood (fig. 1 see baffles 112a-f direct flow through pathway and assist in fluid retention; column 18, ln 1-24; column 21, ln 55-65). Passive structures for preventing backflow are well known in the art for improved blood collection by preventing contaminated blood from returning to a patient. Accordingly, it would have been obvious to a person having ordinary skill in the art to have included a passive structures as taught by Karwoski in the device taught by Kurin in order to prevent return flow to the patient for improved blood sampling.

Regarding claim 7, Kurin in view of Karwoski teach the blood sequestration device in accordance with claim 5, and Kurin modified by Karwoski further teaches wherein the one or more passive structures include two or more staggered baffles extending from an inner surface of the junction (Karwoski fig. 1 see baffles 112a-f direct flow through pathway and assist in fluid retention; column 18, ln 1-24; column 21, ln 55-65).

Regarding claim 13, Kurin teaches the blood sequestration device in accordance with claim 11, wherein the junction includes one or more passive structures configured to inhibit a return to the inlet path of any of the first portion of blood received by the sequestration chamber. However, in similar art, Karwoski teaches a blood collection device (see fig. 1; column 4, ln 20-40). Karwoski further teaches wherein a pathway of the blood collection devices includes one or more passive structures configured to inhibit a return to an inlet path of any of a sample of blood (fig. 1 see baffles 112a-f direct flow through pathway and assist in fluid retention; column 18, ln 1-24; column 21, ln 55-65). Passive structures for preventing backflow are well known in the art for improved blood collection by preventing contaminated blood from returning to a patient. Accordingly, it would have been obvious to a person having ordinary skill in the art to have included a passive structures as taught by Karwoski in the device taught by Kurin in order to prevent return flow to the patient for improved blood sampling.

Regarding claim 15, Kurin in view of Karwoski teach the blood sequestration device in accordance with claim 13, and Kurin modified by Karwoski further teaches wherein the one or more passive structures include two or more staggered baffles extending from an inner surface of the junction (Karwoski fig. 1 see baffles 112a-f direct flow through pathway and assist in fluid retention; column 18, ln 1-24; column 21, ln 55-65).

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

Pending processing

Form PCT/ISA/237 (Supplemental Box) (revised January 2019)

SEARCH HISTORY

Application Number	PCT/US 20/23617
Search Conducted By	EAW
Search Approved By	SCL

CPC/IPC Classifications Searched	IPC(8): A61B 5/15, A61B 5/153, A61B 5/154, A61B5/157 (2020.01) CPC: A61B 5/15003, A61B 5/150213, A61B 5/150251, A61B 5/150992, A61B 5/150206, A61B 5/150221, A61B 5/150946
Date Conducted	7 June 2020 (07.06.2020)

Documentation Searched	IPC(8): A61B 5/15, A61B 5/153, A61B 5/154, A61B5/157 (2020.01) CPC: (keyword limited; see below)
Search Terms Used	baffle*, prevent*, inhibit*, back*, return*, sequestration*, flow*, blood*, sample*, restrict*
Date Conducted	7 June 2020 (07.06.2020)

Electronic Database Searched	PatBase
Files Searched	Full-text: AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO Bibliographic: (European) AT BA BE BG CH CS CY CZ DD DK EE ES FI GE GR HR HU IE IS IT LT LU LV MC MD MT NL NO PL PT RO RS SE SI SK SM TR UA YU (Asia) EA GC HK ID IL IN KZ MN MY PH RU SG SU TH TJ TW UZ VN (North America) CA CR CU DO GT HN MX NI PA SV TT (South America) AR BR CL CO EC PE UY (Australasia) AU NZ (Africa) AP DZ EG KE MA MW OA ZA ZM ZW
Date Conducted	7 June 2020 (07.06.2020)
Search Logic:	

Search 1: PA=(Kurin inc) (Results 5)

Search 2: PN=(US2018/0177445) (Results 1)

Search 3: ctb 2 or ctf 2 (Results 5)

Search 4: CPC=(A61B5/15003) (Results 2650)

Search 5: 4 and ft=(baffle%) (Results 36)

Search 6: 4 and ft=((prevent* or inhibit*) near (back* or return*)) (Results 226)

Search 7: 6 and ft=(sequestration) (Results 3)

Search 8: 6 and ft=(flow*) (Results 182)

Search 9: IPC=(A61B5/15 or A61B5/153 or A61B5/154 or A61B5/157) (Results 13750)

Search 10: CPC=(A61B5/15003 or A61B5/150213 or A61B5/150251 or A61B5/150992 or A61B5/150206 or A61B5/150221 or A61B5/150946) (Results 3410)

Search 11: 9 or 10 (Results 14204)

Search 12: 11 and ft=(sequestration) (Results 32)

Search 13: 11 and ft=((prevent* or inhibit*) near (back* or return*)) (Results 535)

Search 14: 13 and ft=(blood* near sample*) (Results 335)

Search 15: 14 not 8 (Results 198)

Search 16: ft=(sequestration* and baffle* and blood*) (Results 170)

Search 17: 16 not (14 or 8) (Results 170)

Search 18: ft=(blood* and sequestration* and (restrict* near flow*)) (Results 176)

Electronic Database Searched	Google
Files Searched	Patents
Date Conducted	7 June 2020 (07.06.2020)

Search Logic:

blood sampling sequestration device prevent backflow

blood sampling sequestration device baffle directs flow

blood sampling collection device prevent backflow

blood sampling device valve restricts backflow controls flow

blood sequestration junction prevents backflow blood sequestration junction flow restriction

Electronic Database Searched	Google
Files Searched	Web
Date Conducted	7 June 2020 (07.06.2020)
Search Logic:	
blood sampling sequestration device prevent backflow blood sampling sequestration device baffle directs flow blood sampling collection device prevent backflow blood sampling device valve restricts backflow controls flow blood sequestration junction prevents backflow blood sequestration junction flow restriction	

Notice of Reasons for Refusal

Application number: Japanese Patent Application No. 2019-534792
Date of Drafting: Reiwa 3(2021) June 8
Patent examiner: SETOI, Ayana 1569 2Q00
Representative/Applicant: MIYOSHI, Hidekazu (and 3 others)
Applied Provisions: Article 36

This application should be refused for the reason mentioned below. If the applicant has any opinion(s) against the reason, a written opinion should be submitted within 3 months from the date on which this notification was dispatched. Reason

1. (Clarity) This patent application does not fulfill the requirement of the provision of Patent Act Article 36(6)(ii) in terms of the item(s) listed below regarding the statement of the scope of claims.

Note

- Reason 1 (Clarity)

- Claim 1-20
It describes in Claim 1 as "the aforementioned wall." Claim 1 has the description an "outer wall" as a related description. In these descriptions, "the aforementioned wall" has pointed out the same composition as an "outer wall" -- or it is not clear whether different composition is pointed out. Since there is no description which specifies a "wall" before the description "the aforementioned wall" in the case of the latter, it is unknown which description the "above" has pointed out. The same point is pointed out also in invention concerning Claims 8 and 15. Therefore, The invention in the Claims 2-7 and 9-14 which cite either invention concerning Claims 1, 8 and 15, and the claim concerned, and 16-20 is not clear.

- Claims 4-5, 11-12, and 18-19
Although it describes in Claim 4 as "the aforementioned wall", since there is no description which specifies a "wall" in Claim 1 which Claim 4 cites, it is unknown which description the "above" has pointed out. The same point is pointed out also in invention concerning Claims 11 and 18. Therefore, The invention in the Claims 5, 12 and 19 which cite either invention concerning Claims 4, 11 and 18, and the claim concerned is not clear.

- Claim 8-14
It describes in Claim 8 as "the aforementioned blood extraction course." Claim 8 has the description a "blood collecting course" as a related description. In these descriptions, "the aforementioned blood extraction course" has pointed out the same composition as a "blood collecting course" -- or it is not clear whether different composition is pointed out. Since there is no description which specifies a "blood extraction course" before the description "the aforementioned blood extraction course" in the case of the latter, it is unknown which description the "above" has pointed out. Therefore, The invention in the Claims 9-14 which cite an invention according to claim 8 and the claim concerned is not clear.

Record of the result of prior art search

- Technical fields searched:

IPC
A61B 5/15-5/157

- Prior art documents: JP 2016 - 504075A
International Publication No. WO2014/058945

This record of the result of prior art search does not constitute the reasons for refusal.

<Suggestions in amending>
(1) When making amendment to the description or the scope of claims, the amended parts should be underlined so as to be clearly identified (please refer to Note 6 and 7 of Form 13, Regulations under the Patent Act).
(2)The amendment shall be made within the scope of the matters stated in the translation of the description or drawings (limited to descriptions in the drawings) of the international patent application at the international filing date, the translation of the scope of claims of the international patent application at the international filing date (in the case where a translation of the amended scope of claims under the provisions of Article 19 (1) of the Patent Cooperation Treaty is submitted, the relevant translation), or the drawing of the international patent application at the international filing date (except the descriptions in the drawings) (hereinafter referred to as a translation, etc.) (in the case of having amended the description, scope of claims or the drawings by submitting a mistranslation correction document, the translation, etc. or the amended description, amended claims or amended drawings). In addition, for the evidence of the legality of each amendment, allege the legality of each amendment in a written opinion with clear indication of the corresponding parts in the translation, etc. (in the case of amending the description or drawings by submitting a Correction of Mistranslation, the translation, etc., or the amended description, or the scope of claims, or the drawings).

(3) One should make sure not to perform any corrections that invoke a violation against Patent Act Article 17-2(4) when amending the scope of claims.

If you have any question or are willing to make an interview with the examiner to discuss issues on this notification of reasons for refusal, please contact us at:When sending of a draft amendment etc. is wished by E-mail etc., please inform me of that by telephone.

The first partial analysis diagnosis (medicine diagnosis) of an examination a current -- Toi ** (it is with * and there is Aya)
TEL.03-3581-1101 Extension 3291

A Director General(p.p.), a Director(p.p.), an examiner, an assistant examiner, OKUMA, Yasuo, SETOI, and 9710 1569

拒絶理由通知書

特許出願の番号	特願２０１９-５３４７９２
起案日	令和　３年　６月　８日
特許庁審査官	▲瀬▼戸井　綾菜　　１５６９　２Ｑ００
特許出願人代理人	三好　秀和（外　３名）　様
適用条文	第３６条

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．（明確性）この出願は、特許請求の範囲の記載が下記の点で、特許法第３６条第６項第２号に規定する要件を満たしていない。

記

●理由１（明確性）について

・請求項　１-２０
請求項１に「前記壁」と記載されている。また、関連する記載として、請求項１に「外壁」という記載がある。
これらの記載において、「前記壁」は「外壁」と同じ構成を指しているのか、もしくは、異なる構成を指しているかが明確でない。
また、後者の場合、「前記壁」という記載よりも前に「壁」を特定する記載がないため、「前記」がどの記載を指しているかが不明である。
請求項８、１５に係る発明においても、同様の点が指摘される。
よって、請求項１、８、１５に係る発明及び当該請求項のいずれかを引用する請求項２-７、９-１４、１６-２０に係る発明は明確でない。

・請求項　４-５、１１-１２、１８-１９
請求項４に「前記内壁」と記載されているが、請求項４が引用する請求項１には「内壁」を特定する記載がないため、「前記」がどの記載を指しているかが不明である。
請求項１１、１８に係る発明においても、同様の点が指摘される。

よって、請求項４、１１、１８に係る発明及び当該請求項のいずれかを引用する請求項５、１２、１９に係る発明は明確でない。

・請求項　８－１４
請求項８に「前記血液採取経路」と記載されている。また、関連する記載として、請求項８に「採血経路」という記載がある。
これらの記載において、「前記血液採取経路」は「採血経路」と同じ構成を指しているのか、もしくは、異なる構成を指しているかが明確でない。
また、後者の場合、「前記血液採取経路」という記載よりも前に「血液採取経路」を特定する記載がないため、「前記」がどの記載を指しているかが不明である。
よって、請求項８に係る発明及び当該請求項を引用する請求項９－１４に係る発明は明確でない。

＜先行技術文献調査結果の記録＞

・調査した分野　　ＩＰＣ　　Ａ６１Ｂ　５／１５－５／１５７

・先行技術文献　　特表２０１６－５０４０７５号公報
国際公開第２０１４／０５８９４５号

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。電子メール等で補正案等の送付を希望される場合は、その旨を電話でお知らせください。

審査第一部　分析診断（医学診断）　瀬戸井綾菜（せといあやな）
ＴＥＬ．０３-３５８１-１１０１　内線３２９１

部長／代理	審査長／代理	審査官	審査官補
	大熊　靖夫	▲瀬▼戸井	
	９７１０	１５６９	

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

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)

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)

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	
US 3648684 A	14-03-1972	NONE	
EP 1665986 A1	07-06-2006	BR PI0505336 A	11-07-2006
		EP 1665986 A1	07-06-2006
		JP 4914601 B2	11-04-2012
		JP 2006150083 A	15-06-2006
		US 2006129064 A1	15-06-2006
US 4056101 A	01-11-1977	NONE	
US 2013317391 A1	28-11-2013	US 2013317391 A1	28-11-2013
		US 2015099996 A1	09-04-2015
		US 2015351678 A1	10-12-2015

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
PCT/US2016/043709

TITLE: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

APPLICANT: CALLIOPE SOLUTIONS, 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 P04A42

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.

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Anaesth Intens Care 1993, 21, 20-23

Hazards of Bacterial Contamination of Blood Products

T. GOTTLIEB*

Department of Microbiology and Infectious Diseases, Repatriation General Hospital, Concord, New South Wales

SUMMARY

Post-transfusion bacterial sepsis is infrequent. It is, however, associated with a high mortality due to septic shock. This reflects the release of endotoxin from gram negative bacteria. Lesser transfusion reactions are usually under-reported. These are frequently caused by gram positive bacteria. Gram positive species such as staphylococci and other skin surface organisms may be cultured from platelets stored at room temperature. Typically, gram negative "psychrophyllic" species which survive storage at 4°C are cultured from stored refrigerated blood implicated in transfusion reactions. These include Yersinia enterocolitica, Pseudomonas fluorescens *etc. Bacterial contamination of the blood supply can occur via an endogenous or an exogenous source. Endogenous donor bacteraemia due to* Y.enterocolitica *may be asymptomatic or may follow an episode of gastroenteritis. Exogenous infections occur through some defect in the usual collection practice. Transfusion-acquired syphilis is now extremely uncommon. In the third world, beside the need for effective screening for viral pathogens, infections with protozoa, in particular plasmodia, trypanosoma and leishmania remain a major obstacle to ensuring safe blood supplies. Prevention of transfusion reactions demands rigorous attention to details of collection, storage, reissuing and infusion of blood products, as well as prompt treatment, testing and reporting of suspected reactions.*

Key Words: TRANSFUSION: reaction, post-transfusion bacterial sepsis, bacterial contamination, Yersinia enterocolitica, Pseudomonas fluorescens, Pseudomonas, Trypanosomiasis

In recent years attention has focused on the likelihood of transmission of viral pathogens such as HIV, HTLV-I, hepatitis B and C via blood transfusion. By contrast, reactions following transfusion of bacterial pathogens are less well recognised. These may however be acutely life-threatening with a mortality of up to 25%. From 1975 to 1989, 14 fatal transfusion-related events were reported to the United States Food and Drug Authority (FDA).[1] When all blood products were considered (red blood cells, platelets and plasma) 24 fatal events were reported in a similar time period (1976-85).[2] Although non-fatal events are more frequent, these often are under-reported, estimates of 1-7/1000 having been quoted.[1]

Transfusion of contaminated blood may cause septic shock. This may in part be due to massive release of endotoxin from gram-negative bacteria. Nausea and vomiting, fevers, chills, tachycardia and hypotension can occur during or following transfusion.

Numerous bacteria have been incriminated in post-transfusion sepsis. Of 36 bacteria causing clinical sepsis after red cell transfusion,[3] the most frequently isolated bacteria were *Yersinia enterocolitica* (17) and *Pseudomonas fluorescens* (10). Other bacteria included other pseudomonads (3), enterobacter, flavobacteria (2), *Treponema pallidum* (2) and *Campylobacter jejuni*. A similar group of organisms were seen following platelet and plasma transfusions, i.e. pseudomonas, serratia and enterobacter species. However gram-positive bacteria, such as *Streptococcus pyogenes*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, have also been not infrequently cultured in episodes of clinical sepsis after platelet transfusions,[2,3] (vide infra).

It is possible to divide transfusion reactions into those originating from an endogenous source (donor bacteraemia or parasitaemia) or an exogenous source (surface colonisation or contamination).

ENDOGENOUS BACTERIA (AND PROTOZOA)

Donor bacteraemia may occur in several settings.

Bacteraemia may occur during chronic or low-grade infections, usually unrecognised by the patient. Examples include osteomyelitis, endocarditis and specific diseases such as syphilis and brucellosis. A case report documents a donor with salmonella osteomyelitis who transmitted salmonella to seven

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Accepted for publication August 25, 1992.

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platelet recipients.[4] Subacute parasitic infections with plasmodia (malaria) and with trypanosoma (Chagas' disease) are frequent causes of blood transfusion transmission in the tropics and in South America.

Bacteraemia may follow recovery from an episode of bacterial gastroenteritis, particularly after infection with *Yersinia enterocolitica* and salmonella sp.[5,6] In a review of seven cases of yersinia transfusion reactions, four patients had preceding diarrhoea within four weeks of transfusion and one had concomitant diarrhoea. However, two patients gave no history of diarrhoeal symptoms. Asymptomatic bacteraemia was usual at the time of donation.

Transient bacteraemia may follow procedures such as dental work. The bacteraemia is usually of a very short duration, not exceeding 30 minutes, unless endocarditis ensues. In such instances the micro-organisms comprise oral streptococci and anaerobes. These are generally of lesser virulence and are unlikely to survive refrigeration compared with gram-negative bacteria.

EXOGENOUS BACTERIA

In this instance bacteria enter blood through some defect in the usual collection practice. Most commonly contamination occurs through inadequate skin preparation.[1,3,7] Less frequently bacteria may colonise collection tubing as occurred in an outbreak of serratia infection.[8] Contamination may occur during storage. An episode of sepsis due to *Pseudomonas cepacia* followed port contamination after the thawing of platelets in a water bath.[9]

A review of UK reports of exogenous post-transfusion sepsis documented 14 episodes between 1980-89.[10] Of these, ten were due to "environmental" pseudomonads (eight were *Pseudomonas fluorescens*) and eight of the ten patients died. Of the many organisms that may colonise skin surfaces, pseudomonas species, serratia, flavobacteria etc, are notable in that they can survive paltry disinfection or may actually be present in the disinfectant solution. These gram-negative isolates are associated with more severe transfusion reactions compared with gram-positive species such as coagulase-negative staphylococci and viridans streptococci.

The increase in notification of bacterial infections is paralleled by the increase in demand for platelet transfusion. Storage at room temperature enhances bacterial proliferation. In many cases bacteria are grown on culture without clinical disease: in these the bacteria are usually skin saprophytes such as pro-*Pionibacterium acnes* or corynebacterium species, often referred to as "diphtheroids". However any of a large number of both gram-positive and negative organisms have been isolated in episodes of sepsis.

Following refrigeration most gram-positive bacteria will not survive. Moreover these are often present in low number and are usually destroyed by host defences—complement, lysosyme and other opsonins. By contrast, gram-negative, psychrophilic (cold-loving) bacteria will survive refrigeration.

PSYCHROPHILIC BACTERIA

Bacteria can be divided into thermophiles growing at $>50°C$, mesophiles, and psychrophiles capable of growth at $<5°C$. The latter organisms prefer growth at room temperature but will survive refrigeration. At 5°C metabolism is significantly reduced and growth occurs at a slow linear rate. After prolonged storage, between one and three weeks, there is sufficient build-up of bacteria or endotoxin to cause a severe transfusion reaction. Alternately once blood is rewarmed these organisms will re-establish their usual logarithmic growth within two to four hours.[1] Metabolic enzymes with optimal activity at room temperature will be switched on. This highlights the need for proper storage and transportation of blood.

The psychrophile most commonly associated with transfusion reactions is *Yersinia enterocolitica*. Other species encountered include enterobacter, klebsiella species, pseudomonas species especially *P. fluorescens* and *P. putida*, and *E. coli*.

Yersinia enterocolitica

Yersinia belongs to the enterobacteriaceae and is a facultative anaerobe. It is usually a zoonotic organism and is transmitted to humans via the food chain, especially from contaminated pork as well as from water and milk. Yersinia lacks siderophores necessary to scavenge iron when bound to transferrin. As they require exogenous free iron, their growth and virulence is enhanced in the presence of iron overload states such as haemachromatosis, cirrhosis and following the use of desferrioxamine.

Gastroenteritis is the usual presentation of yersinia infection. When bacteraemia occurs, symptoms may range from endotoxic shock to an asymptomatic carrier state. Numerous examples of yersinia blood transfusion infection have been reported including several from Australia.[1-3,5,10-16] Diarrhoea may precede blood donation by 8-30 days, however yersinia is rarely cultured from the donor's stool. A rise in yersinia antibodies can however be detected in the donor. In most reports transfused blood had been stored for more than three weeks prior to transfusion.

KUR-MAG-DE004375

OTHER BACTERIA

Treponema pallidum

Transfusion-acquired syphilis is now uncommon both due to donor screening and due to reduced disease prevalence. One should note a rise in syphilis in the United States more recently. Storage at 4°C will inactivate *T. pallidum.*[3] However transmission may occur following transfusion of fresh blood products.

PARASITES (PROTOZOA)

Plasmodia which parasitise red blood cells, and trypanosoma and leishmania which parasitise reticulo-endothelial cells can all be transmitted by blood transfusion. These are important in tropical and subtropical areas of the world, and in perspective the scale of the problem of transmission of protozoa overshadows our concern with bacterial infection. Over three thousand cases of transfusional malaria occur yearly. However the true incidence is considerably higher.

Trypanosoma cruzi (Chagas' disease) is endemic in Central and South America. Twenty million people are believed to be infected, and at least twenty thousand cases of Chagas' disease are acquired through blood transfusion yearly. There is a 15-20% infection rate following transfusion of blood from an infected but asymptomatic donor. Such donors are potentially infective for life. In Brazil, 0.4% crystal violet, which is trypanosomocidal, is added to stored blood for transfusion. Several reports of transfusion-associated acute trypanosomiasis have now been reported from non-endemic areas (USA, Canada).[17-19] One in a thousand residents of Los Angeles are seropositive. Serology is available in special circumstances.

Leishmania donovani is a protozoan organism transmitted by sandflies. Leishmania species have been detected in blood from more than twenty US army personnel who served in the Middle East during Operation Desert Storm.[20] In response to this donations of blood have been recently deferred from this group until 1993.

PREVENTION OF TRANSFUSION REACTIONS

Blood donors should be questioned rather than asked to tick boxes. Specific details of recent medical procedures, dental work, febrile illnesses, tattooing etc. should be sought. Whether patients with recent abdominal pain and/or diarrhoea should be excluded from blood donation remains a vexed question. Patient description of recent symptoms is very likely to be influenced by the manner of questioning. A detailed patient assessment of recent gastrointestinal symptoms could lead to considerable wastage of blood products.

Collection of blood requires detailed attention to antisepsis. Patients with scarred phlebotomy sites may require exclusion.

Blood should be visually inspected prior to transfusion. The presence of haemolysis and the presence of any particulate matter may indicate contamination. Bacteriological screening of blood has been recommended by some.[3] However considering the low frequency of bacterial transfusion reactions this is likely to have a low yield, be expensive and lead to discarding of blood falsely culture-positive.

Blood that has been stored at room temperature for more than 30 minutes is recommended for rejection for re-use. This has recently been questioned.[1] It has been suggested that two hours may be more practicable and less wasteful, in view of the lag period before bacterial growth is re-established after warming to room temperatures. However the safety margin for error may be reduced by such eased restrictions which may lead to even longer periods during which blood is held at room temperature in operating theatres.[16] If these blood units are then returned and re-used they be more likely to be associated with transfusion reactions by virtue of storage for more than 21 days and prolonged periods of time at room temperature.

Storage of blood in ward refrigerators should not occur. These may have poor temperature regulation, may be used for other purposes and consequently be frequently opened and closed.

Prolonged infusions of blood for greater than four hours should be avoided.

Platelets are held at room temperature for up to seven days. Recently this period was reduced from seven to five days in the United States.

MANAGEMENT OF BACTERIAL TRANSFUSION REACTIONS

In the case of a suspected bacterial transfusion reaction, the specimen being transfused should be gram stained. Both donor and recipient bloods should be cultured, as should any related blood products. Any residual blood should be refrigerated promptly. Syphilis serology can be subsequently tested on donor blood.

Broad spectrum antibiotics should be started quickly. The choice of antibiotic may be determined by gram stain result. In its absence, broad spectrum gram-negative antibiotic cover should be provided. Antibiotics of choice would include anti-pseudomonal penicillins, timentin, piperacillin, or the third generation cephalosporins such as cefotaxime or ceftriaxone. Initially these should be combined with an aminoglycoside such as gentamicin, at least until the presence of a pseudomonas species infection is excluded.

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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

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Contamination Rates of Blood Cultures Obtained by Dedicated Phlebotomy vs Intravenous Catheter

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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.

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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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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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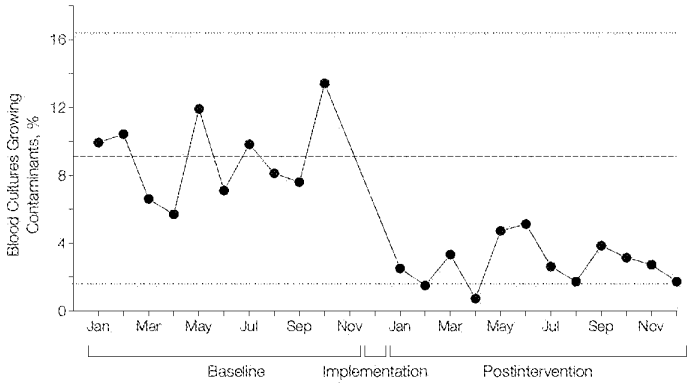
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Table 2. Blood Culture Contaminants in the Baseline and Postintervention Periods of Study

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**

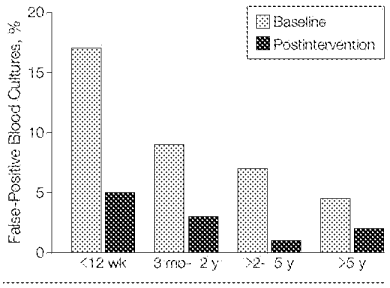
*There were 191 contaminated specimens growing 243 organisms in the baseline phase and 56 contaminated specimens growing 65 organisms in the postintervention phase of the study.

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]

Author Contributions: *Study concept and design:* Norberg, Christopher, Ramundo, Berman.
Acquisition of data: Norberg, Christopher, Ramundo, Berman.
Analysis and interpretation of data: Norberg, Christopher, Bower.
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Critical revision of the manuscript for important intellectual content: Norberg, Christopher, Ramundo, Bower, Berman.
Statistical expertise: Christopher.
Administrative, technical, or material support: Norberg, Berman.
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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

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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-

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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

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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.

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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-

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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-

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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

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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-

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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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majority of cases this is not necessary and is better not done, for reasons to be mentioned later. In most cases the herniated part of the disc lies medial to the affected nerve root, so the nerve is carefully taken medially over the herniation until the disc is sufficiently exposed. Epidural bleeding, if present, is checked by placing small pieces of wet cotton below and above the disc in the epidural space. After this, the herniated disc is removed by incision and extraction in the usual manner.

DISC REMOVAL

We have the impression that many surgeons try to remove too much disc tissue. We are not in favour of this. It is necessary to remove the extruded part of the ring cartilage, and it is advisable to remove some nuclear tissue as well, but it is not recommended that as much tissue as possible be removed. The nucleus pulposus will dry and shrink rapidly after operation, and ingrowing fibrous tissue will make a recurrence of this part of the disc herniation very unlikely. In the majority of recurrences, the cause of the pain is not a new herniation, but rather the occurrence of scar tissue at the operative site, or nerve damage during operation. Of the ring cartilage, only the herniated part should be removed; the rest cannot be reached adequately, and, unless bony fusion of the spine is performed, it is better to leave as much ring cartilage as possible to give more support. Also, removal of nearly the whole disc is inadvisable without foraminotomy. The same holds true for scraping the cartilage of the vertebral bodies and crushing the intravertebral articulation. None of these procedures should be done unless fusion of the spinal column is performed.

When a definite disc herniation is found and there is no clinical or roentgenological evidence of a rupture at a lower or higher level, we end the operation by apposing the muscles and fascia with interrupted sutures, a running suture being used for the skin. Before closing, however, the patient is asked to move his back and legs, and to cough and strain; when all this causes none of the pain that it did before operation, it may be concluded that the operation has been successful, and that no pressure is left on the freed nerve root or at any other level. In this clinical testing on the operating table lies the third advantage of local anæsthesia.

When no herniation is found, we explore the higher and lower discs as indicated, and if there is no evident herniation we inject one c.c. of absolute alcohol into the suspected disc, to obtain shrinkage of the nucleus.

With the above technique, the great majority of cases can be operated on within thirty minutes. The short time of operation is important because the patient is under local anæsthesia, and also this short period may be significant in preventing infection of the disc, of which several cases have been reported in the recent literature. An intravenous drip or blood transfusion is never necessary.

With this technique we have obtained a complete cure (that is, no complaints, and return to former occupation) in 75% of cases, according to a follow-up study of 125 cases five years after operation.

SUMMARY

A technique for herniated disc removal is described using local anæsthesia. We believe the advantages of this technique are simplicity, less bleeding, a safeguard against nerve root damage, and the possibility of checking the operative result during the operation.

A METHOD FOR THE RELIABLE DETERMINATION OF CLOTTING TIME IN WHOLE BLOOD*

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THE INVESTIGATION of the clotting time of whole blood has for a long time been a routine procedure in medical practice. Though clotting-time values in health and in various pathological conditions are recorded in many textbooks and publications, these observations are difficult to interpret because different and not properly standardized techniques are used. Even the well known and widely used Lee-White method[1] has been shown to give varying results due to subjective differences in the performance of the test.[2]

In a preliminary study of the Lee-White method we noted differences up to ±40% in parallel determinations when the test was performed by different interns and technicians following the instructions of different textbooks. In the hands of the author, even under the most rigidly standardized conditions the Lee-White method showed a standard error of ±14%. Since errors and differences in the technique occur easily and frequently, not only in routine work but also in research, we can understand how difficult is the proper interpretation of the clotting-time data in different reports.

A rigorously standardized technique may improve the Lee-White method, but this can be achieved only by long training and a special study of the problem; it is unlikely that in routine

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work this improved accuracy can be attained. In spite of high degrees of skill, the technical error is high.

This indicated to us the necessity of finding a method which has fewer sources of error and can be performed easily with a high degree of accuracy by an average technician. After careful study of all sources of error in the different methods, we adopted the following procedure to obtain reliable and accurate clotting-time values.

MATERIALS

1. 10 ml. all-glass syringe (preferably with Luer-lock).
2. Sharp 21-gauge needle with short bevel.
3. Three-way stop cock (optional). (Items 1 to 3 are autoclaved for each determination.)
4. Glass capillary tubes of 100 mm. length and of 1.6 to 1.8 mm. diameter. One end of each tube is marked with a small piece of adhesive tape.
5. Plasticine.
6. Stop-watch.
7. A large thermos-flask with rubber cork for a water-bath.

Since this type of flask is available only without an insulating and protective case, an aluminium pail of adequate size with a carrying handle should be made by a plumber. This water-bath can be carried easily to the bedside. Some fibre-glass insulating material should be placed between the thermos-flask and its container. The flask is filled with about three litres of water at 21° C. The temperature of the water will be constant for three to five hours when the external environmental temperature is between 15 and 28° C. The temperature of the water should be checked every hour and if necessary should be adjusted with cold or hot water. To prevent sinking of the capillary tubes to the bottom, we constructed a simple rack of hard-rubber tubes, wire, and a foam-rubber plate to fit in the flask. The flat top of the rack is about 2 cm. under the water level. With this arrangement we can take out the tubes easily without immersing our hands in the water-bath.

The temperature of the water-bath should be checked with an accurate mercury thermometer.

METHOD

(1) After application of a tourniquet to the arm a neat venipuncture is made and approximately 5 to 8 ml. of blood drawn slowly into the syringe. This blood washes out from the needle the tissue juice which might have been picked up during the stab. Since the blood in the syringe is not used for the test, the admixture of tissue juice with the tested blood is practically eliminated.

(2) For filling the capillary tubes we have two equally good techniques:

(a) After disconnecting the syringe but leaving the needle *in situ*, the end of a capillary tube is introduced into the butt of the needle and filled with blood. Since for later handling it is important to be sure which end of the capillary tube the blood entered first, we recommend marking the opposite end with adhesive tape.

(b) If we do not wish to discard the blood drawn into the syringe (which may be important in small animal experiments, where a 5 to 8 ml. blood-loss is considerable), we can use the three-way stop-cock between the needle and the syringe. We draw the blood into the syringe, and then switch the stop-cock between the needle and the third side opening, and through this we collect the first blood drops in the capillary tube. By switching back we connect the needle with the syringe and reinject the blood into the vein.

(3) The stop-watch is started when the blood enters the capillary tube.

(4) Both ends of the capillary are sealed immediately with plasticine, and placed horizontally in the water-bath.

(5) After three or four minutes, small pieces should be broken off every 30 seconds from the end which the blood entered first (opposite the tag). After each break the capillary should be resealed and replaced in the water-bath.

The breaking of the capillary tubes needs some skill. A brisk movement may cut the first fragile fibrin thread. To avoid this we suggest holding the capillary tube with the index fingers and thumbs of both hands, keeping these four fingers tightly together and breaking only in this position. This will prevent too brisk a separation of the broken parts and the cutting of the fibrin thread by the sharp glass edges. It is also important to have a clear white background (sheet of white paper) to be able to see the first very thin fibrin strand.

(6) The end-point is marked by the presence of a white thin fibrin thread 2 cm. in length. As the earliest fibrin can be detected at the end of the capillary tube where the blood entered, it is important to start breaking at this end. The first fibrin thread is very fragile and breaks easily. In 20 to 30 seconds its resistance increases and one can draw longer and longer threads. When a 2 cm. thread can be drawn without disruption the arbitrary end-point has been reached. The fibrin thread is first a yellowish translucent filament. After the end-point has been reached, it is covered with little beads of blood, and later the whole blood is clotted and can be pulled out of the tube. The blood droplets on the filament signify that our arbitrary end-point is just passed, while the thick blood clot signifies considerable overtime.

When the clotting time is elevated, fibrin formation is slower. Two to four minutes may elapse between the first sign of fibrin formation and the end-point.

DISCUSSION

(1) In accordance with other workers[1, 3, 4] we have found that the major source of error in the different clotting-time methods is the mixture of tissue juice with the blood. This error in technique occurs frequently and results in erroneous readings. In our procedure this source of error is easily avoided; the first 5 to 8 ml. of blood are not used and the blood passing out of the needle afterwards is relatively free of disturbing tissue juice.

(2) Since the coagulation of blood involves stoichiometric and enzymatic reactions, it is obvious that the environmental temperature must

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significantly influence the speed of the process. Several authors[2, 4-7] have demonstrated clearly the inverse relationship between clotting time and environmental temperature. The temperature to be adopted is a matter of dispute. Most authors recommend body temperature (37° C.), claiming that this is the temperature at which coagulation takes place physiologically.

We had some objections to this proposal and adopted 21° C. temperature. Firstly, 37° C. is not physiological, as the temperature of blood in the body is higher than this. Secondly, for maintaining a 37° C. temperature, one would need an electric water-bath carried to the bedside, while a lower temperature such as 21° C. can be easily maintained in an inexpensive large thermos-flask. Thirdly, at 37° C. the clotting time is too short to detect minor differences. Fowler[8] has noted that 10 minutes after intravenous injection of 25 mgm. heparin the clotting time at room temperature was prolonged, but it was within normal limits when the test was carried out at 37° C. We have noted also that the higher temperature decreases the sensitivity of the test.

(3) The effect of glass surface on the clotting process has been clearly demonstrated.[3] Since the extent of the blood-glass contact in the method with syringe and test tubes cannot be standardized, coating of glassware with different substances was suggested. In spite of the valuable observations obtained with these materials in the research of clotting mechanism, this method is not popular in routine work because of the extremely prolonged clotting time so obtained.

In the method suggested by us the extent of blood-glass surface is standardized by the use of capillary tubes of similar size and by exclusion of the variable effect of syringe and test tubes.

We must mention that Pichotka *et al.*[9] described a method for the estimation of clotting time in animals which resembles ours. These authors recommended sealing a capillary tube into the butt of a needle with paraffin. The needle is introduced into the vein without using a syringe and the first drop of blood collected in the glass capillary tube. The presence of a fibrin thread marks the end-point. This method merely represents a modification of the well-known technique using capillary blood in capillary tubes. It retains the same major source of error—the admixture of tissue juice with the tested blood. This erroneous step occurs in many other suggested methods, in which it is postulated that all the blood drawn from a vein is free of tissue juice. Since not only the first few drops but also the first few ml. of venous blood may contain considerable amounts of tissue juice,[3] with marked influence on the clotting time, the results with the method suggested by Pichotka *et al.*[9] could not have been accurate. In fact, the literature shows no further reports on this technique.

ACCURACY OF THE METHOD

We performed this test on 50 occasions, blood being collected from the same subject through the same needle by several interns and the author. The clotting times were measured under the above-mentioned conditions. The readings exhibited a standard error of the differences of the means of ±6%.

In 30 healthy male adults the test was made on both arms simultaneously by different interns and the author. The pooled data of the investigators showed a standard error of ±7.5%. It it noteworthy that the interns did not have special training in the technique.

NORMAL VALUES

In the 30 healthy male adults in a postabsorptive state, the clotting time measured by the same investigator following our procedure was 9.2 min., the standard error being ±0.41 min. (±4.4%).

SUMMARY

(1) A standardized test for determination of clotting time is described. It is easily performed by untrained workers with inexpensive material, and gives reproducible and accurate results.

(2) The standard error of the technique in normal bloods is ±0.41 min. (±4.4%).

(3) Since the possibility of subjective error is minimal, comparison of results of different workers is possible.

The author wishes to express his thanks to Dr. W. F. Connell, Professor of Medicine and Head of the Department, for his suggestions and aid in the preparation of this paper.

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COMPLICATIONS FOLLOWING CEREBRAL ARTERIOGRAPHY

In a recent article Perese *et al.* comment on the dangers of cerebral arteriography. In a series of 234 consecutive arteriographic studies with 35% iodopyracet there were 37 complications. Three permanent hemiplegias and 19 transient hemipareses were observed; transient sensory changes occurred in six patients, and one patient had a partial occlusion of the retinal artery. One fatality was due to an excessive amount of contrast medium, and the deaths of six patients appeared to be hastened by the procedure.—*A. M. A. Arch. Neurol. & Psychiat.*, 71: 105, 1954.

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Japanese Patent Application Laid-Open No. 08-257018

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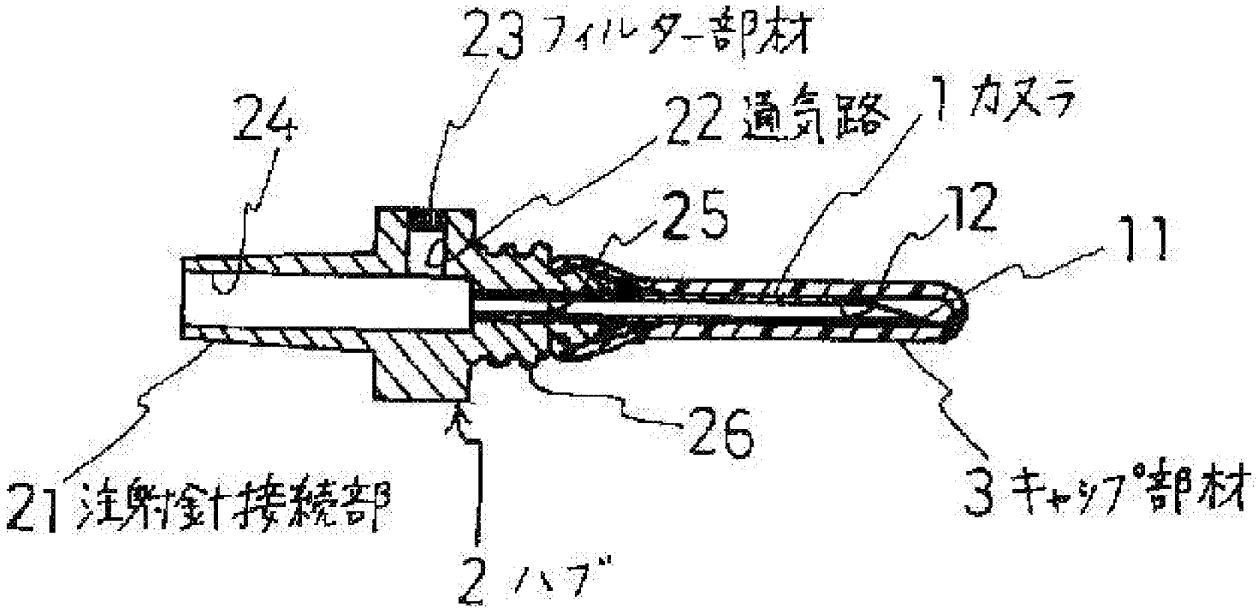
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wrap up close

(57) [Summary]
[Purpose] When the cutting edge of an injection needle connected to this needle is inserted in to a blood vessel, blood flows into the intermediate portion of the transparent hub, which caus es the cutting edge to be inserted into the blood vessel. To provide a blood collection adapter capable of confirming that
The blood collection adapter comprises a hollow cannula 1 having a cutting edge 11 at its tip, a transparent hollow hub 2 supporting and fixing the rear end of the cannula 1 at its tip, and a cannula 1 crowned. It consists of a cap member 3 made of a rubber elastic body. An injectio n needle connecting portion 21 is provided at the rear end portion of the hub 2, and an air pa ssage 22 is provided at the intermediate portion of the hub 2. The outlet of the air passage 22 is gas-permeable and liquid-impermeable. is closed with a filter member 23 of .



The scope of the claims open

[Scope of Claims]

[Claim 1] A hollow cannula having a cutting edge at its tip, a tip supporting and fixing a rear end of the cannula, and a liquid-tight hub of an injection needle at the rear end of the cannula. It consists of a transparent hollow hub equipped with an insertable injection needle connector, and a cap member made of a rubber elastic body covering the cannula, and a hollow between the tip of the hub and the injection needle connector. A blood collection adapter in which an air passage is provided in a portion to communicate the hollow portion with the outside air, and an outlet of the air passage is closed with a gas-permeable and liquid-impermeable filter member.

2. The blood collection adapter according to claim 1, wherein the injection needle connecting portion is formed on a luer tip that can be fitted to the hub of the injection needle.

3. The blood collection adapter according to claim 2, wherein the luer tip is concentrically and externally provided with female coupling means that can be coupled with the hub of the injection needle.

4. A blood collection needle comprising an injection needle connected to the blood collection adapter of claim 1.

detailed description open —

Description: BACKGROUND OF THE INVENTION

1.

Field of the Invention The present invention relates to blood collection adapters. More specifically, it is a blood-collecting adapter used for a vacuum blood-collecting tube for collecting blood from a blood vessel, which can be used as a blood-collecting needle by connecting an ordinary injection needle, and has a cutting edge inserted into the blood vessel. The present invention relates to a blood collection adapter capable of confirming that

2.

Description of the Related Art Conventionally, when collecting blood using a blood collection tube, a blood collection needle as shown in FIG. 4 is used to collect blood. . However, in such blood sampling, which relies on intuition and experience, it is not possible to check whether the cutting edge has been inserted into the blood vessel for beginners with little intuition or experience, or for patients with narrow blood vessels that are difficult to see or cannot be seen. As a result, it places a heavy burden on both the person collecting blood and the person receiving blood. Blood collection had to be repeated, which was uneconomical. Therefore, there has been proposed a blood collection needle that can confirm that the cutting edge has been inserted into a blood vessel (Japanese Unexamined Patent Publication No. 4-132541, etc.).

[0003] In the blood collection needle disclosed in JP-A-4-132541, the hub is provided with a v entilation hole for communication between the inner cavity of the elastic tip and the outside at mosphere, and an air-permeable filter is attached to the outer opening of the ventilation hole. By confirming the blood (so-called flashback) flowing into the blood collection needle, it is con firmed that the cutting edge has been inserted into the blood vessel. However, since the blood collection needle described above tries to guide the blood that has flowed into the elastic tip t o the ventilation hole of the transparent hub, it is necessary to confirm flashback.It takes a lo ng time, and there is a problem that the blood collected inside the elastic tip may leak. SUMM ARY OF THE INVENTION The present invention has been made in view of the above-mentione d circumstances

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To provide a blood collecting adapter which enables confirmation of the insertion of a cutting e dge into a blood vessel by blood flowing into an intermediate part of the blood vessel. Another object of the present invention is to provide a blood collection needle comprising a combinatio n of this blood collection adapter and an injection needle.

[0005]

To solve the above problems, the present invention provides a hollow cannula having a cutting edge at its distal end, and a distal end of the hollow cannula supporting and fixing the rear en d of the cannula. and a transparent hollow hub equipped with an injection needle connecting portion to which the injection needle hub can be inserted in a liquid-tight manner at its rear e nd, and a cap member made of a rubber elastic body covering the cannula, An air passage is provided in the hollow portion between the distal end portion of the hub and the injection nee dle connection portion to communicate the hollow portion with the outside air, and the outlet of the air passage is closed with a gas-permeable and liquid-impermeable filter member. A re movable blood collection adapter is used. In addition, a configuration in which an injection ne edle is connected to this blood collection adapter is adopted. Here, the injection needle conne ction part may be formed in a luer tip that can be fitted with the hub of the injection needle c onnected thereto, and the luer tip is concentrically threaded with the hub of the injection need le. A female coupling means may be provided which may be mated or luer coupled.

[0006]

[Operation] According to the above configuration, when the blood collection adapter is attache d to the blood collection needle holder, the injection needle is connected to the injection needl e connecting portion, and the injection needle is inserted into the blood vessel, the hollow por tion of the injection needle and the blood collection are removed. Air existing in the hollow por tion of the adapter passes through the gas-permeable filter member through the gas-permea ble filter member by the inflowing blood, and is expelled to the outside. It flows into the hollo w portion of the adapter and then through the air passage to reach the filter member. Therefo re, by observing the air passage formed in the transparent hub, insertion of the injection need le into the blood vessel can be easily confirmed. Also, at this time, since the filter member is i

mpermeable to liquid, blood does not leak through the filter member to the outside.

[0007]

Next, an embodiment of the present invention will be described with reference to the drawing s. FIG. 1 is a vertical cross-sectional view of a blood sampling adapter according to one embo diment of the present invention, FIG. 2 is a diagram showing another embodiment, and FIG. 3 shows a state in which an injection needle is attached to the blood sampling adapter shown in FIG. FIG. 10 shows. As shown in FIG. 1, the blood collection adapter of the present invention comprises a hollow cannula 1 having a cutting edge 11 at its distal end, and a transparent holl ow hub 2 supporting and fixing the rear end of this cannula 1 at its distal end. , the rubber ela stic body crowned on the cannula 1It consists of a cap member 3 made of An injection needle connecting portion 21 is provided at the rear end portion of the hub 2, and an air passage 22 i s provided at the intermediate portion of the hub 2. The outlet of the air passage 22 is gas-pe rmeable and liquid-impermeable. is closed with a filter member 23 of .

The hub 2 is a hollow member made of transparent synthetic resin such as polyethylene, poly propylene, polyester, or polystyrene, and consists of a front end, an intermediate portion, and a rear end. The rear end of the cannula 1 generally made of stainless steel is inserted into the hollow portion 25 at the tip of the hub 2 and fixed with an adhesive. It is covered with a cap member 3 made of isoprene rubber, butadiene rubber, nitrile rubber or the like. A male coupli ng means such as a male screw 26 is formed on the outer wall of the tip of the hub 2 so that i t can be screwed into a blood collection needle holder (not shown).

[0009] The rear end of the hub 2 is an injection needle connecting portion 21 having a hollow portion 24 communicating with a hollow portion 25 at the distal end of the hub 2, and is gene rally external so that a hub 41 of the injection needle 4 can be fitted. It is formed into a so-cal led luer tip whose diameter is reduced in a tapered shape. For example, as shown in FIG. A h ood-shaped female coupling means 27 extending concentrically from the intermediate portion of the hub 2 toward the injection needle connection portion 21 is provided, and a male couplin g means (not shown) is provided on the outer wall of the end portion of the hub 41 of the inje ction needle 4 . (not connected) may be threaded or luer connected. As the injection needle c onnecting portion 21, a male coupling member that is inserted into the hub 41 of the injection needle 4 is usually employed. coupling members can also be employed.

The intermediate portion of the hub 2 is a wide brim-like projecting portion, and is provided w ith an air passage 22 that communicates a hollow portion 24 with the outside air. ing. This filt er member 23 is a gas-permeable and liquid-impermeable filter (hydrophobic filter), and as su ch a filter, a layered filter made of a polymer sintered body such as polypropylene or polyethyl ene is usually preferably employed. However, a film-like so-called membrane filter made of a hydrophobic resin such as polypropylene or polyethylene may also be used.

Next, use of the blood collection adapter of the present inventionwill be described with referen ce to FIG. First, the blood collection adapter A is attached to a blood collection needle holder (not shown), and the injection needle 4 is connected to the injection needle connecting portio

n 21 of the blood collection adapter A. As shown in FIG. Next, when the cutting edge 43 of th e injection needle 4 is pierced into the blood vessel, the air existing in the hollow portion 44 of the injection needle 4 and the hollow portions 24 and 25 of the blood collection adapter A is p ushed into the air passage of the blood collection adapter A by the inflowing blood. 22, it per meates the gas-permeable filter member 23 and is expelled to the outside. Then, the blood p asses through the hollow portion 44 of the injection needle 4 and flows into the hollow portion 24 of the blood collection adapter A, passes through the air passage 22 and reaches the filter member 23 . Therefore, by observing the injection needle connecting portion 21 and the air p assage 22 provided on the transparent hub 2, it is possible to easily confirm that the cutting e dge 43 of the injection needle 4 has been inserted into the blood vessel. At this time, since th e filter member 23 is impermeable to liquid, the blood will not pass through the filter member 23 and leak to the outside.

INDUSTRIAL APPLICABILITY

As is clear from the above description, the following effects can be obtained by adopting the b lood sampling adapter of the present invention.

①It is economical because it can be used as a blood collection needle by connecting a normal injection needle.

②Since it can be easily confirmed that the cutting edge of the injection needle connected to t his has been pierced into the blood vessel, it is possible to eliminate the burden on the subjec t of blood collection due to re-insertion of the injection needle.

③No need to redo blood collection.

Brief description of the drawing

open —

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a vertical cross-sectional view of a blood sampling adapter according to one embodi ment of the present invention;

FIG. 2 is a diagram showing another embodiment of the present invention;

3 is a view showing a state where an injection needle is attached to the blood collection adapt er shown in FIG. 1; FIG.

FIG. 4 is a diagram showing a conventional blood collection needle;

[Description of Reference Symbols]

1 Cannula

2 Hub

21 Injection needle connecting portion

22 Air passage

23 Filter member

27 Female coupling means

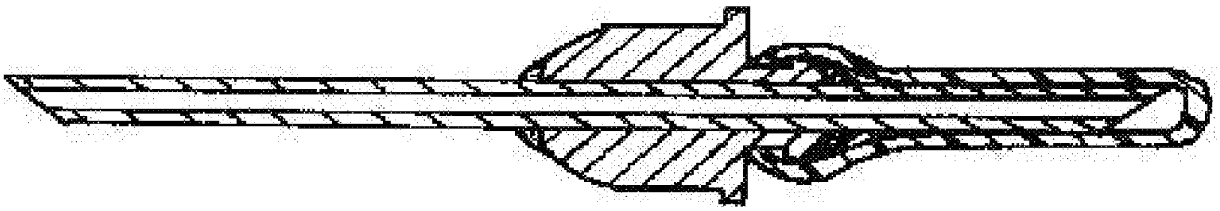
3 Cap member

4 Injection needle

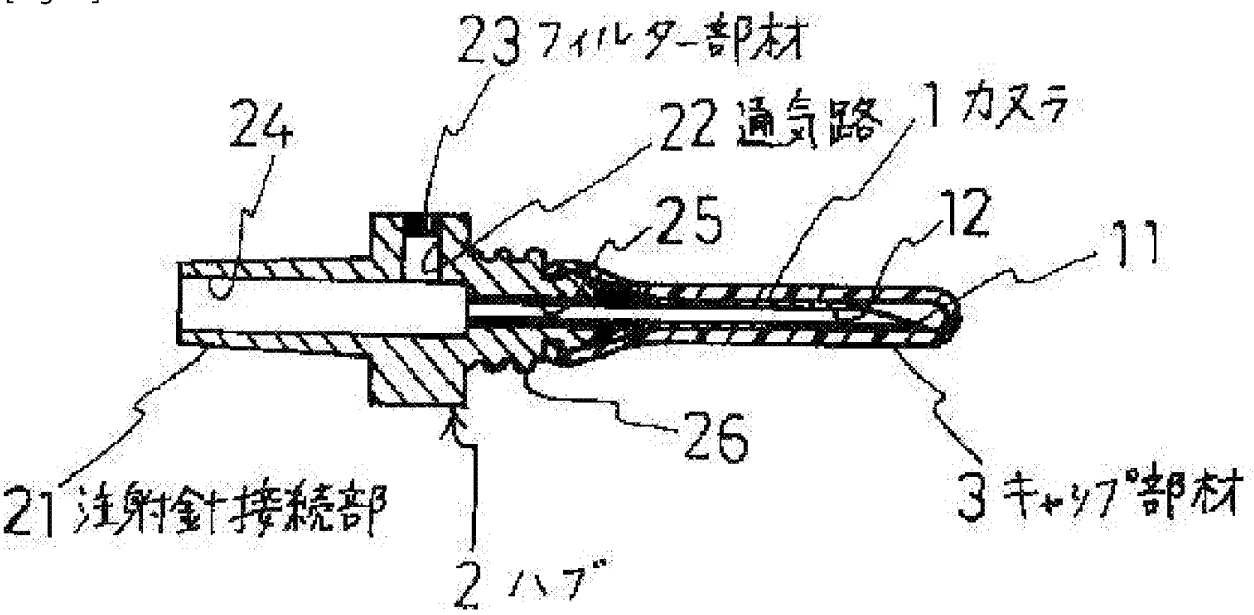
A Blood sampling adapter

drawing open —

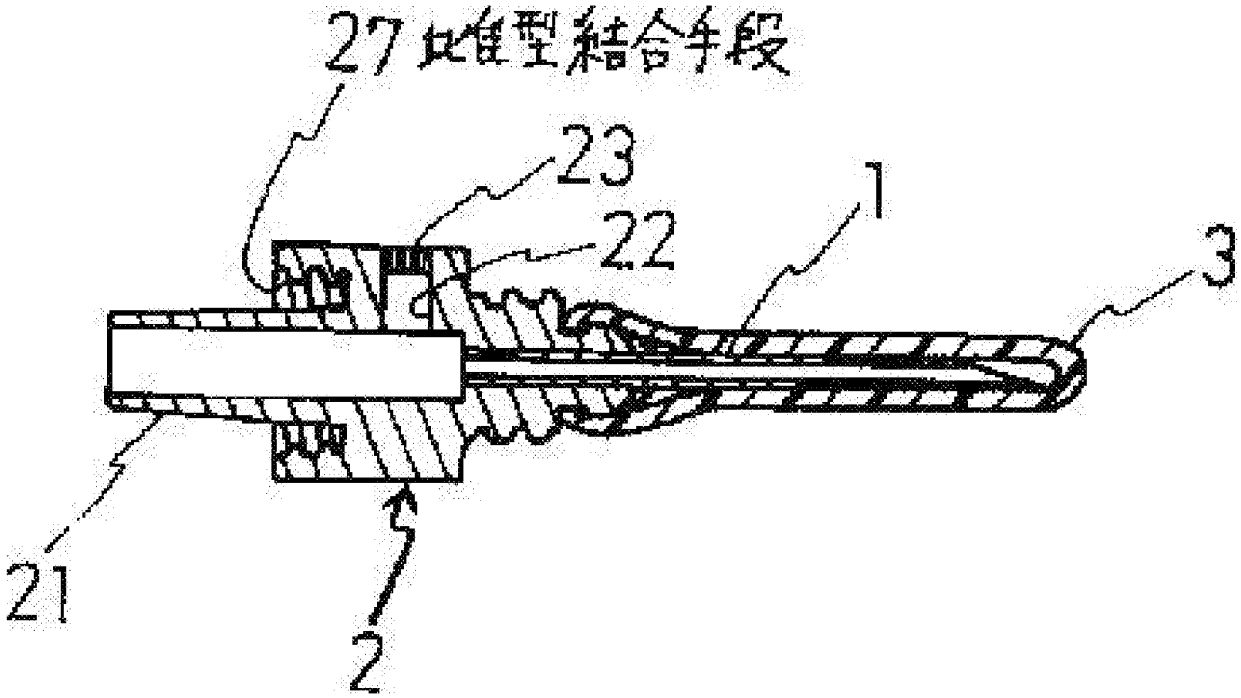
[Figure 4]



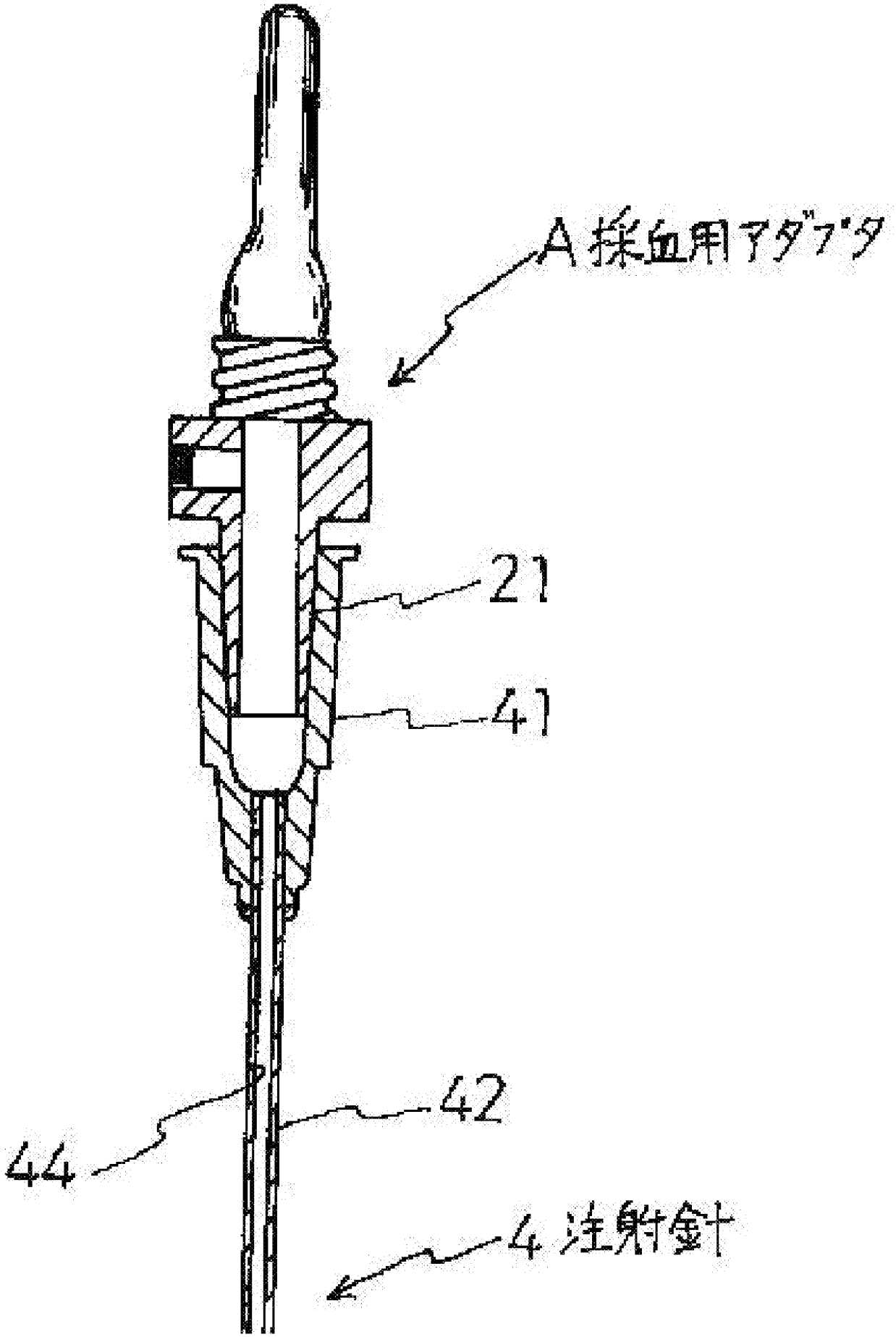
[Fig. 1]



[Figure 2]



[Figure 3]


A 採血用アダプタ
21
41
42
44
4 注射針

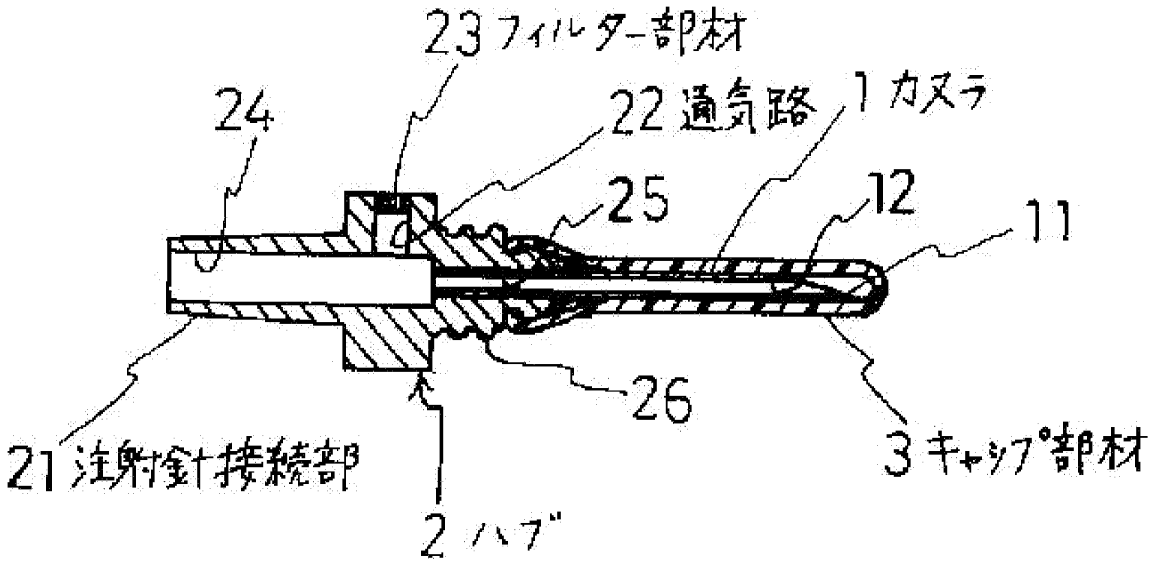


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open

Representative drawing | 1 | 2 | 3 | Four

Magnify and Rotate



Representative drawing

1 / 1 display

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Bibliographic data: JPH08257018 (A) — 1996-10-08

BLOOD-GATHERING ADAPTER

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Applicant(s): NISSHO KK ± (NISSHO CORP)

Classification: **- international:** ***A61B5/15; A61B5/154; A61M5/32;*** (IPC1-7): A61B5/14; A61M5/32

- cooperative: **A61B5/15003 (EP)**; **A61B5/150213 (EP)**; **A61B5/150389 (EP)**; **A61B5/150473 (EP)**; **A61B5/150503 (EP)**; **A61B5/150732 (EP)**; **A61B5/1535 (EP)**; A61B5/150572 (EP); A61B5/1545 (EP)

Application number: JP19950062943 19950322

Priority number(s): JP19950062943 19950322

Abstract of JPH08257018 (A)

PURPOSE: To provide a blood-gathering adapter by which the fact that the edge tip is stuck into a blood vessel can be confirmed since blood flows in an intermediate part of its transparent hub when the edge tip of an injection needle connected to this is stuck into a blood vessel. CONSTITUTION: A blood gathering adapter is composed of a hollow cannula 1 having the edge tip 11 on the tip, a transparent hollow hub 2 to support and fix a rear end part of this cannula 1 by its tip part and a cap member 3 which is put on the cannula 1 and is made of a rubber elastic body. An injection needle connecting part 21 is arranged in a rear end part of the hub 2, and a ventilating passage 22 is arranged in an intermediate part of the hub 2, and an outlet of this ventilating passage 22 is blocked up by a gas permeable and liquid impermeable filter member 23.

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Ａ６１Ｍ	5/32			Ａ６１Ｍ	5/32	

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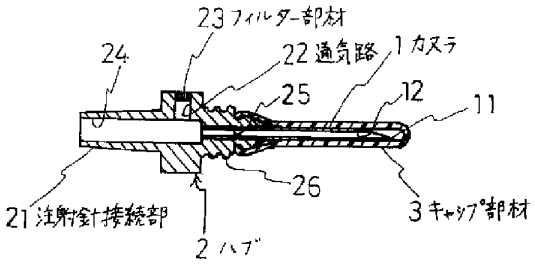
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(54)【発明の名称】　採血用アダプタ

(57)【要約】

【目的】　これに接続される注射針の刃先が血管に刺入されたときに、その透明なハブの中間部分に血液が流れ込み、これによって刃先が血管内に刺入されたことを確認できる採血用アダプタを提供する。

【構成】　採血用アダプタは、先端に刃先１１を有する中空のカヌラ１と、その先端部でこのカヌラ１の後端部を支持し固定する透明な中空のハブ２と、カヌラ１に被冠されたゴム弾性体製のキャップ部材３からなっている。そして、ハブ２の後端部には注射針接続部２１が設けられており、ハブ２の中間部には通気路２２が設けられ、この通気路２２の出口はガス透過性かつ液体不透過性のフィルター部材２３で塞がれている。



【特許請求の範囲】
【請求項１】　先端に刃先を有する中空のカヌラと、その先端部で該カヌラの後端部を支持し固定するとともに、その後端部に注射針のハブを液密に挿着可能な注射針接続部を備えた透明な中空のハブと、前記カヌラに被冠されたゴム弾性体製のキャップ部材とからなり、前記ハブの先端部と注射針接続部の間の中空部分に、該中空部分を外気と連通する通気路が設けられ、該通気路の出口がガス透過性かつ液体不透過性のフィルター部材で塞がれてなる採血用アダプタ。
【請求項２】　注射針接続部が注射針のハブと嵌合可能なルアーチップに形成されている請求項１に記載の採血用アダプタ。
【請求項３】　ルアーチップと同心状かつその外側に注射針のハブと結合可能な雌型結合手段を設けた請求項２に記載の採血用アダプタ。
【請求項４】　請求項１の採血用アダプタに注射針を接続してなる採血針。
【発明の詳細な説明】
【０００１】
【産業上の利用分野】本発明は採血用アダプタに関する。より詳しくは、血管より血液を採取するための真空採血管に用いる採血用アダプタであって、これに通常の注射針を接続することにより採血針として使用できるとともに、刃先が血管に刺入されたことを確認することができる採血用アダプタに関する。
【０００２】
【従来の技術】従来より、採血管による採血に際して、図４に示すような採血針を用いて採血しており、勘と経験によって刃先が血管内に入ったことを確認していた。しかしながら、このような勘と経験に頼る採血では、勘や経験の乏しい初心者や、血管が細くて見にくいまたは見えない患者の場合、血管内への刃先の刺入を確認できないため、何回も刺し直したりすることがあり、そのため、採血者にとっても被採血者にとっても大きな負担を強いられることになり、また、場合によっては、新たに真空採血管、採血針、その他の採血器具を用意して採血のし直しをしなければならず、不経済であった。そこで、刃先が血管に刺入されたことを確認することができる採血針が提案されている（特開平４－１３２５４１号公報など）。
【０００３】上記特開平４－１３２５４１号公報の採血針は、ハブに弾性チップの内腔部と外部雰囲気とを連通させる通気孔を設け、この通気孔の外部口部に通気性フィルタを取り付けたことを特徴とするもので、採血針に流入する血液（いわゆるフラッシュバック）を確認することにより、刃先が血管に刺入されたことを確認するようにしたものである。しかしながら、上記の採血針は弾性チップ内に流入した血液を透明なハブの通気孔に導こうとするものなので、フラッシュバックの確認に要する時間が長く、また、弾性チップの内部に溜まった血液が漏れる虞があり問題である。
【０００４】
【発明が解決しようとする課題】本発明は、上記の事情に鑑みてなされたもので、これに接続される注射針の刃先が血管に刺入されたときに、その透明なハブの中間部分に血液が流れ込み、これによって刃先が血管内に刺入されたことを確認できる採血用アダプタを提供することを目的とする。また、この採血用アダプタと注射針の組合せからなる採血針を提供することを目的とする。
【０００５】
【課題を解決するための手段】本発明は、上記の課題を解決するために、先端に刃先を有する中空のカヌラと、その先端部で該カヌラの後端部を支持し固定するとともに、その後端部に注射針のハブを液密に挿着可能な注射針接続部を備えた透明な中空のハブと、前記カヌラに被冠されたゴム弾性体製のキャップ部材とからなり、前記ハブの先端部と注射針接続部の間の中空部分に、該中空部分を外気と連通する通気路が設けられ、該通気路の出口がガス透過性かつ液体不透過性のフィルター部材で塞がれてなる採血用アダプタを採用している。また、この採血用アダプタに注射針を接続した構成を採用している。ここで、注射針接続部はこれに接続される注射針のハブと嵌合可能なルアーチップに形成してもよく、また、ルアーチップの外側にはこれと同心状に注射針のハブと螺合あるいはルアー結合可能な雌型結合手段を設けてもよい。
【０００６】
【作用】上記構成によれば、採血用アダプタを採血針ホルダーに取り付け、その注射針接続部に注射針を接続して、この注射針を血管に刺入すると、注射針の中空部分および採血用アダプタの中空部分に存在する空気が、流入する血液により採血用アダプタの通気路を通りガス透過性のフィルター部材を透過して外部に追い出されるので、血液は注射針の中空部分を通って採血用アダプタの中空部分に流入し、さらに通気路を通ってフィルター部材に達する。従って、透明なハブに形成された通気路を観察すれば、容易に注射針の血管内への刺入を確認することができる。また、この時、フィルター部材が液体不透過性なので、血液がフィルター部材を透過して外部に漏れることはない。
【０００７】
【実施例】次に本発明の実施例について図面に基づいて説明する。図１は本発明の一実施例に係る採血用アダプタの縦断面図であり、図２は他の実施例を示す図、図３は図１に示す採血用アダプタに注射針を取り付けた状態を示す図である。図１に示すように、本発明の採血用アダプタは、先端に刃先１１を有する中空のカヌラ１と、その先端部でこのカヌラ１の後端部を支持し固定する透明な中空のハブ２と、カヌラ１に被冠されたゴム弾性体

製のキャップ部材３からなっている。そして、ハブ２の後端部には注射針接続部２１が設けられており、ハブ２の中間部には通気路２２が設けられ、この通気路２２の出口はガス透過性かつ液体不透過性のフィルター部材２３で塞がれている。

【０００８】ハブ２は例えばポリエチレンやポリプロピレン、ポリエステル、ポリスチレンなどの透明な合成樹脂で中空に形成された部材であり、先端部と中間部および後端部からなる。ハブ２の先端部の中空部分２５には一般にステンレス鋼で形成されたカヌラ１の後端部が挿入され、接着剤で固定されており、このカヌラ１にはゴム弾性体の例えば天然ゴムや、イソプレンゴム、ブタジエンゴム、ニトリルゴムなどで形成されたキャップ部材３が被せられている。また、ハブ２の先端部の外壁には雄型結合手段の例えば雄ネジ２６が形成されており、採血針ホルダー（図示していない）に螺合できるようになっている。

【０００９】ハブ２の後端部はハブ２の先端部の中空部分２５と連通する中空部分２４を有する注射針接続部２１になっており、注射針４のハブ４１を嵌合できるよう一般に外径がテーパ状に縮径された所謂ルアーチップに形成されている。ルアーチップに形成された注射針接続部２１の外側には、採血操作の途中で注射針４のハブ４１が注射針接続部２１から脱落することがないように、例えば図２に示すように、ハブ２の中間部から注射針接続部２１方向にこれと同心状に延びるフード状の雌型結合手段２７を設け、注射針４のハブ４１の端部外壁に設けた雄型結合手段（図示していない）と螺合またはルアー結合するようにしてもよい。尚、注射針接続部２１としては通常、注射針４のハブ４１に挿着される雄型の結合部材が採用されるが、注射針のハブを雄型の結合端に形成することにより雌型の結合部材を採用することもできる。

【００１０】ハブ２の中間部は幅広の鍔状に突出した部分であり、中空部分２４を外気と連通する通気路２２が設けられており、通気路２２の出口はフィルター部材２３で塞がれている。このフィルター部材２３はガス透過性かつ液体不透過性のフィルター（疎水性フィルター）であり、このようなフィルターとしては、通常ポリプロピレンやポリエチレンなどのポリマー焼結体からなる層状のフィルターが好適に採用されるが、ポリプロピレンやポリエチレンなどの疎水性樹脂からなる膜状のいわゆるメンブレンフィルターであっても構わない。

【００１１】次に、本発明の採血用アダプタの使用について図３を用いて説明する。先ず、採血用アダプタＡを採血針ホルダー（図示していない）に取り付け、採血用アダプタＡの注射針接続部２１に注射針４を接続する。次に注射針４の刃先４３を血管に刺入すると、注射針４の中空部分４４および採血用アダプタＡの中空部分２４、２５に存在する空気が、流入する血液により採血用アダプタＡの通気路２２を通りガス透過性のフィルター部材２３を透過して外部に追い出される。すると、血液は注射針４の中空部分４４を通って採血用アダプタＡの中空部分２４に流入し、さらに通気路２２を通ってフィルター部材２３に達する。従って、透明なハブ２に設けられた注射針接続部２１や通気路２２を観察すれば、容易に注射針４の刃先４３の血管内への刺入を確認することができる。また、この時、フィルター部材２３が液体不透過性なので、血液がフィルター部材２３を透過して外部に漏れることはない。

【００１２】

【発明の効果】以上説明してきたことから明らかなように、本発明の採血用アダプタを採用することにより、次のような効果を奏することができる。

通常の注射針を接続することにより採血針として使用することができるので、経済的である。

これに接続された注射針の刃先が血管に刺入されたことを容易に確認できるので、注射針の刺し直しによる被採血者の負担を無くすることができる。

採血のし直しをしなくて済む。

【図面の簡単な説明】

【図１】本発明の一実施例に係る採血用アダプタの縦断面図である。

【図２】本発明の他の実施例を示す図である。

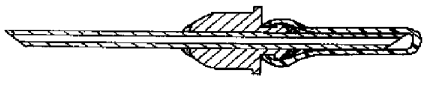
【図３】図１に示す採血用アダプタに注射針を取り付けた状態を示す図である。

【図４】従来の採血針を示す図である。

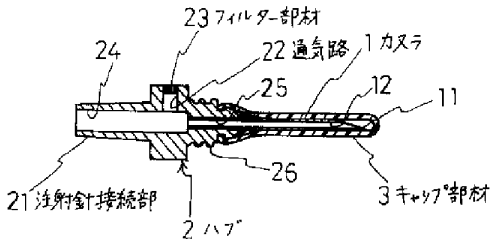
【符号の説明】

１　カヌラ
２　ハブ
２１　注射針接続部
２２　通気路
２３　フィルター部材
２７　雌型結合手段
３　キャップ部材
４　注射針
Ａ　採血用アダプタ

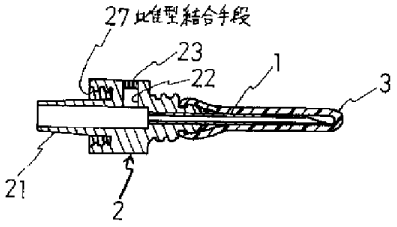
【図４】



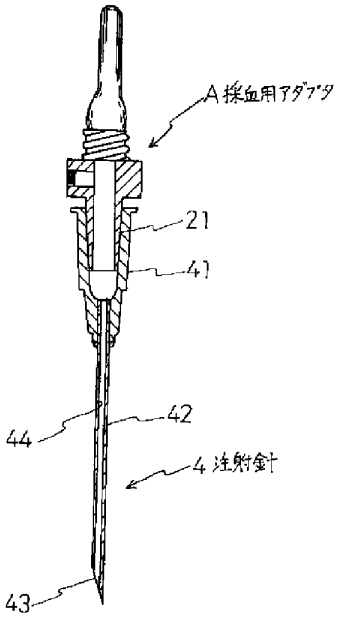
【図１】


23 フィルター部材
24
22 通気路
1 カヌラ
25
12
11
21 注射針接続部
26
2 ハブ
3 キャップ部材

【図２】


27 血液型結合手段
23
22
1
3
21
2

【図３】


A 採血用アダプタ
21
41
42
44
4 注射針
43

Original Article

Quality of Processed Blood for Autotransfusion

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University of Texas Medical Branch, Galveston, Texas

Keywords: red cell mass flow rate, speed, plasma washout, quality

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ABSTRACT

Centrifugal red blood cell washers for intraoperative autotransfusion process shed blood during surgery. In this study, the quality of processed fresh, human bank blood was assessed in a standardized laboratory setting during standard, medium, and high flow processing. Red cell recovery rates and plasma washout efficiencies were compared using three different devices. The accurate parameters measuring effectiveness and product quality were red cell mass (RCM) flow rate and the plasma washout efficiency. Cobe BRAT 2, a system with discontinuous flow (DF) and a cylindrical centrifuge bowl, permitted processing in standard and medium flow of 26 and 35 mL RCM/min, respectively, with washout of residual plasma albumin of 93.2 and 91.2%. The Medtronic Sequestra 1000, a DF system with a conical centrifuge bowl processed blood at 15 and 23 mL RCM/min and eliminated plasma albumin with 98.4 and 96.8% washout during standard and medium flow, respectively, with significant red cell loss occurring during medium flow. The respective speeds of high-flow programs with BRAT 2 and Sequestra 1000 were 15 and 22 mL RCM/min, related to a hematocrit in the holding bag, less than that of the incoming blood from the reservoir. Washout was 58.2 and 58.3%, respectively. Fresenius CATS, a continuous flow (CF) device, produced flow rates of 19, 24, and 43 mL RCM/min and plasma albumin elimination of 97.8, 94.4, and 93.3% in standard, medium, and high-flow, respectively. Holding bag hematocrits with CF exceeded that of DF. Standard, medium, and high-flow programs of CATS may be used without restriction.

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INTRODUCTION

The red blood cell recovery rate and washing efficiency of centrifugal devices used for intraoperative autologous transfusion (IAT) have an impact on the safety, purity, and potency of the processed product. Standard programs of most IAT devices have shown satisfactory performance during vascular surgery (1), cardiothoracic surgery (2), and major orthopedic surgery (3–7). However, accurate data on processing at high speeds are limited. The operating principles of centrifugal equipment are based either on discontinuous (DF) or continuous flow (CF). DF devices employ conical or cylindrical bowl geometries, which may affect results of the washing procedures. Manufacturers provide defined preprogrammed washing procedures with various washing speeds. In addition, operator-defined options are available, allowing for alteration of processing parameters of centrifuge speed and flow rates. Although changes that may affect the characteristics of the blood product are indicated, no exact data are provided.

The goal of this study is to perform a well-defined laboratory comparison of the processing speed and quality of the washed red cell product of three autotransfusion devices, each with operating principles based on different technology. Three speeds were studied in standard, medium, and high flow programs using nondistributable donor red cells reconstituted with compatible plasma and at three dilutions with saline, simulating conditions in the operating room.

MATERIALS AND METHODS

Washing programs were based on an ordinary requirement (standard flow), rapid (medium flow), and a very rapid (high flow), each representative of routine, rapidly processed, and emergency methods, respectively. The Cobe BRAT 2[a], the Fresenius CATS[b], and the Medtronic Sequestra 1000[c] were employed during this study. Manufacturer-specified programs for DF using Sequestra 1000 with a conical centrifuge bowl and CATS with CF were selected as corresponding standard, medium, and high flow programs. The programs for comparable function on BRAT 2 with DF and a cylindrical centrifuge bowl were the standard flow program as specified by the manufacturer, medium and high flow are available as operator-defined procedures (Table 1).

Compatible fresh frozen plasma and nondistributable donor packed red cells, less than 5 days from the time of collection, were pooled to achieve an hematocrit (HCT) of approximately 40%. To simulate blood collected from a surgical field, an adjustment was made with normal saline to dilute pools with target HCT of approximately 30, 20, and 10%, each confirmed before processing. After thorough mixing, the pool was divided into separate bags and used as blood reservoirs. The devices were used with the same disposable sets for each respective instrument in the three corresponding programs. Variability between individual lots are not expected to influence test results significantly because of the known high reproducibility of the manufacturing process involved. A fresh portion of the identical blood pool was processed on each device in three separate consecutive runs in the automatic modes. The processing times using the 250-mL bowl with BRAT 2 and the 225-mL bowl with Sequestra 1000 were recorded each for one completely filled bowl until the system stopped automatically; residual packed red blood cells in the emptying lines to the holding bags were transferred by activating the "Empty" routine twice more. The processing time with CATS was measured during accumulation of an equivalent volume of 225 mL packed red cells in the holding bag as measured by digital display on the instrument's control panel. To be consistent, the residual red cell volume in the emptying line to the holding bag was retained in the line. Volumes of blood from the reservoir and packed red cells in the holding bag were calculated from weights before and after processing. The weight differences were divided by densities according to measured HCT levels (8), respectively, to calculate volumes of blood drawn from reservoirs and packed red cells collected into holding bags. Volumes of five mL blood each were sampled from the reservoirs before and from holding bags after processing for CBC with the MAXM[d] blood cell counter and tested within 2 hours. Similarly, separate samples were collected, the centrifuged supernatant separated and frozen at −30°C, pending batch analysis of plasma albumin measured immunochemically with the Behring BN Laser Nephelometer[e] as the indicator for plasma washout.

Processing speeds, red cell recovery, rates of albumin elimination, and residual albumin transfusion were calculated as follows:

$$\text{blood flow rate from reservoir (mL/min)} = \frac{\text{blood volume processed}}{\text{processing time}}$$

$$\text{PRBC flow rate into holding bag (mL/min)} = \frac{\text{Volume of PRBC}}{\text{processing time}}$$

$$\text{RCM flow rate into holding bag (mL/min)} = \frac{\text{Volume PRBC} * \text{HCT}_{\text{PRBC}}}{\text{processing time}}$$

$$\text{RBC recovery rate in the holding bag (efficiency \%)} = \frac{\text{PRBC volume} * \text{HCT}_{\text{PRBC}}}{\text{Blood volume} * \text{HCT}_{\text{blood}}} * 100$$

[a] Cobe Laboratories, Inc., Arvada, CO 80004
[b] Medtronic Inc., Parker, CO 80134
[c] Fresenius Hemotechnology, Inc., Concord, CA 94520
[d] Coulter, Miami, FL
[e] Dade-Behring, Deerfield, IL

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Table 1. Processing parameters of three autotransfusion devices tested in three different programs with reconstituted human bank whole blood in three saline dilutions

Program	Parameter	BRAT 2	CATS	Sequestra 1000
Standard flow	Fill speed (mL/min)	400	35 mL/min*	300
	Wash speed (mL/min)	800	WF = 5**	300
	Empty speed (mL/min)	600		300
	Wash volume (mL)	1000		1000
Medium flow	Fill speed (mL/min)	700	50 mL/min*	500
	Wash speed (mL/min)	1000	WF = 3**	500
	Empty speed (mL/min)	1000		500
	Wash volume(mL)	1000		1000
High flow	Fill speed (mL/min)	1300	100 mL/min*	1000
	Wash speed (mL/min)	1300	WF = 1**	1000
	Empty speed(mL/min)	1300		1000
	Wash volume(mL)	1000		750

*Default blood flow to holding bag (packed red blood cells).
**WF = wash factor = mL saline/mL packed red blood cells.

Table 2. Hematocrits (mean ± standard deviation %) of blood in the holding bags for three autotransfusion devices using three programs at reservoir hematocrits of 10, 20, and 30% and three replicate procedures in each

	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
Reservoir Hematocrit	Stand	Med	High	Stand	Med	High	Stand	Med	High
10% $N = 3$	49 ± 1	47 ± 1	9 ± 0.0	58 ± 0.0	54 ± 0.0	63 ± 0.0	55 ± 0.0	53 ± 1	5 ± 0.0
20% $N = 3$	45 ± 0.0	41 ± 1	16 ± 0.0	58 ± 1	54 ± 1	58 ± 0.0	53 ± 1	49 ± 2	11 ± 1
30% $N = 3$	44 ± 0.0	39 ± 0.0	24 ± 0.0	54 ± 0.0	53 ± 1	58 ± 0.0	52 ± 2	45 ± 1	18 ± 0.0
Average All $N = 9$	46 ± 2 °|	42 ± 3 °|	16 ± 6 °	57 ± 2 °*	54 ± 5 °*	59 ± 3 °*	53 ± 2 *|	49 ± 3 *|	11 ± 5 *

Average All = means of all hematocrits; °*| = $p < .05$ between corresponding programs.

$$\text{Albumin elimination rate (\%)} = \left[\left| - \frac{\text{Total Albumin}_{\text{PRBC}}}{\text{Total Albumin}_{\text{blood}}} \right| \right] * 100$$

$$= \left[\left| - \frac{\text{Volume PRBC}* (1 - \text{HCT}_{\text{PRBC}})*\text{Albumin}_{\text{PRBC}}}{\text{Volume Blood} * (1 - \text{HCT}_{\text{blood}})*\text{Albumin}_{\text{blood}}} \right| \right] * 100$$

$$\text{Residual Albumin transfusion rate (mg/dL RCM)} = \frac{\text{Albumin}_{\text{PRBC}} * (1 - \text{HCT}_{\text{PRBC}})}{\text{HCT}_{\text{PRBC}}}$$

Mean values and standard deviations were calculated for three replicates of each parameter and program based on three runs each using blood with a HCT of 10, 20, and 30% ($N = 9$). This represented the range of applications encountered clinically.

STATISTICS

Student's *t*-test for unpaired data was used and probability of $p < .05$ was considered significant. Statistically significant differences are indicated by the symbols °*| in the tables and figures for corresponding programs.

RESULTS

The differences between DF and CF are shown in Figure 1. In CF, blood from the reservoir was pumped into a rotating horizontal wash chamber, C-shaped like a spiral, hollow band. First, the red blood cells were concentrated on the outer aspect of the channel, then became resuspended in saline, reconcentrated on the outer aspect, and then transferred to the holding bag in a continuous flow of blood through the system. Plasma and saline wash waste were diverted to the waste bag.

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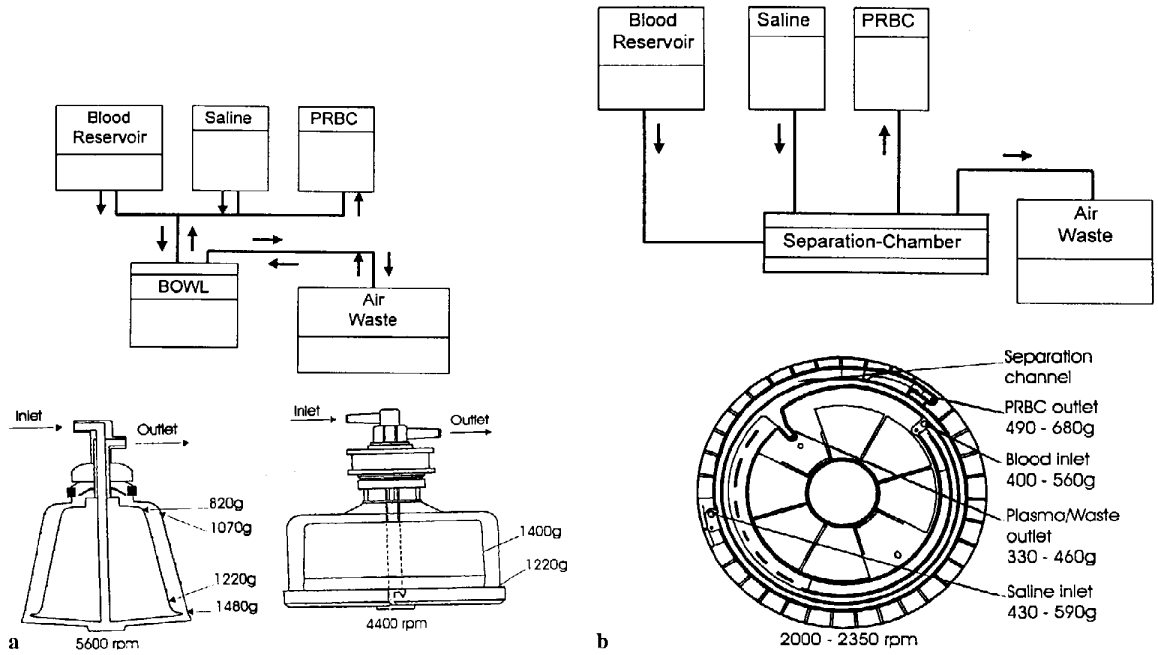


Figure 1: Diagrammatic representations of the flow in systems devised for intraoperative autologous transfusion in (a) discontinuous and (b) continuous flow procedures.

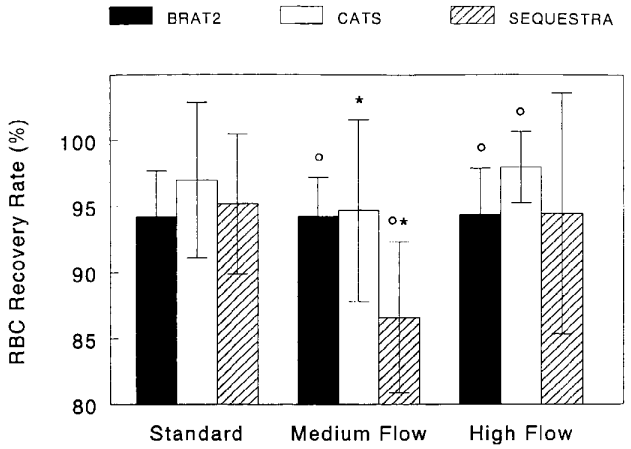


Figure 2: Mean red blood cell recovery rates ± standard deviations for three replicate processing runs using three autotransfusion devices in three programs; ° * = $p < .05$; $N = 9$.

HCT of the processed packed red cells was found to be consistently greatest in all CF (CATS) programs as compared with values obtained with the cylindrical DF (BRAT2) or the conical DF (Sequestra 1000) bowl systems. This was independent of the processing speed and HCT of the incoming blood. In DF, the HCT of packed red cells in the holding bag decreased progressively with greater processing speeds and with a greater HCT of the incoming blood (Table 2). High flow with BRAT 2 and Sequestra 1000 resulted in HCT even less than that of the blood in the reservoir before processing. As the speed was increased during processing with both BRAT 2 and Sequestra 1000, the volume of saline used per mL RCM became increased because of an insufficient red cell content in the bowls. However, with CATS, the volume of saline used per mL RCM decreased significantly (Table 3).

Apart from the medium flow program of Sequestra 1000, the range of red blood cell recovery rates was between 94 and 98% using all devices in all programs (Figure 2). During medium flow on Sequestra 1000, visible red cell loss to waste occurred with a diminished recovery rate of 86%. This was because of formation of an inverted saucer-shaped layer of red cells at the level of the rotating seal (Figure 3), caused by pressure diversion from the inlet port directly to the waste outlet. Red cell flow bypassed separation in the centrifugal field because of pressure buildup from force developed by rapid pump speeds once the bowl capacity was filled to about one-third.

In DF, processing reservoir samples with different HCT levels resulted in variation of the red cell mass flow rate into the holding bags (Table 4). Apart from incoming blood from the reservoir with high flow and an HCT of 10%, the red cell mass flow rate with CATS was found to be constant. The red cell mass flow rate into the holding bag increased progressively for all three devices from standard to medium flow. However, CATS high flow continued to show further increase in red cell mass flow rate, but both DF instruments showed a marked decline ($p < .0001$). The flow rates with high flow for both BRAT 2 and Sequestra 1000 were less than those of standard

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Table 3. Saline volumes per red cell mass processed (mean ± standard deviation; mL saline/mL RCM processed) for three autotransfusion devices using three programs with three replicate procedures in each

Reservoir Hematocrit	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
	Stand	Med	High	Stand	Med	High	Stand	Med	High
Average All	8.9 ± 0.4	9.8 ± 0.8	30.1 ± 12.5	9.6 ± 0.5	6.4 ± 0.2	2.6 ± 0.8	8.7 ± 0.4	9.4 ± 0.6	36.8 ± 18.9
$N = 9$	○	○	○*	○*	○*	○*	*	*	*

○*| = $p < .05$ between corresponding programs.

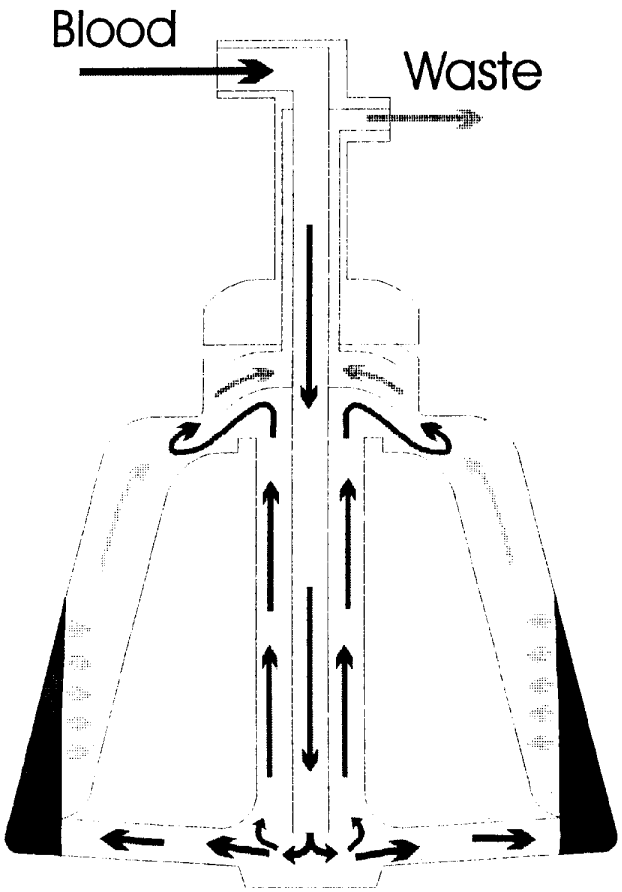


Figure 3: Processing with the conical centrifuge bowl at high flow rates showing red cell loss to waste, presumably due to pressure buildup.

flow because of premature triggering of the optical sensors by unseparated red blood cells. Wash cycles were initiated before filling the bowl properly, and the red cells were diluted further with saline wash solution. The CATS red cell mass high flow was 23% greater than the fastest program with the BRAT 2 (medium flow) and 87% greater than the fastest program of Sequestra 1000 (medium flow). Packed red blood cell flow rates proved to be misleading and erroneously indicated the greatest processing speed with DF in the high-flow programs (Table 5).

There was no visible hemolysis on naked eye examination of the supernatants; however, samples from the BRAT 2 with its cylindrical centrifuge bowl had a pale yellow color consistent with residual plasma. The depth of color increased with greater processing speeds. The washout efficiency was evaluated by comparing initial plasma albumin contents of the reservoir blood supernatant volumes before processing with those of corresponding packed red blood cells in the holding bags after processing. The supernatant residual albumin concentrations of samples taken from the holding bags after processing (packed red cells) are summarized in Table 6. Residual albumin concentration of supernatants in the holding bags increased progressively with greater processing speeds using all devices. Residual albumin concentrations using BRAT 2 was greatest in all three flow programs. In standard flow, comparison of the average albumin elimination rate with CATS and Sequestra 1000 showed no difference (Table 7). Both were greater than those of BRAT 2 ($p < .05$). In medium flow, the average albumin elimination rate with BRAT 2 was less than Sequestra 1000 ($p < .05$). In high flow, CATS was greater than both Sequestra 1000 and BRAT 2 ($p < .0001$). In all systems and programs, the albumin elimination rate decreased with an increase in HCT of the incoming blood. The mean albumin transfusion rates (Figure 4) in standard, medium, and high flow, respectively, with BRAT 2 were 447 ± 340 mg/dL, 604 ± 514 mg/dL, and 2,738 ± 167 mg/dL; with CATS were 90 ± 44 mg/dL, 337 ± 284 mg/dL, and 346 ± 357 mg/dL; and with Sequestra 1000 were 69 ± 36 mg/dL, 217 ± 125 mg/dL, and 2,277 ± 253 mg/dL. Compared with CATS and Sequestra 1000, residual albumin transfusion rates for BRAT 2 ranged up to six times greater in standard flow programs ($p < .01$) and up to three times greater in medium flow ($p < .01$). In high flow, the albumin transfusion rate of BRAT 2 and Sequestra 1000 were up to eight times greater as compared to CATS ($p < .0001$).

DISCUSSION

In confirmation of the value of intraoperative autologous transfusion practice, post-transfusion survival of salvaged red

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Table 4. Red cell mass (RCM) flow rates to the holding bags (mean ± standard deviation; mL/min) for three autotransfusion devices using three programs at reservoir hematocrits of 10, 20, and 30% as well as the means for all hematocrits

Reservoir Hematocrit	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
	Stand	Med	High	Stand	Med	High	Stand	Med	High
10% $N = 3$	19 ± 0.8	29 ± 1.2	12 ± 0.6	18 ± 0.3	23 ± 0.1	28 ± 0.4	11 ± 0.2	19 ± 0.7	7 ± 0.4
20% $N = 3$	27 ± 0.5	37 ± 0.8	22 ± 0.0	19 ± 0.3	25 ± 0.7	49 ± 3.5	17 ± 0.4	24 ± 1.2	14 ± 1.2
30% $N = 3$	32 ± 0.6	40 ± 0.3	34 ± 0.1	19 ± 1.4	24 ± 0.4	53 ± 1.7	18 ± 0.8	26 ± 2.8	24 ± 9.6
Average All $N = 9$	26 ± 5.6 °*	35 ± 4.5 °*	22 ± 9.0 °*	19 ± 1.0 °|	24 ± 0.9 °	43 ± 11.3 °|	15 ± 3.0 *°	23 ± 2.9 *	15 ± 7.0 *

Average All = three replicate procedures in each program; °*| = $p < .05$ between corresponding programs.

Table 5. Packed red blood cell (PRBC) processing rate (mean ± standard deviation; mL/min) for three autotransfusion devices using three replicate procedures in three programs

Reservoir Hematocrit	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
	Stand	Med	High	Stand	Med	High	Stand	Med	High
Average All $N = 9$	58 ± 15 °*	85 ± 17 °*	136 ± 6 °*	33 ± 2 °|	47 ± 5 °|	74 ± 21 °|	29 ± 5 *|	48 ± 7 *|	128 ± 6 *|

Average all = means of all reservoir hematocrits; °*| = $p < .05$ between corresponding programs.

Table 6. Washed packed red blood cell supernatant albumin concentrations (mean ± standard deviation; mg/dL) for three autotransfusion devices using three programs

Reservoir Hematocrit	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
	Stand	Med	High	Stand	Med	High	Stand	Med	High
Average All $N = 9$	358 ± 258 °*	395 ± 310	558 ± 265 °	114 ± 50 *	306 ± 212	474 ± 299	82 ± 45 °	194 ± 94	297 ± 152 °

Average All = means of all programs with three replicates in each; °*| = $p < .05$ between corresponding programs.

blood cells shed during surgery was studied; the radio-labeled chromium half-lives of shed red cells were reported previously to be comparable with normal values (9). In this report, quality of processed blood shed during surgery was evaluated in a defined environment using a single pool of donor banked blood to minimize variation for comparing test results. Red cells, suspended in freshly thawed, compatible frozen donor plasma were used to simulate operating room conditions in terms of blood viscosity and hemoglobin level. Comparable programs for each of the three systems were evaluated by using the same pool of blood with triplicate testing, showing close reproducibility within each program. Of the parameters studied, processing speed was the greatest factor influencing HCT, red cell recovery, and washout quality. Progressively greater processing speeds with DF devices led to decreased HCT of the packed red cells (PRBC) collected into the holding bag, and removal rates of plasma were reduced with all the devices to a varying degree.

Processed RBC must be prepared with a suitable HCT to affect a proper post-transfusion increment. The standard flow program of BRAT 2 and the standard and medium flow programs of Sequestra 1000 achieved a satisfactory HCT. HCT of the red cell products was inversely related to filling rates and the HCT of shed blood. The medium flow of BRAT 2 and high flow of both BRAT 2 and Sequestra 1000 yielded products with unacceptably low HCT. Because the separation capacity, defined by the radius of the bowl and centrifuge rotations per minute, is constant in all DF washing programs, a slower filling

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Table 7. Albumin elimination rates (mean ± standard deviation %) for three autotransfusion devices using three programs and three replicate procedures in each at 10, 20, 30%

Reservoir	Cobe BRAT 2			Fresenius CATS			Medtronic Sequestra		
Hematocrit	Stand	Med	High	Stand	Med	High	Stand	Med	High
10% $N = 3$	98.7 ± 0.4	98.4 ± 0.3	59 ± 0.4	99.4 ± 0.2	98.5 ± 0.5	98.3 ± 0.5	99.5 ± 0.04	98.6 ± 0.2	57.5 ± 2.9
20% $N = 3$	96.4 ± 2.5	96.1 ± 2.8	74.3 ± 18.2	98.3 ± 0.8	96.8 ± 0.2	94.7 ± 0.9	98.5 ± 0.5	98.0 ± 1.4	61.2 ± 2.0
30% $N = 3$	84.5 ± 0.7	79.3 ± 0.5	54.9 ± 2.8	96.2 ± 0.3	92.6 ± 1.2	86.8 ± 0.2	96.6 ± 0.1	93.3 ± 0.1	56.4 ± 1.0
Average All $N = 9$	93.2 ± 6.4 °*	91.2 ± 8.7 °	62.8 ± 3.5 °	97.8 ± 1.4 °	94.4 ± 4.6	93.3 ± 4.8 °*	98.4 ± 1.2 *	96.8 ± 2.3 °	58.3 ± 2.9 *

Average all = means for all hematocrits; °*| = $p < .05$ between corresponding programs.

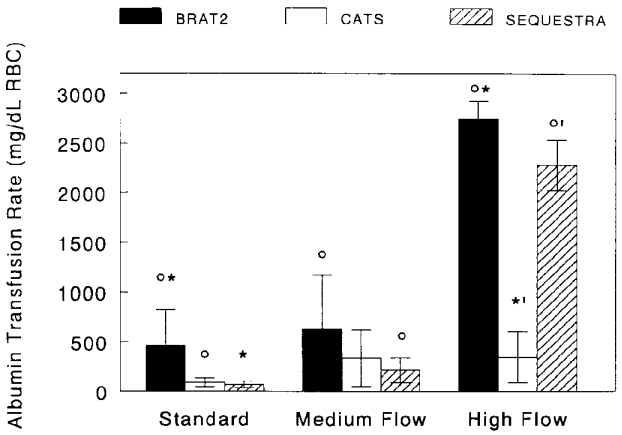


Figure 4: Mean holding bag supernatant albumin transfusion rates ± standard deviations (mg/dL/RCM) for three replicate processing runs using three autotransfusion devices in three programs; ° * = $p < .05$; $N = 9$.

rate increases the time that the red blood cells settle in the centrifuge bowl, facilitating more concentration. With increased flow and increased HCT, packing of red blood cells is reduced and, at even greater flow, poorly separated red blood cells may trigger optical sensors, falsely detecting the appropriate PRBC filling level in the bowl and initiating a premature wash cycle. Residual air in the bowl is replaced with saline wash, further diluting red cell mass. Improper red blood cell sedimentation in respective centrifuge bowls of DF devices permits excess saline retention, leading to errors with false packed red blood cell flow rates and albumin concentration measurements.

HCT was maintained at a high level during progressively increased processing speeds with CATS (54–59%). As shown in previous clinical studies at standard flow, HCT using CATS was consistently greater than a variety of DF systems (1, 5, 7, 10). HCT was between 55 and 78% using the high flow wash (2–4, 11), also confirmed in the author's operating room experience. While clinical experience with most DF equipment documented HCT results between 44 and 56% using standard flow (1, 5, 7, 10), no published data were found on the use of medium and high flow.

All laboratory and clinical data reviewed (1, 2, 5, 6) revealed no significant differences in RBC recovery using DF and CATS with standard flow programs. In medium flow of Sequestra 1000, diminished red cell recovery from red cell loss to waste was noted in the effluent line from the bowl, and was also noted in the author's operating room experience at flow rates higher than 500 mL/min; at 1000 mL/min there was almost complete red cell loss to waste. This observation was not seen with BRAT 2 and may be related to the design of the conical centrifuge bowl.

This study describes the importance of accuracy in reporting the data for red blood cell processing speeds. Packed red blood cell flow rates are invalid because of variability of HCT of samples from the holding bag. A system yielding packed red blood cells with a lower HCT seems to process blood more rapidly, but the RCM flow rate is low, and a salvaged red cell unit of inadequate potency results. The RCM flow rate is the accurate measurement. Although RCM flow increased significantly from standard to medium flow using all three systems evaluated, increased pump speeds with high flow actually failed to compensate for progressive decline in HCT of the packed red blood cells in DF systems. This was attributable to inadequate separation of red cells in the bowl of DF. Using CATS, there was progressive increase in RCM flow rates with greater processing speeds; in contrast the high flow programs of BRAT 2 and Sequestra 1000 showed markedly decreased RCM flow rates. The manufacturers of CATS claim that a constant packed red blood cell flow rate and HCT is related to preprogrammed specification of the various programs. This is substantiated in this study, even with high flow, as in the emergency wash procedure. In CATS, the RCM flow rate to the holding bag remains constant because of automatic varia-

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tion of incoming blood flow resulting from instrument adaptation to HCT of the blood from the reservoir. The processing speed with CATS may be modified during operation by selecting a processing program deemed more applicable while good product quality is maintained. In contrast, parameters of DF devices, including blood and saline flow, wash volume, and centrifuge speed, independently may be modified by the operator to increase processing speed. As shown in this study, this may lead to poor PRBC quality, even if used within permissible ranges that are recommended by the manufacturers. Changing processing parameters of DF during operation on quality may necessitate more stringent manufacturer limitations for the ranges of adjustable parameters to prevent transfusion of PRBC with questionable potency and purity.

As an indicator of plasma washout, plasma albumin endogenous in the samples proved to be a suitable analyte, because sampling or hemolysis did not interfere. Immunochemical analysis is relatively inexpensive, readily available in most clinical laboratories, and may be deferred while samples of red cell supernatant are maintained in appropriately frozen storage. Although used by many (1–3, 6–8, 11–13), potassium concentration is unreliable as a marker for washout because of spurious concentration increases from hemolysis or delay in separating supernatant from red cells. In addition, because measurement with the potassium ion selective electrode is optimized for testing in a plasma or serum medium, reproducibility was poor when measuring saline supernatants. Flame photometry, the appropriate analytical method, is very seldom used in clinical laboratories. Free hemoglobin and heparin measurements were also used by many (1–6, 12) but, because of very high dilution requirements for measurement, these methods may be too insensitive for levels encountered in shed blood. Fibrinogen and activated factor XII also were used (6) but may be unreliable markers, because erratic changes in concentration may be associated with incomplete anticoagulation.

All systems showed decreased washing efficiency with greater processing speeds. In contrast with the supernatant albumin concentration, which increased only slightly with greater flow rates, the albumin elimination rates decreased, and residual albumin transfusion rates increased very significantly. This observation was characteristic of DF systems, especially when comparing standard and high flow programs. These findings indicate that contaminating plasma proteins, including activated clotting factors, are transfused in relatively high amounts and could be significant in patients enduring estimated blood losses of one liter and more. The albumin concentration of supernatant in the holding bags is misleading; the albumin elimination and transfusion rates also reflect the variation in HCT of the packed red blood cells and are the proper parameters of quality control. Using DF devices reduced plasma washout with progressively greater processing speed related to a decreased HCT of the packed red blood cells, which reflected improper filling of the bowls. In DF, the phase of major elimination of plasma during red cell processing is when the plasma is separated to waste in a bowl that is filled properly. A respective separation of the plasma effluent during the filling cycle and the wash solution during the wash cycle into separate receptacles confirmed that 75% of plasma-free hemoglobin from shed blood was recovered in the separated plasma, and only 13% was found in the wash waste (9). Thus, the effect of the wash procedure in DF at the higher flow rates is minor and cannot compensate for insufficient plasma separation when bowls are filled incompletely.

The standard and medium flow programs of Sequestra 1000 may result in a satisfactory plasma protein elimination rate from shed blood in all surgical procedures. Using BRAT 2 with standard flow and parameters defined by the manufacturer, elimination of plasma is significantly less, and, in situations with poor blood quality, orthopedic surgery for example, using BRAT 2 may be questionable. In high-flow programs of the DF devices tested, the HCT and elimination of plasma are unacceptably low, and use of DF equipment is discouraged. All programs of CATS consistently yielded red cell products with preferred purity and potency. CATS provided red cell units with the greatest HCT, at the fastest processing speed and with the most elimination of plasma constituents, even when using high flow and may be recommended in all emergency situations without restriction. IAT is recommended as a viable transfusion option in a changing environment where autologous blood transfusion is accepted to be immunologically superior to allogeneic blood products and where costs and problems with the availability of blood products are increasing constantly.

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Effect of Portal Venous Blood Flow Diversion on Portal Pressure

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Research Article

To anticipate the hepatic vascular response to portacaval anastomosis, we studied portal pressure during diversion of portal blood through a temporary extracorporeal umbilical vein to saphenous vein shunt. The relationship of portal pressure to shunted flow was approximately linear. In five schistosomiasis patients (controls) portal diversion to 1,250 ml/min gave portal pressure-shunted flow curve slopes ranging from 0.13 to 0.57 cm water/100 ml per min (0.31±0.18, mean±SD). In 17 cirrhotic patients with portal hypertension a continuum of slopes was observed from within mean±2 SD of control (type A) to larger slopes (type B) indicating failure of portal pressure regulation. When portal flow was augmented by shunting from saphenous vein to portal vein, cirrhotic patients who had slopes less than mean±2 SD of controls during diversion (type A) exhibited a compliant system with small increases in portal pressure, whereas type B patients had significantly greater pressure increases. Selective investigations suggested that changes in portal pressure provoked compensatory changes in hepatic arterial blood flow that tended to maintain portal pressure at a set point. Type B patients demonstrated failure of this mechanism to varying degrees.

After end-to-side portacaval shunt, seven type A cirrhotic patients maintained residual intrahepatic venous pressure unchanged from prior portal pressure, whereas six type B patients had a significant decrease. Residual intrahepatic venous pressure was measured after portacaval shunt [...]

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Effect of Portal Venous Blood Flow Diversion on Portal Pressure

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ABSTRACT To anticipate the hepatic vascular response to portacaval anastomosis, we studied portal pressure during diversion of portal blood through a temporary extracorporeal umbilical vein to saphenous vein shunt. The relationship of portal pressure to shunted flow was approximately linear. In five schistosomiasis patients (controls) portal diversion to 1,250 ml/min gave portal pressure-shunted flow curve slopes ranging from 0.13 to 0.57 cm water/100 ml per min (0.31±0.18, mean±SD). In 17 cirrhotic patients with portal hypertension a continuum of slopes was observed from within mean±2 SD of control (type A) to larger slopes (type B) indicating failure of portal pressure regulation. When portal flow was augmented by shunting from saphenous vein to portal vein, cirrhotic patients who had slopes less than mean±2 SD of controls during diversion (type A) exhibited a compliant system with small increases in portal pressure, whereas type B patients had significantly greater pressure increases. Selective investigations suggested that changes in portal pressure provoked compensatory changes in hepatic arterial blood flow that tended to maintain portal pressure at a set point. Type B patients demonstrated failure of this mechanism to varying degrees.

After end-to-side portacaval shunt, seven type A cirrhotic patients maintained residual intrahepatic venous pressure unchanged from prior portal pressure, whereas six type B patients had a significant decrease. Residual intrahepatic venous pressure was measured after portacaval shunt in 40 cirrhotic patients who were followed for as long as 9 yr (median survival 4.0 yr). The 13 patients who developed chronic encephalopathy had significantly lower pressure (21.1±4.4 cm, mean±SD) and shorter survival (median 0.6 yr) than the other 27 patients (32.6±5.3 cm, 5.0 yr). The preoperative estimation of portal pressure-diverted portal flow curve slope anticipates the hepatic vascular response to portacaval anastomosis and identifies a group of patients in whom loss of portal blood flow results in a low residual intrahepatic venous pressure that is associated with early death and chronic encephalopathy.

INTRODUCTION

The increase in hepatic vascular resistance accompanying liver disease raises portal pressure and diminishes portal venous flow to the liver. Prograde portal flow may cease or even become retrograde as portal-systemic collaterals divert portal flow (1, 2). Increased hepatic arterial flow is presumed to compensate for reduced portal flow and account for normal values of total hepatic flow observed occasionally in cirrhotic patients with portal hypertension and portal systemic collateral circulation (3–6). An abrupt compensatory increase in hepatic arterial flow has been documented during acute portal flow diversion at the creation of a portacaval anastomosis (7–9). These facts imply homeostatic activity of the splanchnic vascular system to maintain portal pressure and/or hepatic blood flow when portal blood flow decreases (10–12). To evaluate the splanchnic hemodynamic response to portal blood flow diversion, we studied the response of portal pressure to acute incremental diversion of portal venous blood through a temporary extracorporeal umbilical vein to saphenous vein portal-systemic shunt (13).

METHODS

Subjects. In the schistosomiasis patients (Table I) described here, portal pressure and liver function tests including Bromsulfalein retention were normal. These patients were assumed to have normal splanchnic hemodynamics. They

This work was presented in part at the annual meetings of the American Association for the Study of Liver Disease, 4 November 1970, 1 November 1972, and 8 November 1978, Chicago Illinois; of the American Federation of Clinical Research, 12 May 1971 and 29 April 1973; and of the American College of Surgery, 14 November 1969. Abstracts were published in *Gastroenterology*. **60:** 169 (1970), **64:** 166 (1973), **75:** 996 (1978); *Clin. Res.* **19:** 406 (1971), **21:** 529 (1973); and *Surg. Forum*. **22:** 351–352 (1971), **23:** 334–336 (1972).

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were studied after heparinization, but before the administration of tartar emetic (13). The initial 17 cirrhotic patients (Table I) with documented esophageal varices were studied after umbilical vein catheterization for measurement of portal pressure (14), for umbilical vein angiography before portal-systemic shunt surgery (15), or for the establishment of an extracorporeal portal-systemic shunt to reduce portal pressure and control life threatening variceal hemorrhage (16). Subsequent patients evaluated before and after or during portacaval shunt received internal therapeutic end-to-side portacaval anastomosis after endoscopically documented variceal hemorrhage (17). In our institution umbilical vein catheterization is the preferred method for evaluating the portal circulation because of its safety and reliability (18). Informed consent was obtained from all subjects. These studies were performed under a research protocol approved by the Research Committee of the Veterans Administration Medical Center, New York, and the New York University School of Medicine.

Except where specifically indicated all procedures were performed under local anesthesia. The umbilical vein was catheterized extraperitoneally (19) and connected to a saphenous catheter by a silicon rubber tube with an occluding roller pump (solid state varistaltic pump; Manostat Corp., New York) and cannulating square wave electromagnetic flow meter (model E-3000; Statham Instruments Inc., Oxnard, Calif.). The umbilical vein catheter has an integral molded wire to prevent collapse and a second 1-mm lumen within its wall to allow continuous recording of portal pressure (model 1956 SP-BJBI, U. S. Catheter and Instrument Co., Glen Falls, N. Y.). Pressures were recorded using Statham P37 perfused strain gauges that permitted a continuous infusion of heparin (0.1 mg/min). Electrical mean pressures were used to obviate respiratory fluctuation. Zero pressure level was taken as 12 cm above the couch.

The hepatic vein was catheterized from an antecubital vein (20, 21). The achievement of a wedged position was confirmed by the demonstration of an arterial pulse in the pressure recording, by the identity of wedged hepatic venous pressure and portal pressure, and by injection of radiopaque contrast at the completion of a study.

Flow through the extracorporeal shunt was monitored by the cannulating square wave flow meter calibrated for zero flow with the shunt occluded. In vitro calibration for flow rates to 3,000 ml/min with pumped whole blood and occluding roller pump yields an accuracy of ±5%. The pumping circuit was primed with 200 ml of normal saline.

Procedure. After catheter placement and shunt construction, portal pressure was recorded and portal to systemic shunting initiated at 100 ml/min. Stabilization of pump rate required 5–10 s. By that time, pressures were stable and were recorded. Shunting was increased in 100 ml/min increments. When maximum hepatofugal flow was achieved as evidenced by portal vein flutter, shunting was stopped and pressure recorded. Systemic to portal shunting was then begun in 100 ml/min increments until limited by saphenous vein flutter. The shunting portion of the procedure required 15–20 min.

The response of portal pressure to shunting at different

TABLE I

Effect of Portal Venous Flow Diversion or Augmentation on Portal Pressure

Case	Diagnosis etiology	Documentation	Ascites (-4+)	Direction portal flow	Basal PP	Hepatofugal pumping			Hepatopetal pumping		
						Max flow	Pressure change	Pressure-flow slope	Max flow	Pressure change	Pressure-flow slope
					cm	*ml/min*	*cm*	*cm/100 ml*	*ml/min*	*cm*	*cm/100 ml*
1	C,A	Biopsy	0	Prograde	37	1,100	0	0.00	500	+2	+0.40
2	S	—	—	Prograde	15	750	−1	−0.13			
3	S	—	—	Prograde	11	1,200	−2	−0.17			
4	C,A	Biopsy	+1	Prograde	35	1,450	−3	−0.20			
5	S	—	—	Prograde	15	1,250	−3.5	−0.28			
6	C	Biopsy	3+	Prograde	27	1,600	−6	−0.38	1,000	+3	+0.30
7	S	—	—	Prograde	14	1,100	−5	−0.43			
8	C,A	Biopsy	0	Retrograde	37	900	−4	−0.44			
9	C,A	Biopsy	0	Prograde	36	1,000	−5	−0.50	700	+1	+0.14
10	S	—	—	Prograde	8	700	−4	−0.57	1,100	0	0.0
11	C,A	Biopsy	2+	Retrograde	39	1,700	−10	−0.59	1,200	+1	+0.08
12	C,A	W,biopsy	0	Prograde	35	2,500	−15	−0.60	900	+2.5	+0.27
13	C,HEM	Biopsy	+1	Prograde	29	1,500	−9	−0.60	600	+3	+0.50
14	C,A	Biopsy	0	Prograde	39	1,500	−13	−0.87	1,000	+16	+1.6
15	C,A	W,biopsy	2+	Prograde	42	600	−6	−1.00	1,400	+6	+0.43
16	C,A	Biopsy	1+	Prograde	26	1,000	−10	−1.00	750	+9	+1.20
17	C,CR	Biopsy	1+	Prograde	29	850	−18	−2.11			
18	C,A	Autopsy	0	Prograde	37	900	−28	−3.10	700	+11	+1.57
19	C,A	Biopsy	2+	Prograde	39	900	−31	−3.44	700	+9	+1.28
20	C,A	Biopsy	4+	Prograde	35	800	−31	−3.87			
21	C,A,HEP	Biopsy	0	Prograde	55	1,100	−48	−4.36			
22	C,A	Biopsy	0	Prograde	35	500	−30	−6.00	500	+18	+3.6

Abbreviations used in this table: C, cirrhosis; S, schistosomiasis; A, alcoholism; HEM, hemachromatosis; HEP, hepatoma; CR, cryptogenic; W, wedged hepatic venous pressure; PP, portal pressure; max, maximum.

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vascular volumes was studied after phlebotomy accomplished by draining the extracorporeal circuit into a sterile infusion bottle containing 20 mg of heparin. 1 liter of blood was withdrawn in 3 min. After studying the response of portal pressure to shunting the blood was reinfused. Then, for volume expansion 5% dextran or blood was infused. Final volume was dictated by the patient's clinical status (22). Since the elapsed time for phlebotomy and volume expansion was <15 min, vascular volume shifts were considered to be negligible. Therefore, changes in blood volume were calculated from the measured quantity withdrawn or infused.

At the completion of a study the direction of portal venous flow (prograde or retrograde) was determined by observing the course of a gentle hand injection of 50% sodium diazotrate (Hypaque, Winthrop Laboratories, Sterling Drug Co., New York) through the primary lumen of the umbilical vein catheter (3). Radiopaque contrast media were not administered before pressure or flow measurements because of their effect on systemic and splanchnic hemodynamics (23). Finally, a pressure injection with serial x rays was used to visualize the portal vasculature (15).

Definition of residual intrahepatic venous pressure. Wedged hepatic venous pressure and portal pressure measured by umbilical vein catheterization are identical in patients with cirrhosis when the portal circulation is intact (24). Simultaneous measurement of wedged hepatic venous pressure and umbilical portal pressure in two cirrhotic patients during shunting of portal flow agreed within ±1 cm water (Fig. 1). After disconnection of the extrahepatic portal venous system from the liver by end-to-side portacaval shunt, residual intrahepatic venous pressure was measured by wedged hepatic venous catheterization or by umbilical vein catheterization of the intrahepatic portal vein. The extrahepatic portal venous system drains into the vena cava.

Construction of portal pressure-shunted portal flow curves. Curves constructed for controls with *Schistosoma mansoni* infections and cirrhotic patients with portal pressure-shunted portal flow curve slopes < -0.67 cm water/100 ml per min diverted flow were linear (Figs. 1 and 2) and allow a simple arithmetic expression of slope as change in pressure/100 ml per min shunted flow. Cirrhotic patients with steep slopes have a smaller range of flow and curves that are increasingly convex (Figs. 2 and 3). For the purpose of this paper, the arithmetic portal pressure-shunted portal flow curve slope is derived from the sum change in pressure divided by maximum flow before vein flutter was detected by palpation of the shunt or pumping was stopped because of increased portal pressure. As indicated, certain patients were studied at laparotomy under anesthesia or during rescuscitation from hemorrhage. These circumstances provide unique opportunities to gain physiologic insights in man but undoubtedly influence to a greater or lesser extent the data obtained. Therefore, we confined data in Table I describing the control (schistosomiasis) patients and values in cirrhotic patients with portal hypertension for portal pressure-shunted portal flow curve slope to subjects studied without anesthesia or laparotomy when hemodynamically stable.

Statistical significance was determined with the Wilcoxon two sample ranked test, unpaired t test, and log rank test (25, 26).

RESULTS

Schistosomiasis (control) subjects

During portal to systemic shunting averaging 1,000 ml/min (range, 700–1,350) in five schistosomiasis pa-

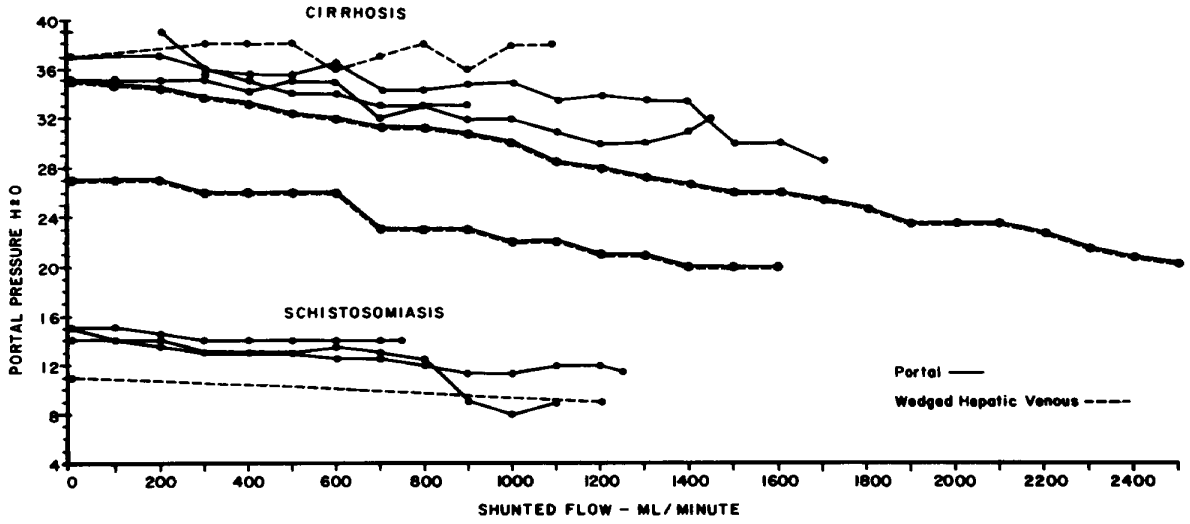


FIGURE 1 Response of portal pressure to portal venous blood flow diversion in type A cirrhotic patients and control subjects. Portal pressure (centimeters water) is plotted against volume of shunted portal venous flow (milliliters per minute) diverted through an umbilicosaphenous shunt. Six representative cirrhotic patients are shown in order of decreasing basal portal pressure (case Nos. 11, 1, 8, 4, 12, and 6, Table I). Four representative controls (2, 5, 7, and 3, Table I) are shown in order of decreasing basal portal pressure. The solid line indicates portal pressure measured through an umbilical vein catheter in the left portal vein. The interrupted line indicates portal pressure measured by wedged hepatic venous catheterization. The combined solid and interrupted lines in two cirrhotic patients (11, 1, Table I) indicate simultaneous measurement of portal and wedged hepatic venous pressures.

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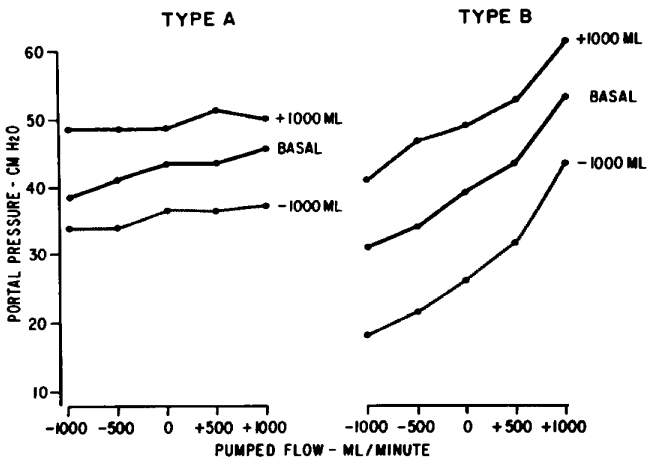


FIGURE 2 Effect of changes in blood volume on portal pressure and portal pressure-shunted flow curve slope. In a single type A patient (left) basal portal pressure of 43 cm was reduced to 36 cm by a 1,000-ml phlebotomy and increased to 48 cm by a 1,000 ml-volume load in addition to replacement of the 1,000-ml phlebotomy, whereas portal pressure-shunted flow slope varied from 0.35 to 0.15 to 0.10 cm/100 ml per min shunted flow, respectively. In a single type B patient, a basal portal pressure of 39 cm was reduced to 26 cm by a 1,000-ml phlebotomy and increased to 48 cm by a 1,000-ml volume load after replacement of the phlebotomy, whereas portal pressure-shunted flow curve slope varied from 1.15 to 1.25 to 1.05, respectively.

tients portal pressure decreased an average of 3.1 cm water (range, 1–4). Portal pressure-shunted portal flow slope averaged -0.31 ± 0.18 (mean±SD) cm water/100 ml per min diverted flow (range -0.13 to -0.57) (Table I).

Cirrhotic patients

In cirrhotic patients (n = 17) with portal hypertension, the response to portal diversion was varied and the portal pressure-shunted portal flow slope ranged from -0.0 to -6.0. In patient 1 (Table I) portal pressure was unchanged by portal diversion of 1,000 ml/min, whereas in patient 22 (Table I) portal pressure fell to central venous levels with diversion of only 500 ml/min (Table I). A histogram (Fig. 4, upper) of portal pressure-shunted portal flow slope during diversion in cirrhotic patients with portal hypertension shows a continuum from slopes similar to *S. mansoni* patients with normal portal pressure (Fig. 4, hatched bars) to extremely high values. A relationship between basal portal pressure and portal pressure-shunted portal flow slope is not apparent (Table I). The lack of correlation between portal pressure and portal pressure-shunted portal flow slope arises, in part, from the influence of blood volume on portal pressure (Fig. 2). Increasing or decreasing blood volume produces a corresponding shift in portal pressure (22) with little change in portal pressure-shunted portal flow slope.

Definition of type A and B cirrhotic patients

Type A cirrhotic patients (Figs. 1 and 2) are defined as those with portal pressure-shunted portal flow slopes < -0.67 cm/100 ml per min (control mean±2 SD). Type B cirrhotic patients have portal pressure-shunted portal flow slopes in excess of -0.67 cm/100 ml per min diverted flow (Table I, Figs. 2 and 3). In the initial 17 patients studied (Table I) the mean basal portal pressure (34.4±4.2 cm of water, mean±SD) of eight cirrhotic patients with portal pressure-shunted flow slopes for portal flow diversion within the mean±2 SD of the five control (schistosomiasis) patients was not significantly different from the mean basal portal pressure (37.4±8.3 cm) of the nine cirrhotic patients with greater slopes. Similarly, in a group of 13 patients clinically considered candidates for portacaval anastomosis (Fig. 5), the basal portal pressures of seven type A patients were not significantly different from the six type B patients. The 23 cirrhotic patients with endoscopically documented bleeding esophageal varices classified as type A or type B when hemodynamically stable under local anesthesia had basal portal pressure ranging from 55 to 26 cm. The 55-cm value (Table I, No. 21) occurred in a patient with hepatoma. Although the three highest values (55, 45, and 42 cm) and the two lowest values (26 and 28 cm) were found in type B patients, the pressures of type A patients were not significantly different (Wilcoxon rank test) from type B.

Mechanism for maintenance of portal pressure during portal venous flow diversion

Hepatic arterial response to extracroporeal portal diversion. Hepatic arterial flow was measured at laparotomy for portacaval anastomosis by noncannulating square wave electromagnetic flow meter in two type A cirrhotic patients before and during diversion of 1 liter/min. Hepatic arterial flow increased 40 and 46%.

Spontaneous total retrograde portal flow in type A portal hypertension. Two (Nos. 8 and 11) of 17 cirrhotic patients described had total retrograde portal venous flow (Table I) (3). Both had type A portal hypertension with portal pressure-shunted portal flow slopes of 0.44 and 0.59 cm/100 ml per min. The presence of total retrograde portal flow implies sufficient portal-systemic collateral vessels for egress from the splanchnic chamber of all splenic and mesenteric inflow and a portion of hepatic arterial flow. The most likely source for additional splanchnic inflow to maintain portal pressure during portal diversion in this situation is the hepatic artery.

Portal pressure response to portal flow augmentation by systemic to portal shunting. In portal hypertension an added load should increase portal pressure, since mechanisms for reducing splanchnic inflow or in-

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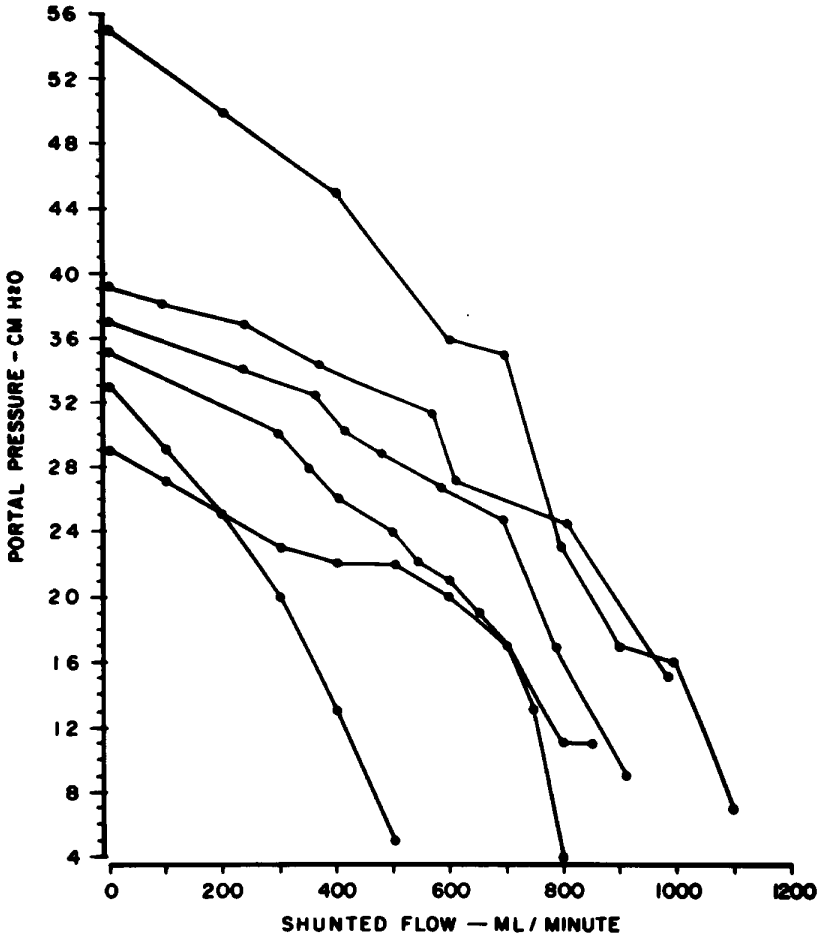


FIGURE 3 Response of portal pressure to portal diversion in type B cirrhotic patients. Portal pressure (centimeters water) is plotted against volume of portal venous flow diverted through the umbilicosaphenous shunt. Six representative type B cases in order of decreasing basal portal pressure (case Nos. 21, 19, 18, 20, 22, and 17, Table I) are shown.

creasing outflow already would be activated by existing portal hypertension. Type A patients accommodate their portal pressure as well to portal flow augmentation as diversion (Table I, Figs. 2 and 4). Portal pressure-shunted portal flow curve slopes are more varied for augmentation but are similar to slopes (Table I) for diversion in the 12 patients where both maneuvers were performed (Fig. 4).

Type A cirrhotic subjects who during portal diversion had portal pressure-shunted portal flow slopes less than the mean±2 SD of control exhibit a compliant system in that relatively small increases in portal pressure were observed (range, +0.08 to +0.50, mean±SD, 0.3±1.6 cm/100 ml per min, $n = 6$). Cirrhotic patients with steep type B slopes during portal diversion demonstrated steep slopes during augmentation (range, +0.43 to +3.60, mean±SD, 1.6±1.1 cm/100 ml per min, $n = 6$) that were increased ($P < 0.01$) when compared to the compliant group. The basal portal pressures of the eight cirrhotic patients with type A slopes (34.4±4.2 cm water, mean±SD) were not significantly different from the nine cirrhotic patients with type B slopes (37.4 ±8.3 cm water).

Induced retrograde portal flow during portal venous flow diversion. If increasing hepatic arterial flow, rather than changing portal-systemic collateral, splenic, or mesenteric inflow, accounts for the maintenance of portal pressure during portal diversion, sampling of indocyanine green from the umbilicosaphenous shunt during diversion should demonstrate extraction of indocyanine green from portal blood when increased hepatic arterial flow reverses through hepatic sinusoids to enter the extracorporeal circuit. At laparotomy for portacaval shunt with 750 ml/min portal diversion, prograde portal flow was evidenced by absence of extraction. Retrograde flow of hepatic arterial blood into the

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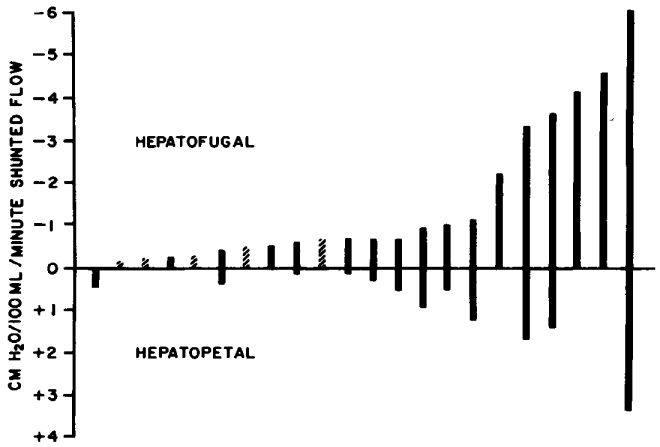


FIGURE 4 Histogram of portal pressure-shunted portal venous flow slope. Patients 1 (left) through 22 (right) are presented in order of increasing slope (Table I). The upper bars refer to the slope for portal diversion (hepatofugal shunting). The lower bars refer to the slope for portal blood flow augmentation (hepatopetal shunting) performed in 12 patients. Hatched bars indicate schistosomiasis patients (controls).

portal vein with extraction occurred at diversion rates in excess of 1,000 ml/min. This type A patient (Table IIA) accommodated to 1,000 ml/min portal diversion or augmentation (portal pressure-shunted portal flow slope −0.3, +0.0) with little change in portal pressure.

Portal pressure and intrahepatic venous pressure response to occlusion of hepatic artery or portal vein. Intraoperative occlusion of hepatic artery or portal vein before and during diversion of blood from the hepatic side of the occluded portal vein was studied in two patients to compare hepatic artery and portal venous (splenic and mesenteric) capacity to sustain intrahepatic venous pressure (Table II). Intrahepatic venous pressure was measured and blood was shunted through the umbilical catheter on the hepatic side of the occluded portal vein.

The type A patient maintained intrahepatic venous pressure with flow from either hepatic artery or portal vein (Table II experiments 5A and 6A). Portal venous flow alone maintained portal venous pressure when the hepatic artery was occluded (experiment 5A) suggesting adequate portal flow to support pressure. When portal flow is stopped, hepatic artery flow is adequate to prevent a reduction in intrahepatic venous pressure (experiment 6A). The response to 1,000 ml/min portal to systemic shunting between the site of portal vein occlusion and the liver (experiment 7A) shows the hepatic artery to have a greater capacity to support intrahepatic venous pressure than mesenteric and splenic vessels, since pressure falls less when the portal vein is occluded and the hepatic artery supplies the liver (experiment 8A) than when the hepatic artery is occluded and the portal vein supplies liver (experiment 7A). This suggests that increased hepatic artery flow is the most important mechanism in maintaining portal pressure during portal diversion in this type A patient.

In a type B patient (Table II) occlusion of the portal vein precipitated an 11-cm decrease in intrahepatic venous pressure (experiment 6B) indicating the failure of hepatic artery flow to maintain pressure. This inadequacy was exaggerated by simultaneous portal vein occlusion and portal diversion (Experiment 8B). This type B patient relies on portal flow to sustain intrahepatic venous pressure. The failure of hepatic artery occlusion to reduce portal pressure (experiment 5B) indicates a small hepatic artery contribution to maintenance of portal pressure in this patient. The steep portal pressure-shunted portal flow slope when the portal vein is patent (experiment 2B) demonstrates the failure of portal-systemic collateral flow to compensate for increasing or decreasing portal flow.

Maintenance of residual intrahepatic venous pressure after end-to-side portacaval anastomosis. If the portal pressure-shunted portal flow slope estimates he-

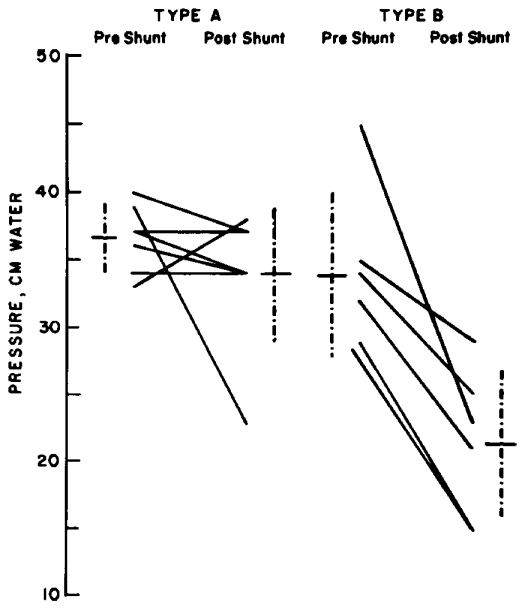


FIGURE 5 Effect of total portal venous flow diversion by end-to-side portacaval anastomosis on intrahepatic venous pressure in type A and type B patients. The horizontal solid bar indicates the mean. The vertical interrupted line indicates SD. Preoperative portal pressures for type A and type B patients were not significantly different. After portacaval shunt mean intrahepatic venous pressure in type B patients (21.3±5.6, $n = 6$) is significantly decreased ($P < 0.01$) when compared to preshunt portal pressure or postshunt intrahepatic venous pressure in type A patients (33.9±5.0, $n = 7$). Four type A and four type B patients shown here had portal pressure-shunted portal flow slope determined under anesthesia at laparotomy for portacaval anastomosis and are excluded from Table I.

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TABLE II
Response of Intrahepatic Venous Pressure to Occlusion of Hepatic Artery and Portal Vein

Experiment	Hemodynamic type	A	B
1	Basal portal pressure	46	29
2	Portal pressure during diversion, 1,000 ml/min	43	16
3	Portal pressure during augmentation, 1,000 ml/min	46	37
4	Pressure-flow slope (cm water/100 ml per min)		
	diversion	−0.3	−1.3
	augmentation	+0.0	+0.8
5	Portal pressure with hepatic artery occluded	44	31
6	Intrahepatic pressure with portal vein occluded	44	18
7	Portal pressure with hepatic artery occluded plus diversion, 1,000 ml/min	35	22
8	Intrahepatic pressure portal vein occluded plus diversion, 1,000 ml/min	39	3

patic vascular capacity to sustain portal pressure during portal venous diversion, the residual intrahepatic venous pressure after end-to-side portacaval anastomosis when the hepatic artery alone supplies the liver should correlate with the preoperative portal pressure and postoperative intrahepatic venous pressure. In 13 patients undergoing end-to-side portacaval anastomosis (Fig. 5) after determination of portal pressure-shunted portal flow slope preoperative portal pressure in seven type A patients (36.6±2.5 cm, mean±SD) was not significantly different from six type B patients (33.8±6.1 cm). After end-to-side portacaval anastomosis in type A patients intrahepatic venous pressure was not significantly changed (33.9±5.0) indicating hepatic vascular compensation for loss of portal venous flow. Type B patients suffered a decrease in intrahepatic venous pressure (21.3±5.6) that was significant when compared to their preoperative portal pressure ($t = 3.38$, $P < 0.01$) or to the postoperative intrahepatic venous pressure of the type A patients ($t = 3.90$, $P < 0.01$).

Residual intrahepatic venous pressure after end-to-side portacaval shunt and prognosis. Our initial clinical observations suggested that type B patients in whom residual intrahepatic venous pressure fell after portacaval anastomosis (Fig. 5) frequently died shortly after surgery or suffered from chronic encephalopathy. Therefore, residual intrahepatic venous pressure was measured in 40 patients with cirrhosis associated with ethanol abuse shortly after interval end-to-side portacaval anastomosis when they were hemodynamically stable. The patients were followed clinically for as long as 9 yr (median, 4.0 yr). 13 patients developed chronic hepatic encephalopathy defined as diminished mental function that was improved by and required continued dietary protein restriction and antibiotic or lactulose therapy. Six of these died within 1 mo of surgery and were classified as early deaths (Fig. 6). The mean residual intrahepatic venous pressure of these 13 patients (21.1±4.4 cm) was significantly less ($P < 0.001$) than the 27 patients that did not have chronic encephalopathy (32.6±5.3 cm).

Life table analysis (25, 26) demonstrated a significantly ($P < 0.01$) shorter survival (median, 0.6 yr) for the 13 patients with lower pressures when compared to the other patients (median, 5.0 yr) (Fig. 7). None of the 27 patients with relatively favorable postoperative courses had a residual intrahepatic venous pressure <25 cm. 6 of 8 patients who died within 1 mo, 8 of 10 patients who died within 1 yr, and 6 of 7 patients who survived the postoperative period, but suffered from chronic encephalopathy, were unable to maintain residual intrahepatic venous pressure above 25 cm. These findings suggest that 25 cm is a critical lower limit of pressure, below which hepatic function is not maintained and chronic encephalopathy with early death supervenes.

DISCUSSION

A lesser fall in portal pressure than would be expected for a given quantity of portal blood flow diversion indicates a compensatory vascular mechanism. Therefore, the steepest portal pressure-shunted portal flow slope observed (Table I, patient 22) most clearly approaches the absence of this postulated mechanism. Lesser slopes result from its activity. The failure of the portal pressure-shunted portal flow slope to be altered by changing blood volume, portal pressure, and presumably cardiac output (27) points to a splanchnic rather than systemic origin of the proposed mechanism. The small portal pressure-shunted portal flow slopes recorded in control subjects may reflect both low and variable hepatic resistance to flow (28, 29). Similarly, a lesser increase in portal pressure than expected during portal blood flow augmentation by systemic to portal shunting in the presence of portal hypertension suggests a compensatory decrease in arterial inflow to the splanchnic chamber since hepatic and portal-systemic collateral outflow resistance should be limiting when cirrhosis and portal hypertension are present (30–32). Failure or absence of this mechanism in some patients with cirrhosis is indicated by the continuum of portal pressure-shunted portal flow slopes observed.

An increase of mesenteric and splenic venous flow

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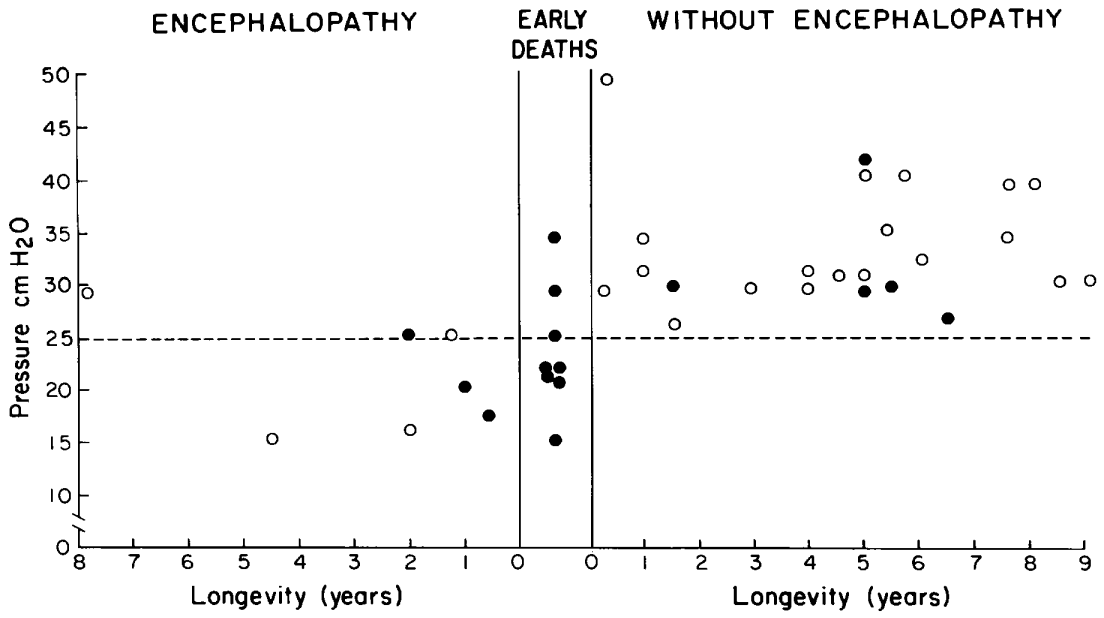


FIGURE 6 Relationship of survival and clinical status (encephalopathy) to residual intrahepatic venous pressure after end-to-side portacaval anastomosis (open circle, alive; closed circle, dead). The 13 patients with encephalopathy (left) had significantly lower pressures than those without encephalopathy (right, $n = 27$) and a significantly shorter survival (median, 0.6 vs. 5.0 yr). Early mortality is defined as death within 1 mo of surgery.

in response to reduced portal pressure is suggested by the maintenance of portal pressure despite hepatic artery occlusion (Table II) and published studies demonstrating an increase in portal and splenic flow after portacaval anastomosis (10, 33). Hepatic (9, 34–36), mesenteric, and splenic (33) arteries may all contribute to maintenance of portal pressure in type A patients when the portal circulation is intact. Conversely, the steep portal pressure-shunted portal flow slopes in type B patients indicate a limited response of all these vessels to changing portal flow and suggests a widespread defect in vascular function.

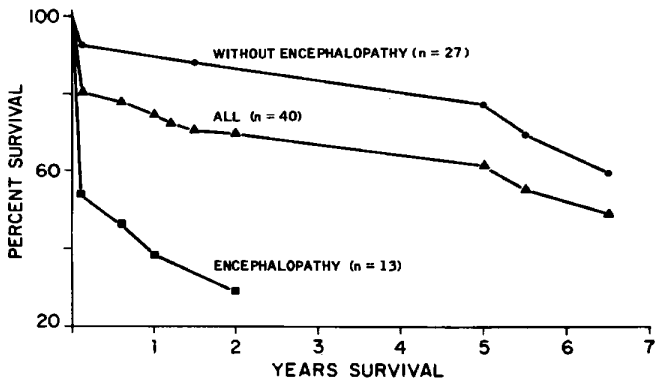


FIGURE 7 Life table analysis of 40 patients followed for up to 9 yr after end-to-side portacaval anastomosis (center curve, all patients). The 13 patients with chronic encephalopathy had a lower residual intrahepatic venous pressure and reduce median survival (0.6 yr, lower curve) when compared to the 27 patients with residual intrahepatic venous pressure > 25 cm and medial survival 5.0 yr who did not have chronic encephalopathy (highest curve). The highest and lowest curves are significantly different (log rank test, $P = 0.01$). Cumulative survival for the 13 patients in the lower curve was not carried beyond 2 yr because experience was limited to only two patients surviving beyond this point.

Abnormal vascular responses in the cardiac (37, 38), pulmonary (39), renal (40), integumentary (41), and splanchnic (36) systems have been demonstrated in patients with liver disease. The increased cardiac output (37) functional renal failure (42) and portal hypertension (43) of liver disease may be reversible. The portal hypertension of cirrhotic patients in this study consisting of an elevated portal pressure setpoint and a variable limitation of the response to changing portal flow also, at least in part, may be a reversible alteration in vascular responsiveness (44) rather than a consequence of the presumed fixed anatomic hepatic outflow block previously conceived as the cause of portal hypertension (45).

Alternatively, the continuum of response to changing portal flow could result from anatomic alterations in the hepatic artery associated with cirrhosis (46, 47). Herrick (48), and later Dock (49), perfused the livers of alcoholic hypertropic cirrhotic patients in vitro and demonstrated a reciprocal relationship between hepatic arterial pressure and portal pressure. They speculated on the role

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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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Literature display help

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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.

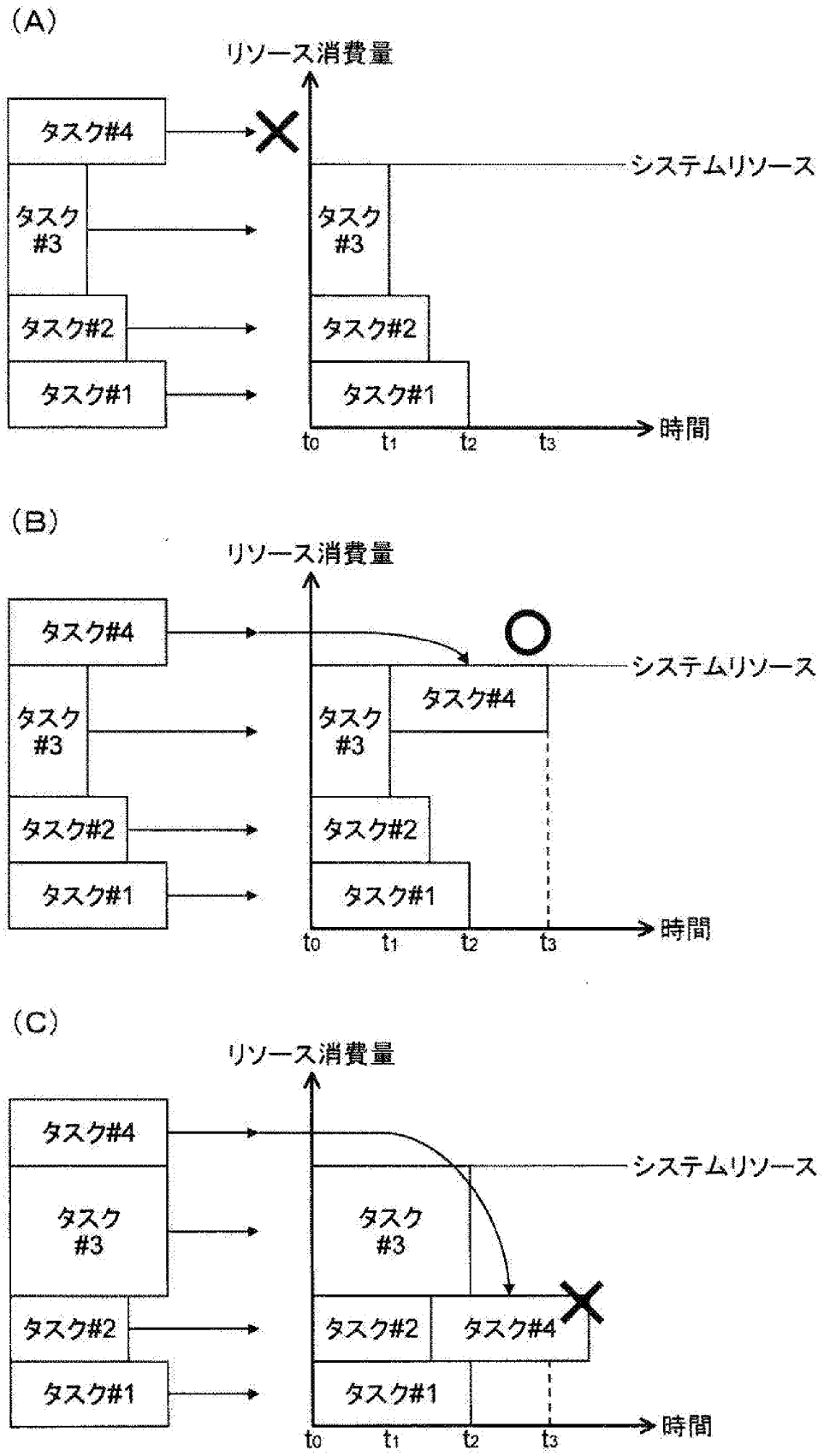
Although the present embodiment has been described above

, 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

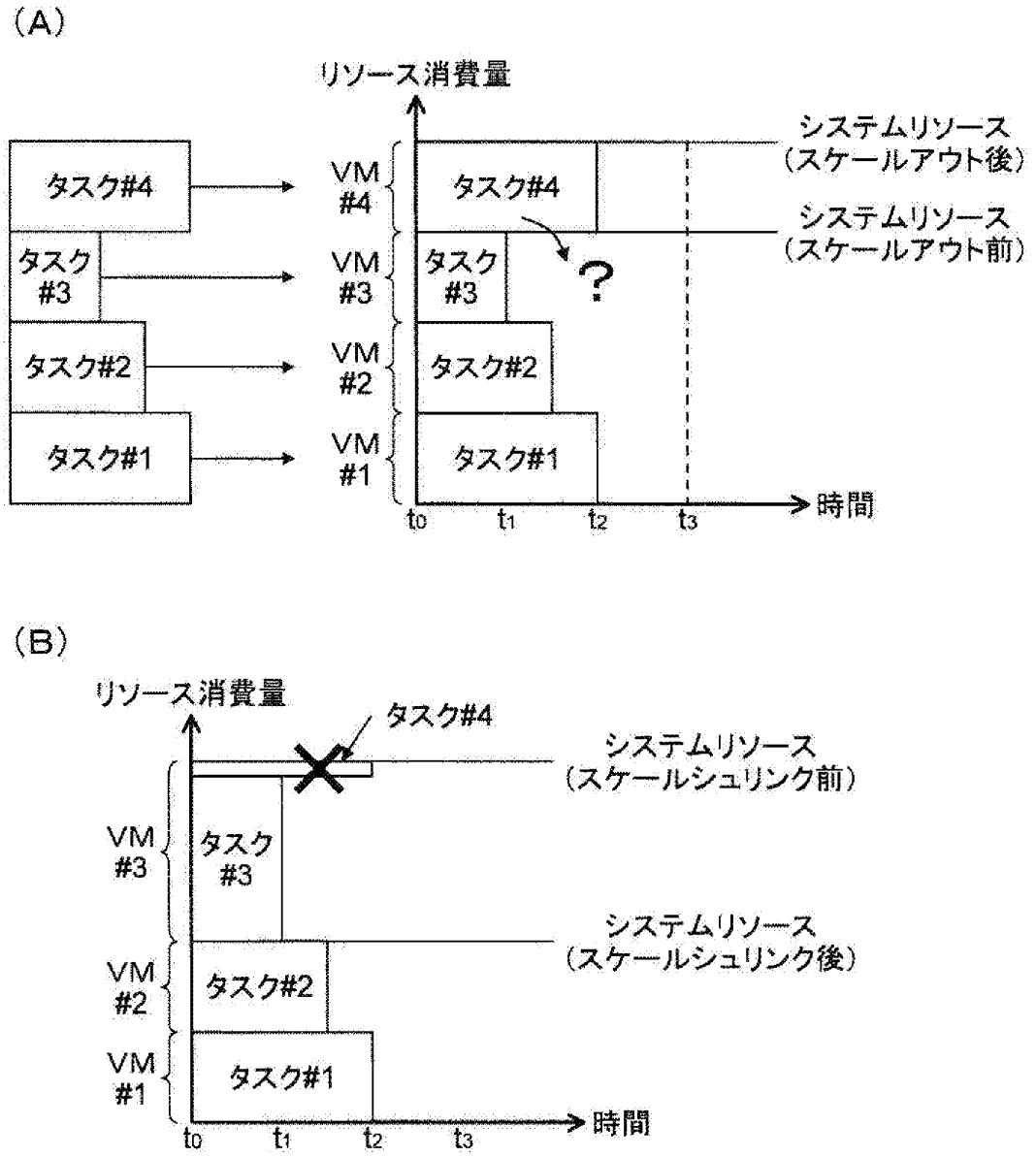
System 110 Master node 111 Client communication unit 112 Schedule processing unit 113 Schedule information storage unit 114 Scale-out processing unit 115 Slave communic ation unit 116 Reschedule processing unit 117 Scale shrink processing unit 120 Slave nod e 121 Master Communication unit 122 Application 200 Client 300 Network

drawing open —

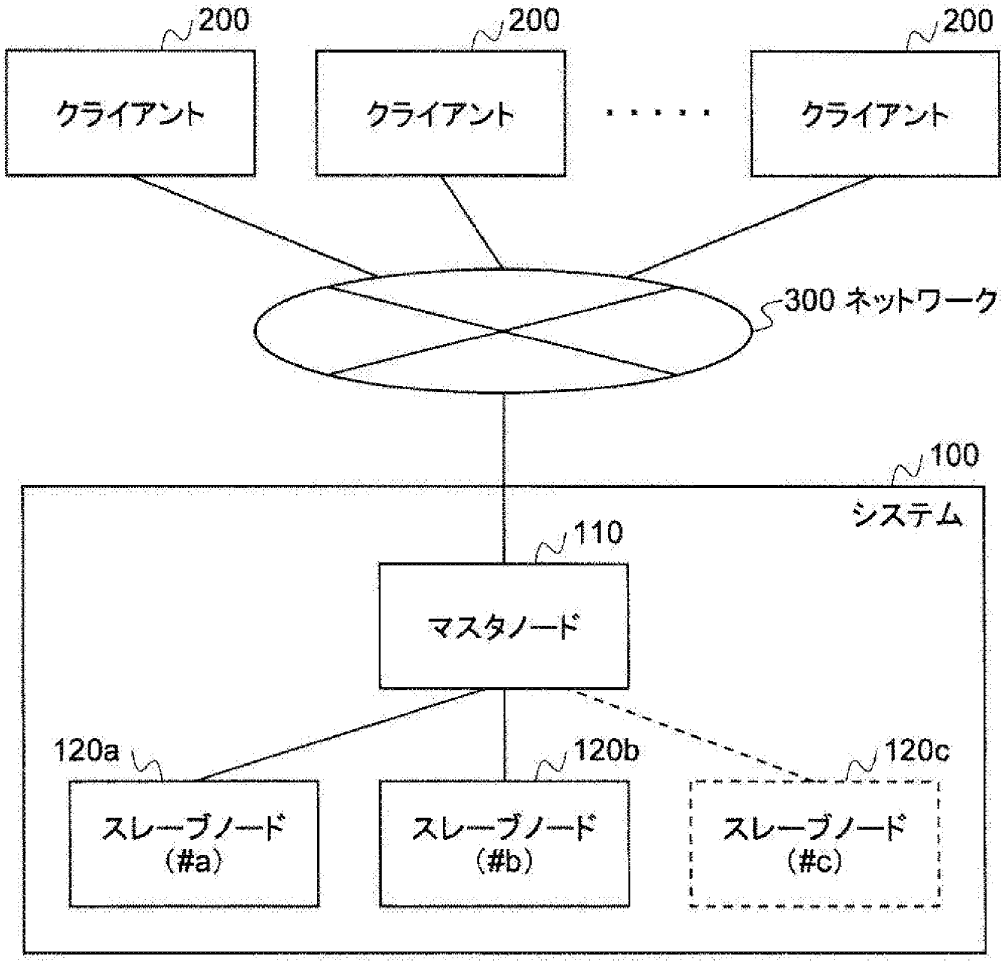
[Fig. 1]


(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

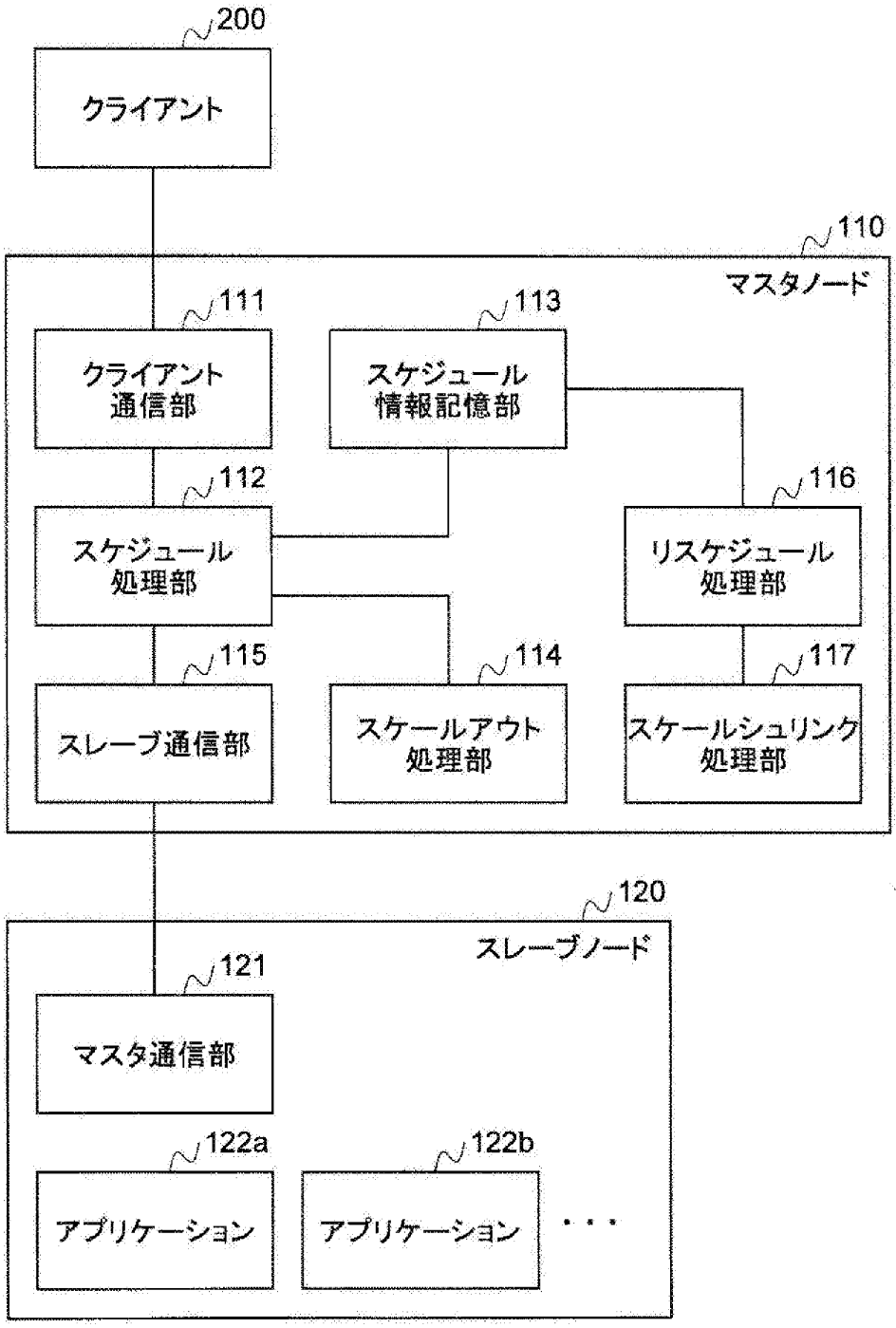
[Figure 2]


(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

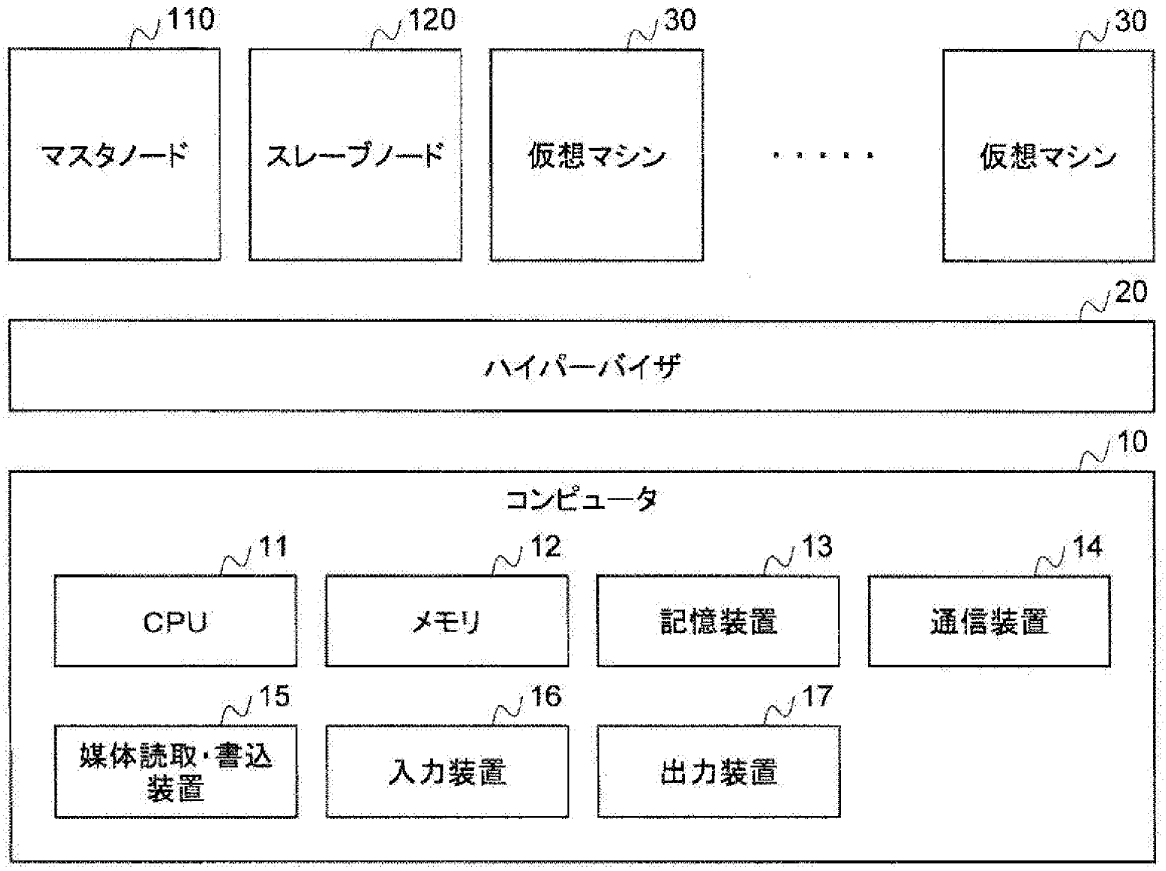
[Figure 3]


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)

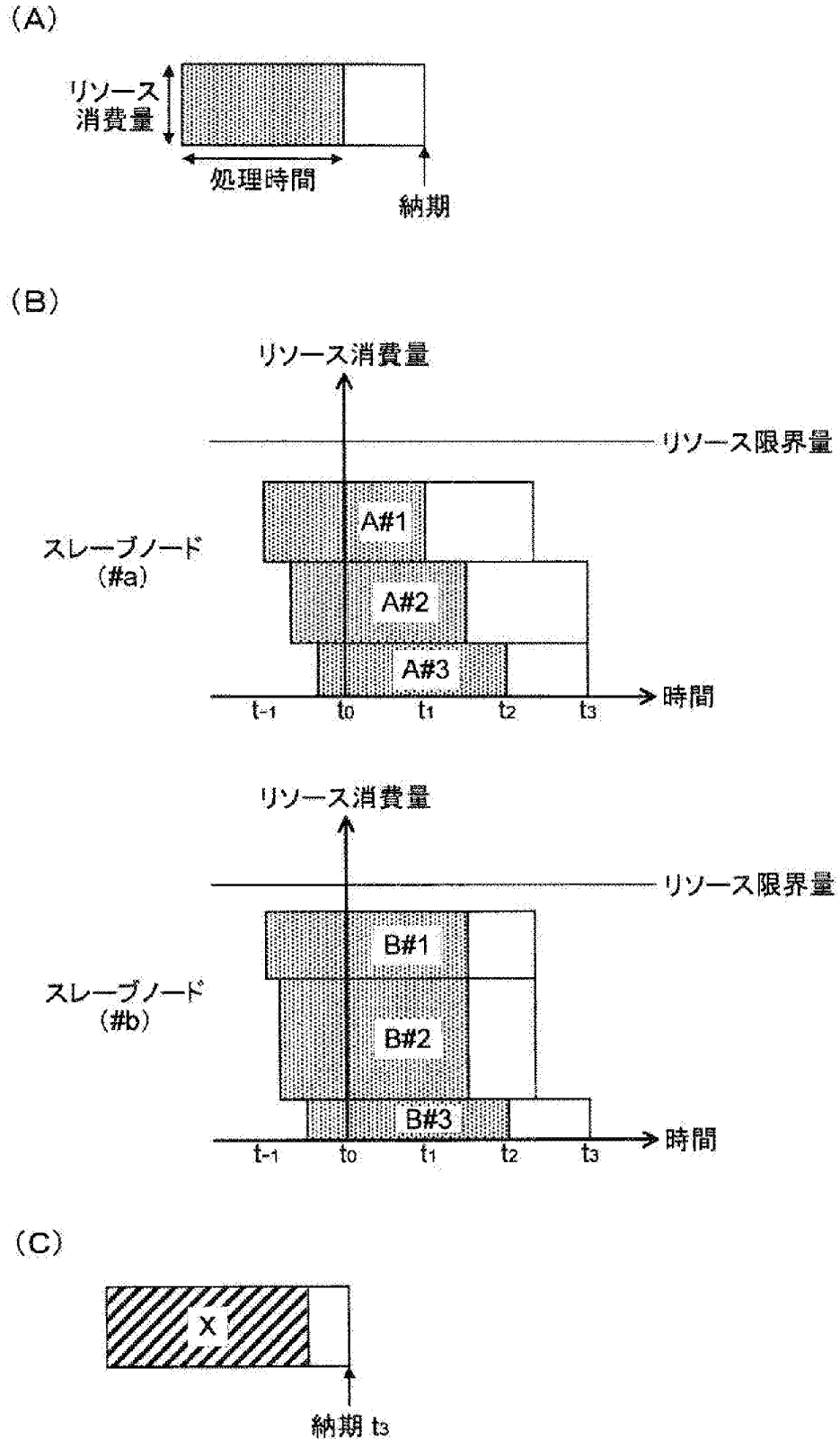
[Figure 4]


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]

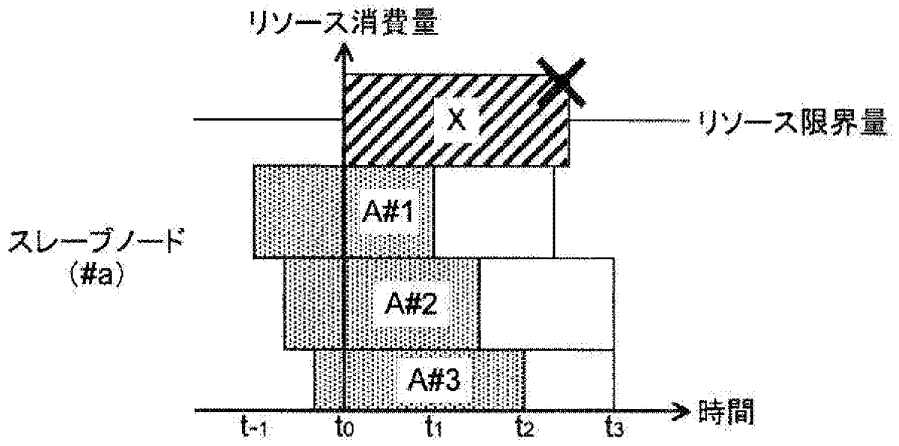

110
120
30
30
マスタノード
スレーブノード
仮想マシン
・・・・・
仮想マシン
20
ハイパーバイザ
10
コンピュータ
11
12
13
14
CPU
メモリ
記憶装置
通信装置
15
16
17
媒体読取・書込装置
入力装置
出力装置

[Fig. 6]

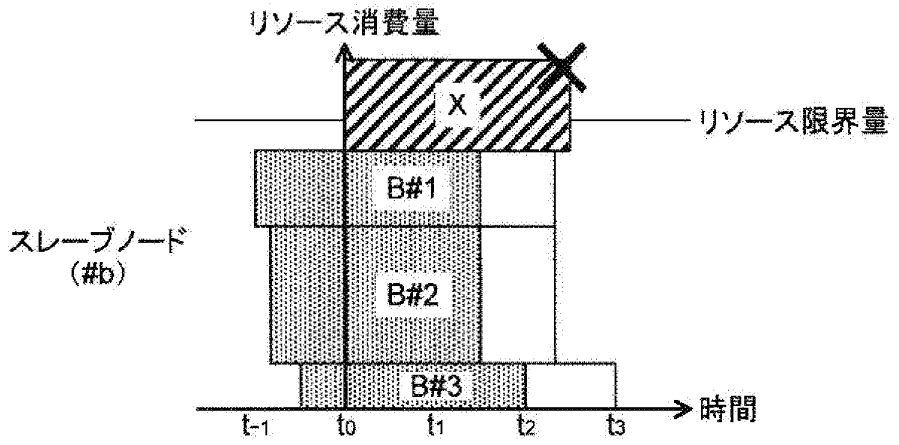

(A)
リソース
消費量
処理時間
納期
(B)
リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
t-1
t0
t1
t2
t3
(C)
X
納期 t3

[Fig. 7]

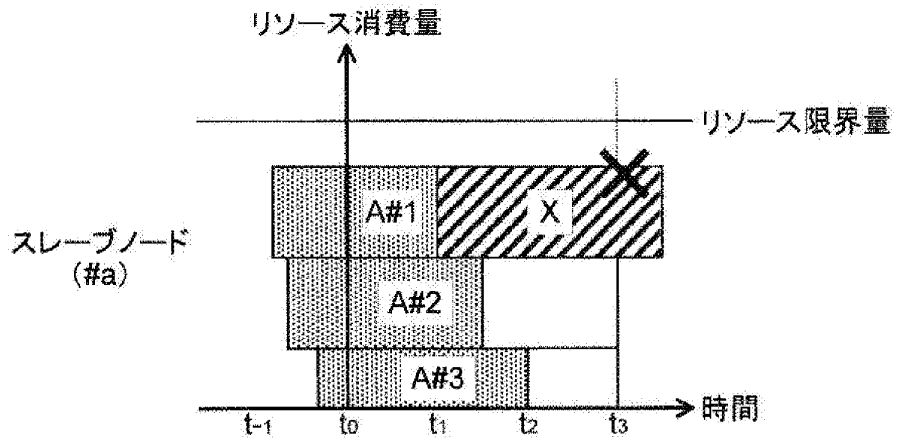
（A）


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

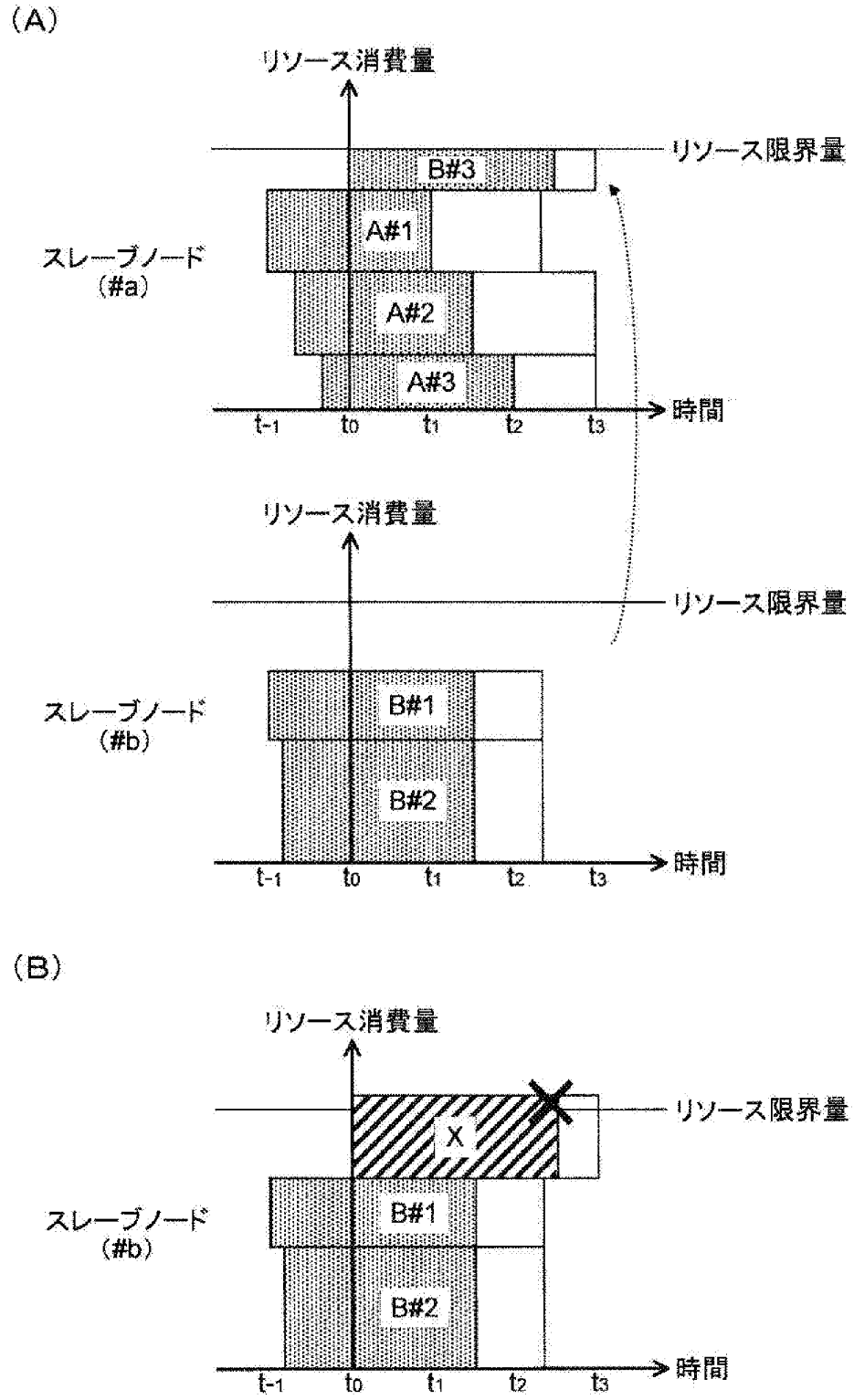
（B）


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

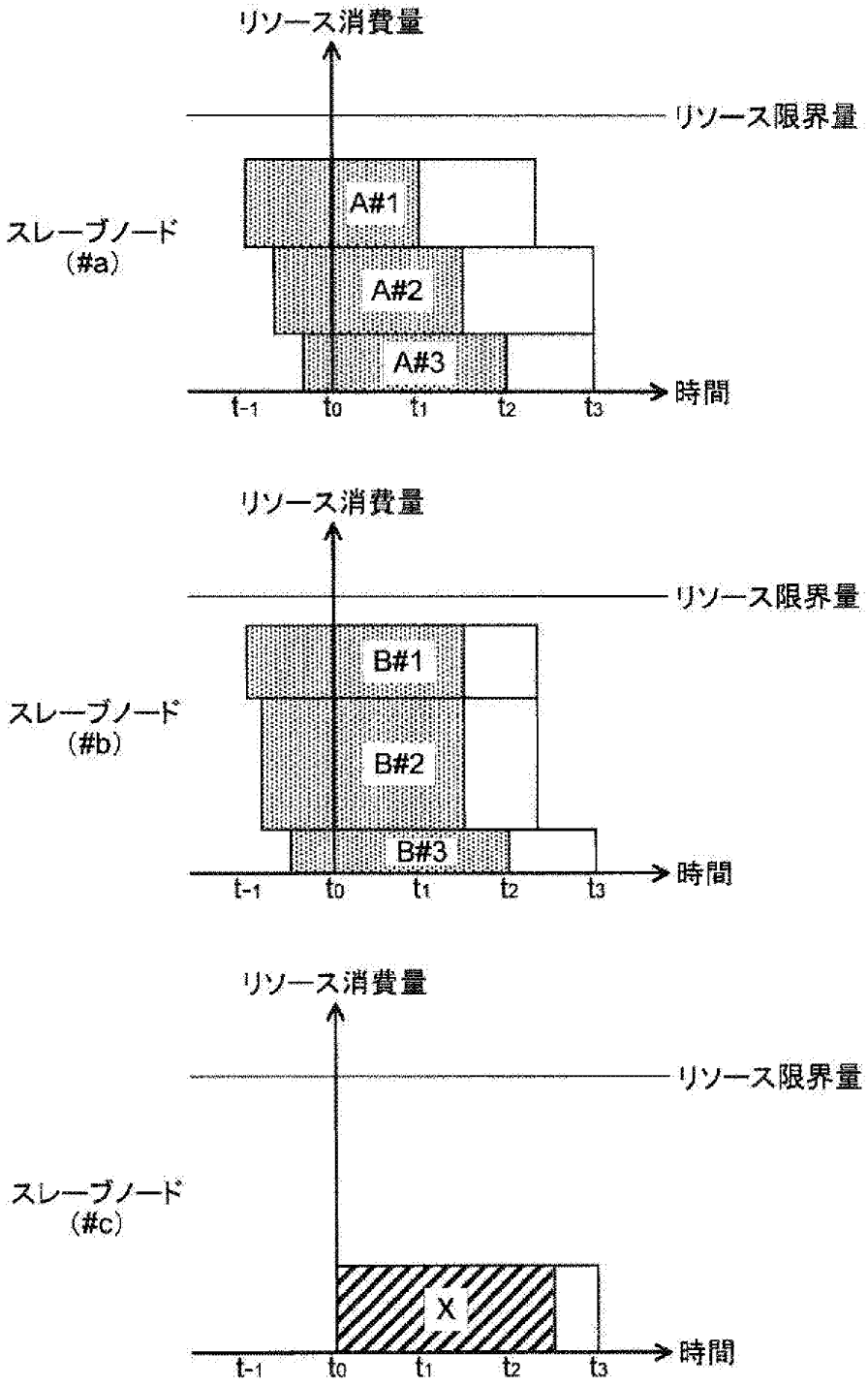
（C）


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

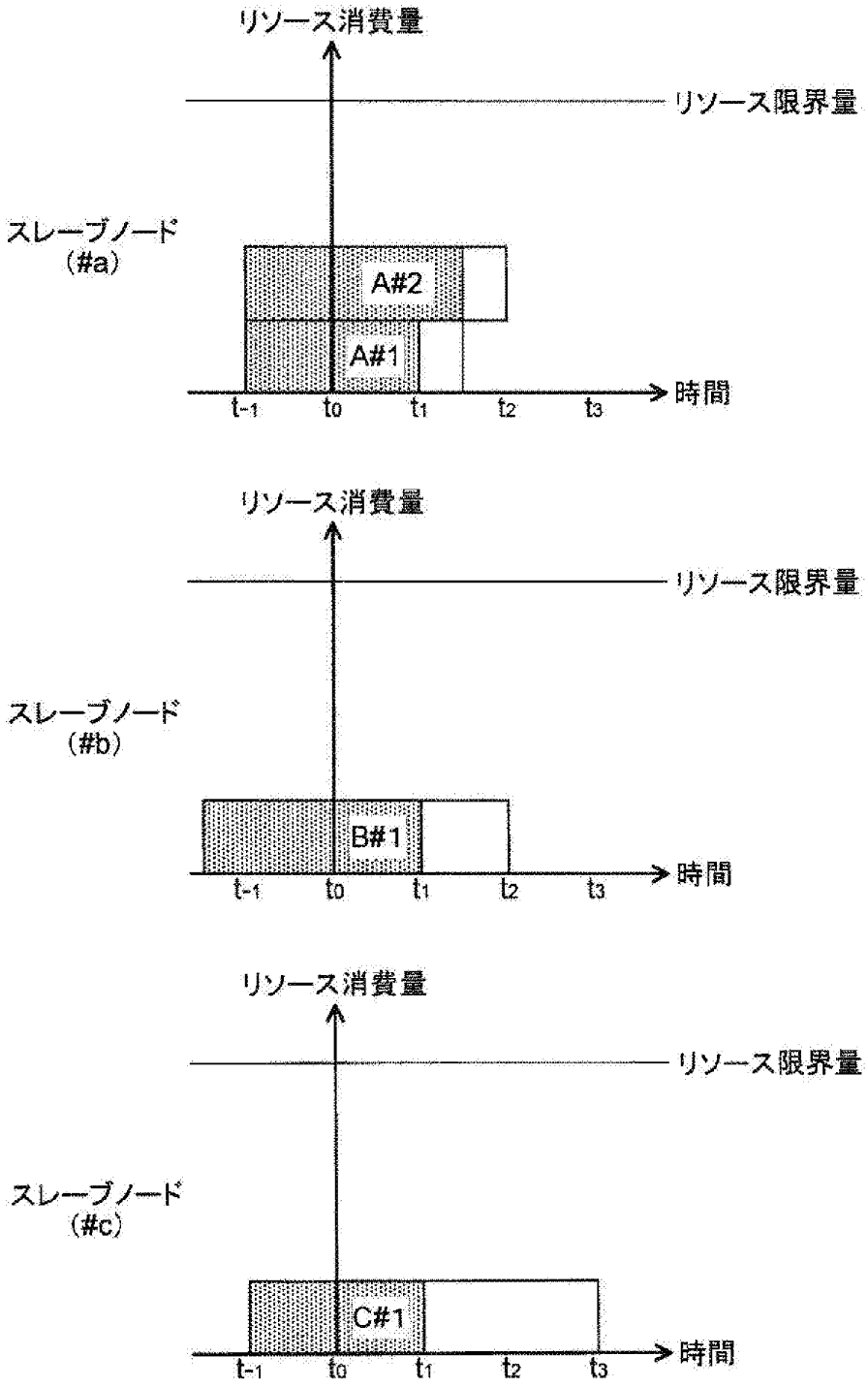
[Fig. 8]


(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]

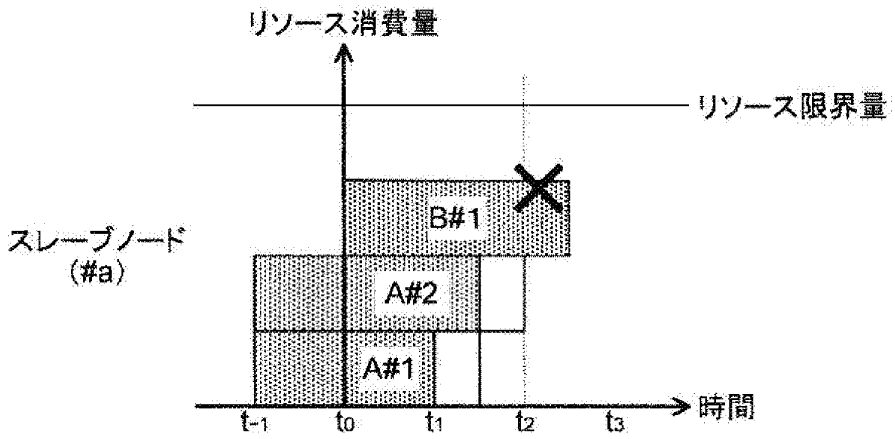

リソース消費量
リソース限界量
スレーブノード
(#a)
A#1
A#2
A#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
B#2
B#3
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#c)
X
時間
t-1
t0
t1
t2
t3

[Fig. 10]

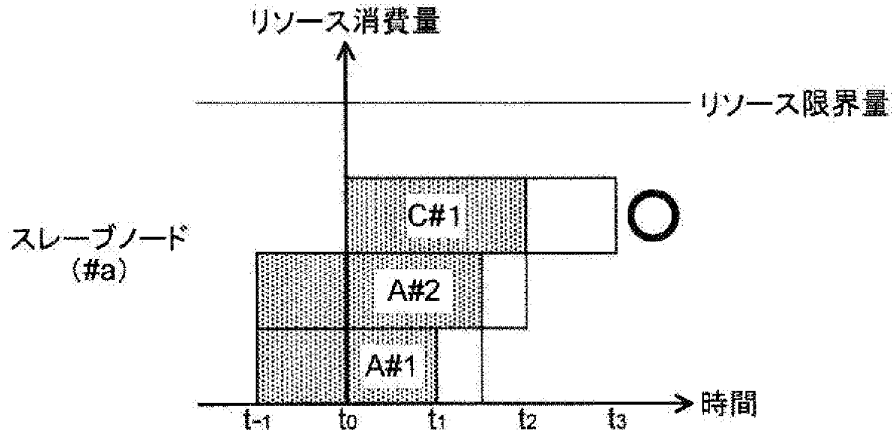

リソース消費量
リソース限界量
スレーブノード
(#a)
A#2
A#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#b)
B#1
時間
t-1
t0
t1
t2
t3
リソース消費量
リソース限界量
スレーブノード
(#c)
C#1
時間
t-1
t0
t1
t2
t3

[Fig. 11]

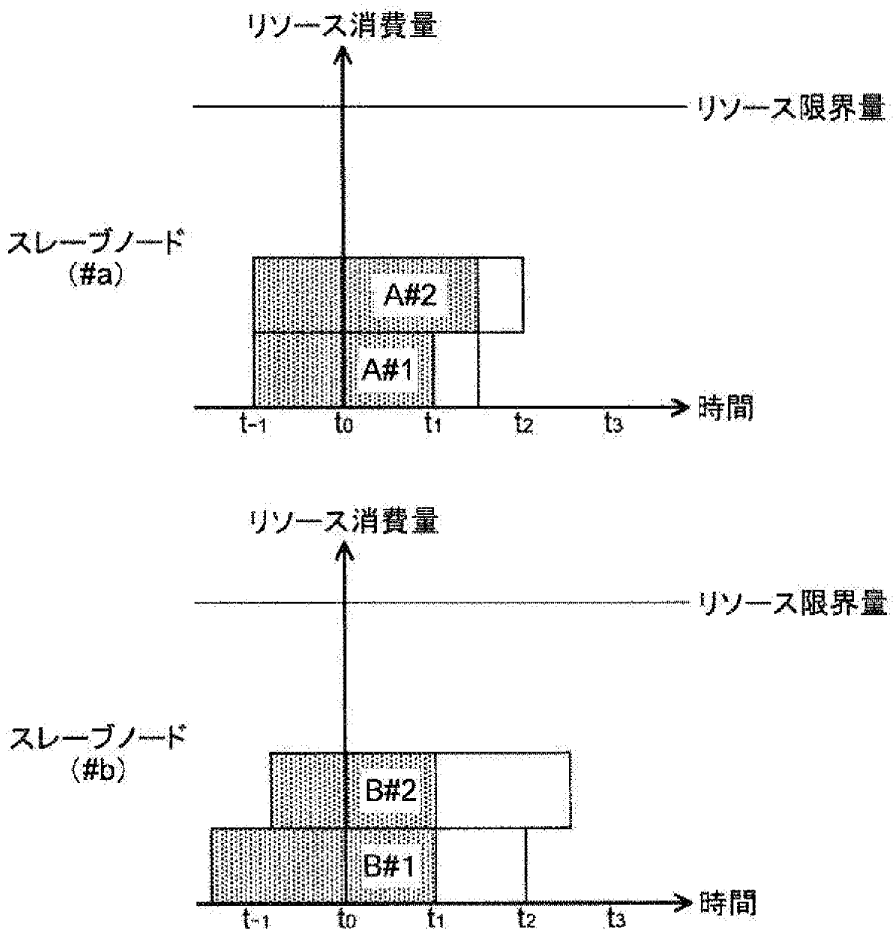
（A）


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

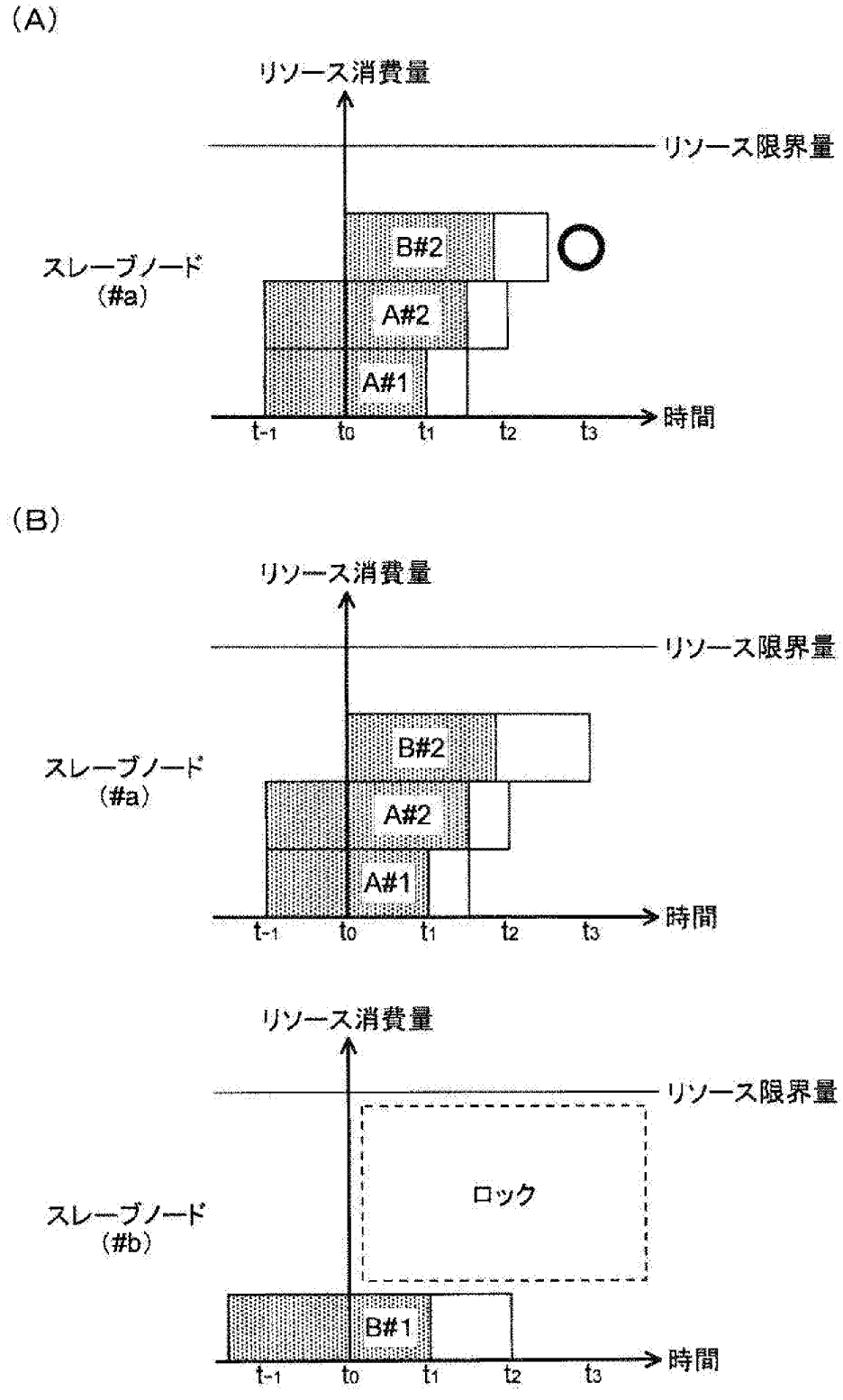
（B）


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

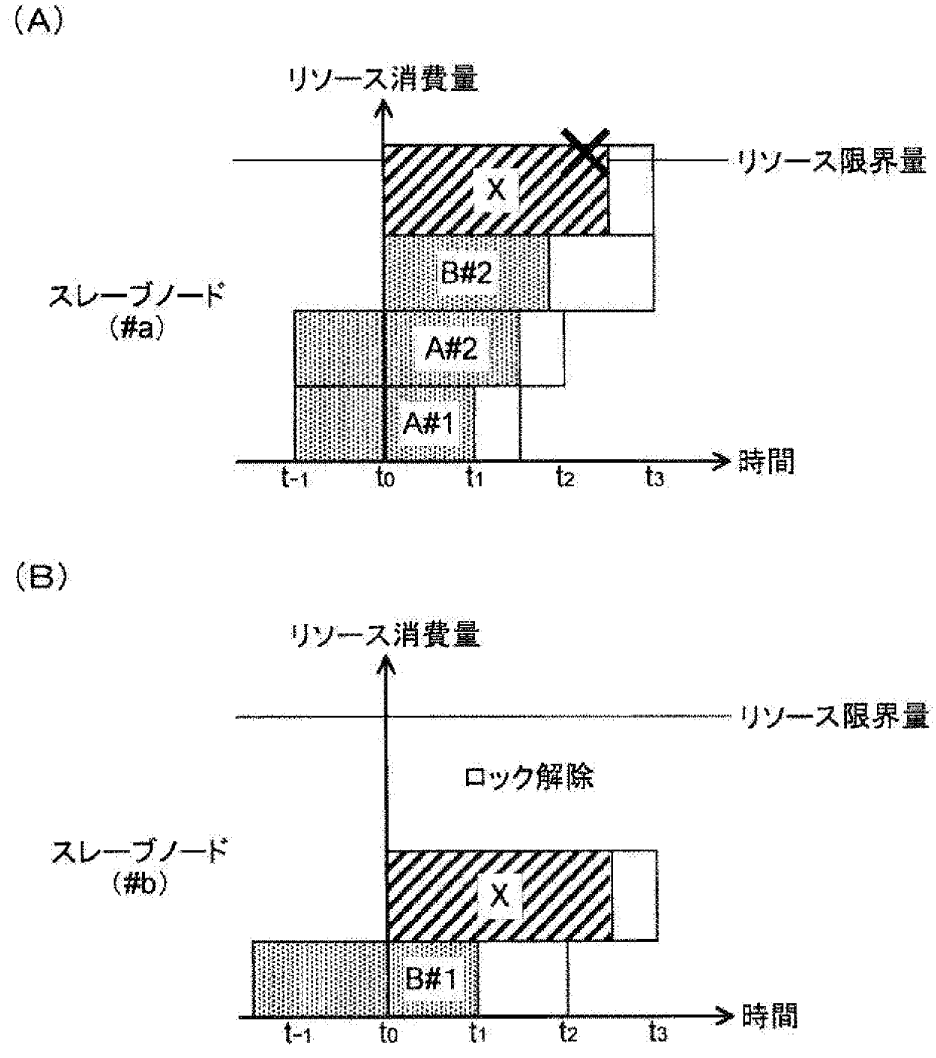
[Fig. 12]


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

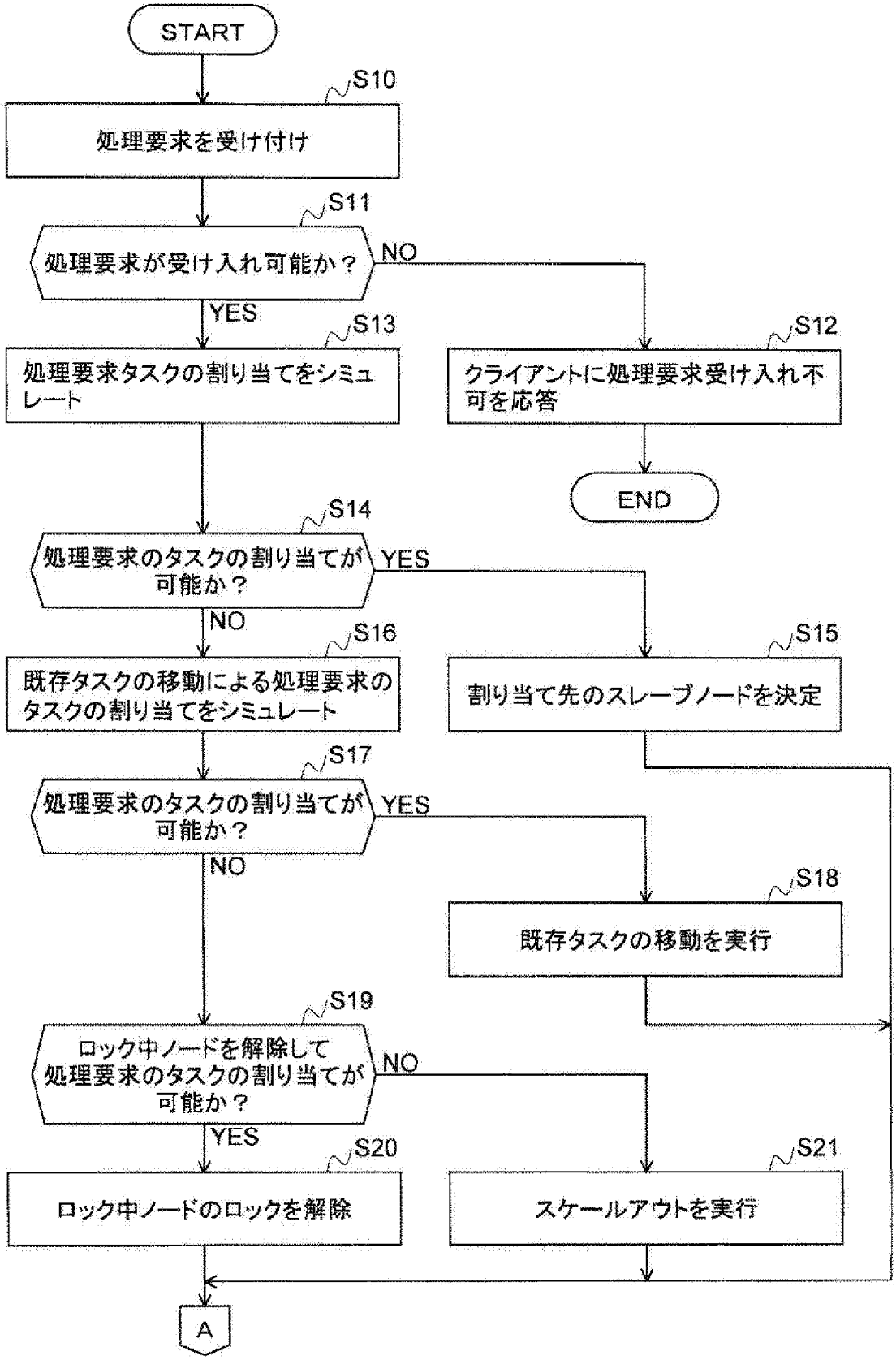
[Fig. 13]


(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

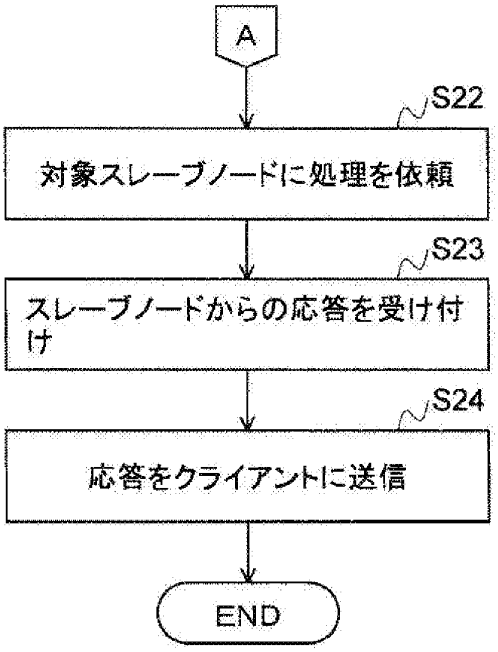
[Fig. 14]


(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

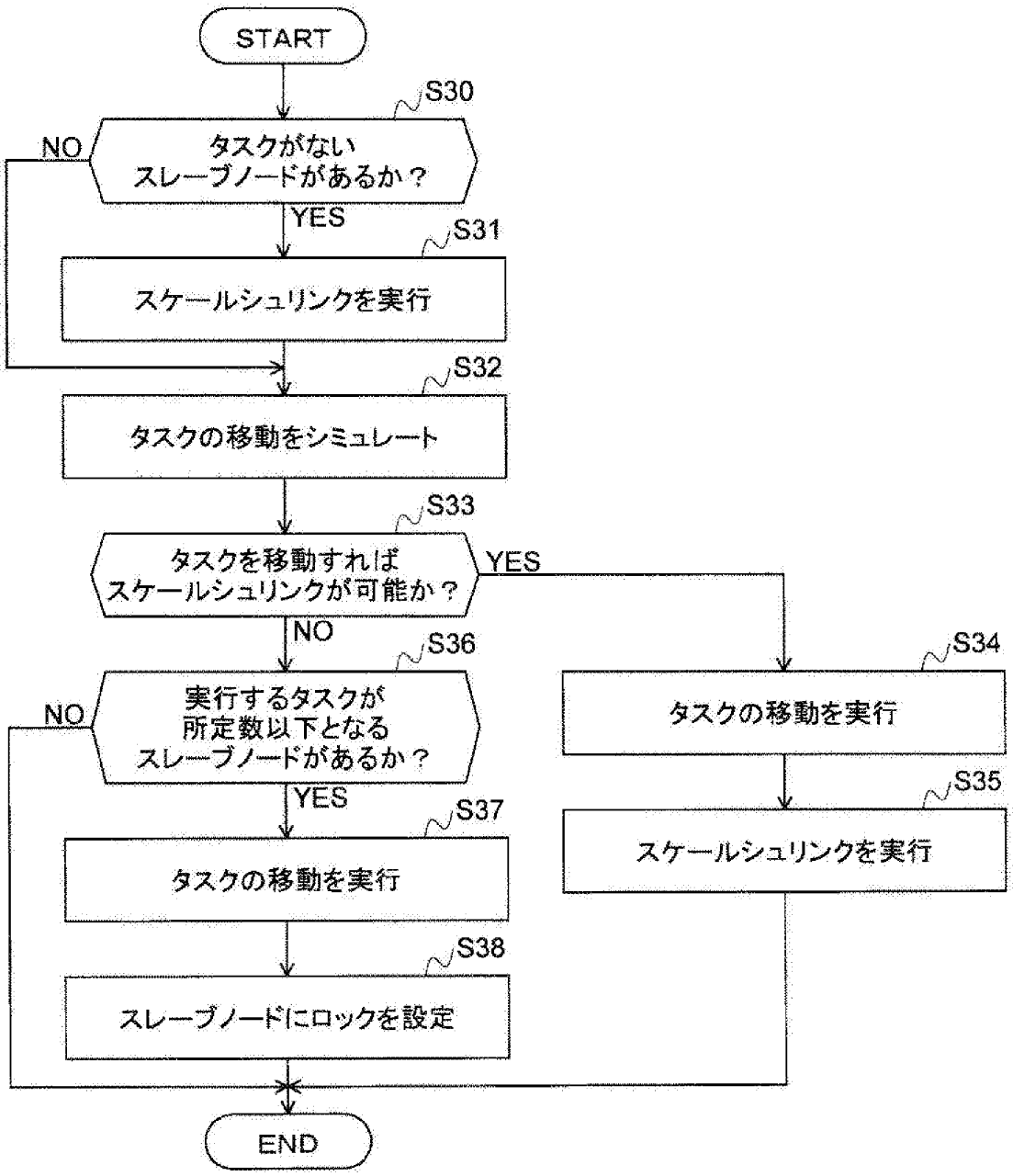
[Fig. 15]


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

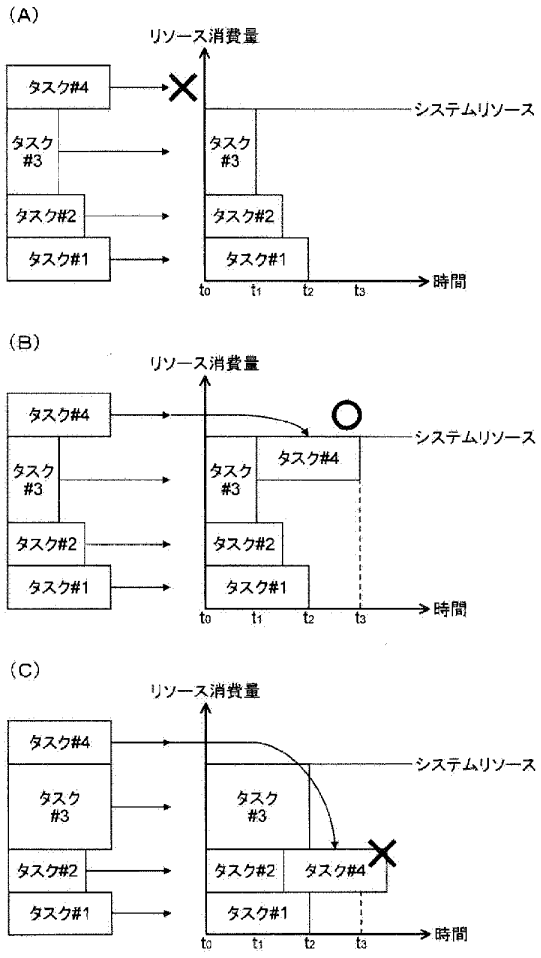


Figure 1

1 / 1 display

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AUTOSCALING METHOD, AUTOSCALING PROGRAM AND COMPUTER NODE

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- cooperative:

Application number: JP20120078501 20120330 Global Dossier

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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】

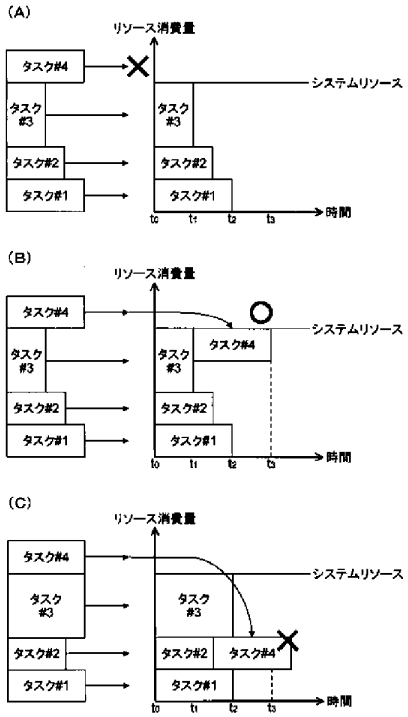
以上，本実施の形態について説明したが，本発明はその主旨の範囲において種々の変形が可能であることは当然である。

【符号の説明】

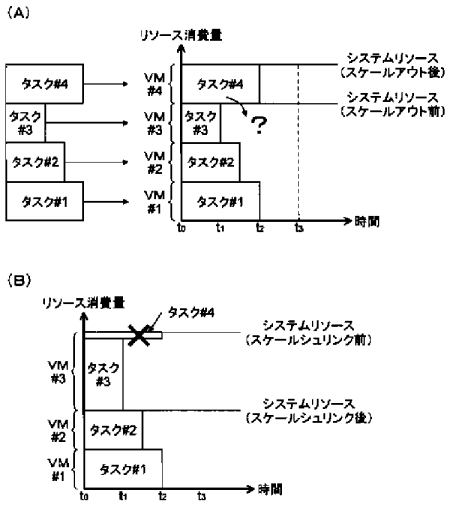
【０１１４】

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

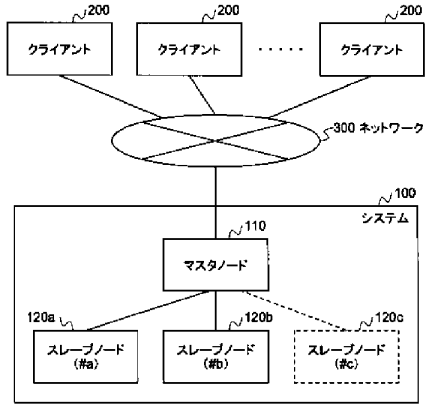
【図１】



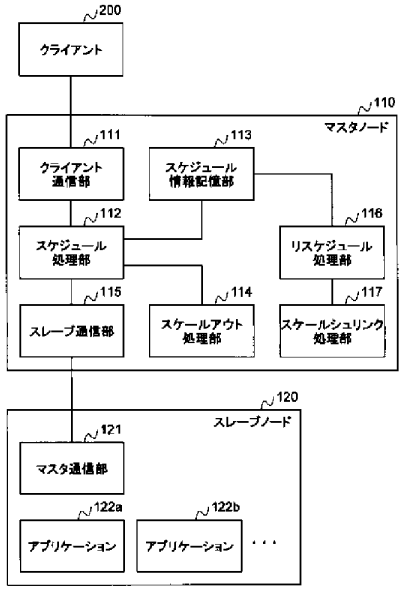
【図２】



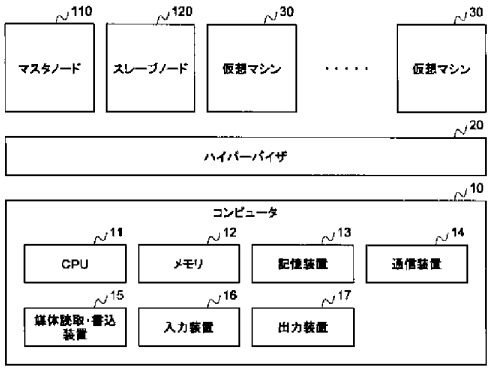
【図３】


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)

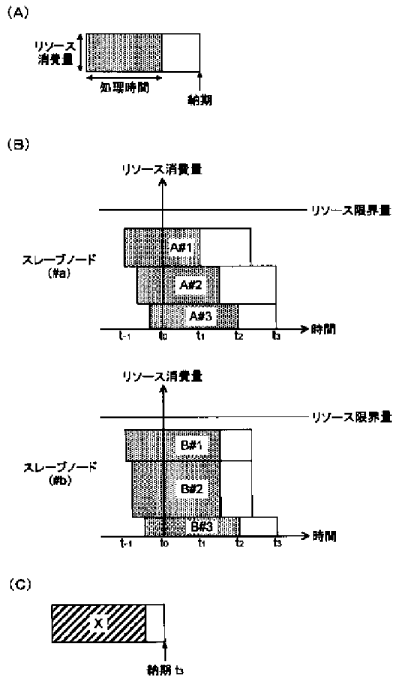
【図４】


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

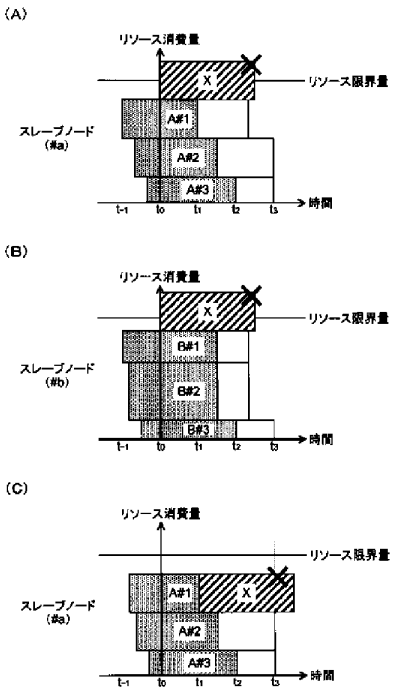
【図５】


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

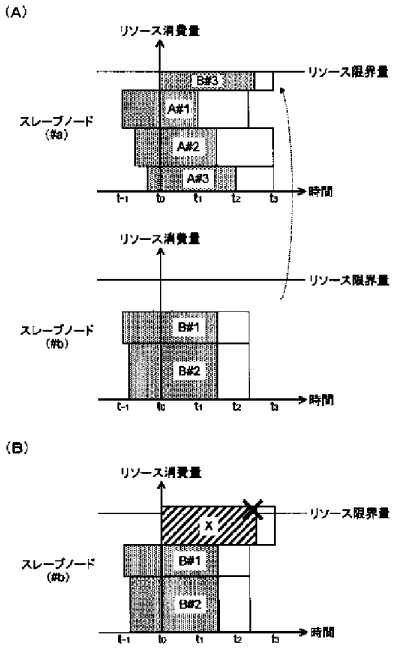
【図６】


(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)
納期 b

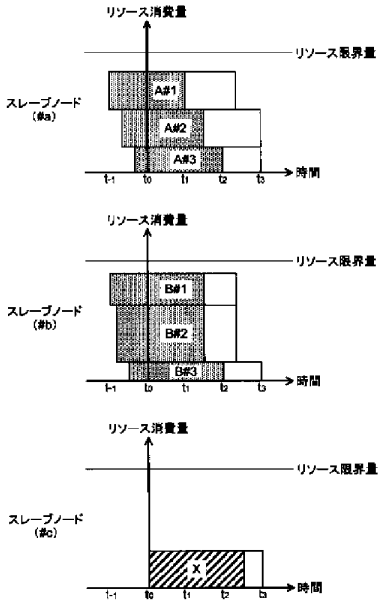
【図７】


(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

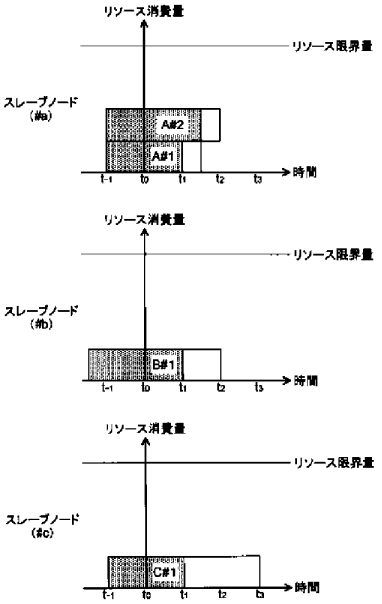
【図８】


(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

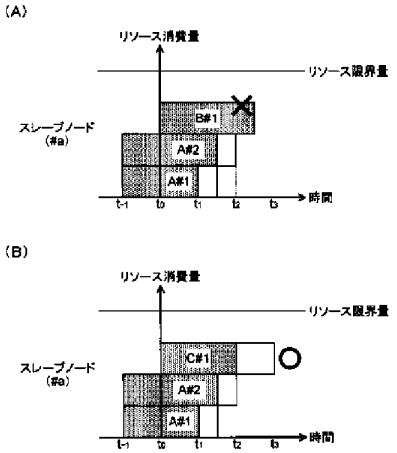
【図９】


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

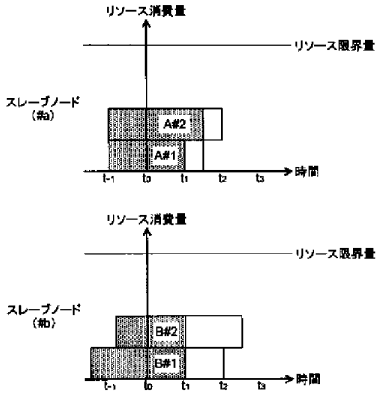
【図１０】


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

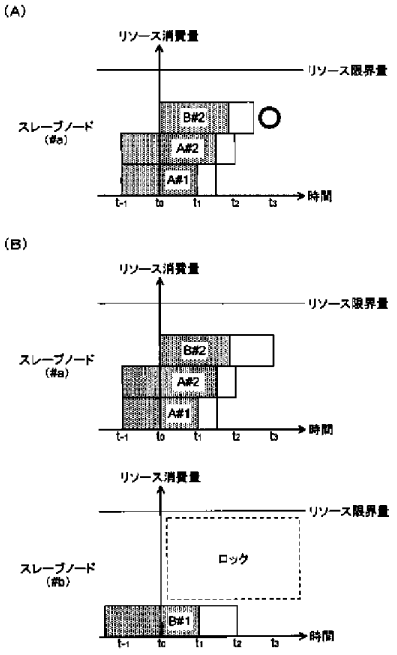
【図１１】



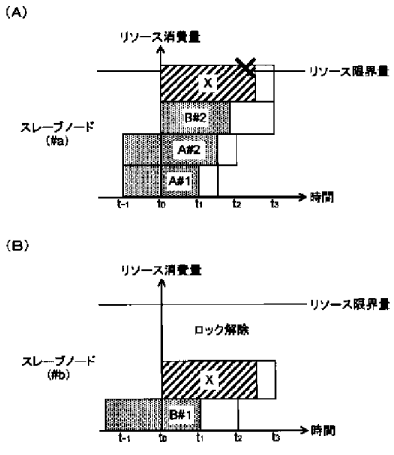
【図１２】



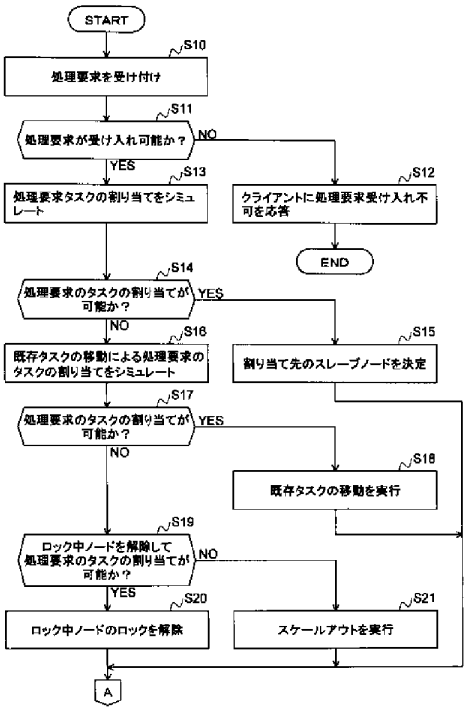
【図１３】



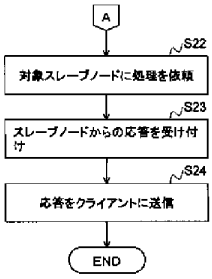
【図１４】



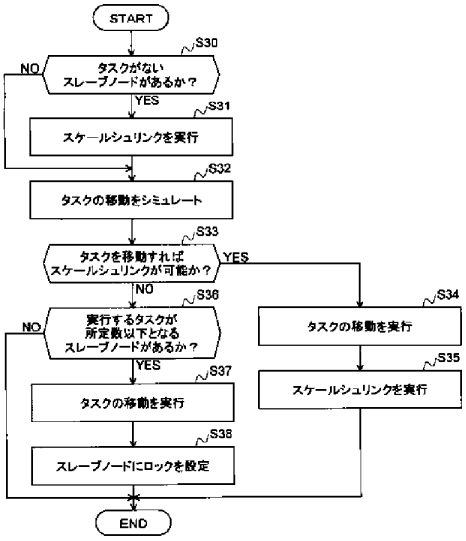
【図１５】


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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審査官 田中 幸雄

(56)参考文献 特開２００９－２６５７７８（ＪＰ，Ａ）
特開２００８－０１５９５８（ＪＰ，Ａ）

(58)調査した分野(Int.Cl.，ＤＢ名)
Ｇ０６Ｆ ９／５０

J-PlatPat 特許情報プラットフォーム English close

Literature display help

1 / 1 display

Special table 09-504726

Document unit PDF | progress information | OPD | search key | URLs

Display format of the document display screen:
text display PDF display

primary literature

bibliography close

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(12) [Type of publication] Published patent publication (A)
(11) [Publication number] Tokuhyo 9-504726
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(51) [International patent classification 6th edition]
A61B 5/14 300
[FI]
A61B 5/14 300 J 0277-2J
[Examination] Claim: Unclaimed
[Preliminary examination request] Unclaimed
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(86) (22) [Filing date] August 22, 1995
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(87) [International publication number] WO96/05875
(87) [International publication date] February 29, 1996

(31) [Priority claim number] 08/296,207
(32) [Priority date] August 25, 1994
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E), AU, CA, JP (71
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[Patent Attorney]
[Name] Michio Akaoka (1 other person))

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.

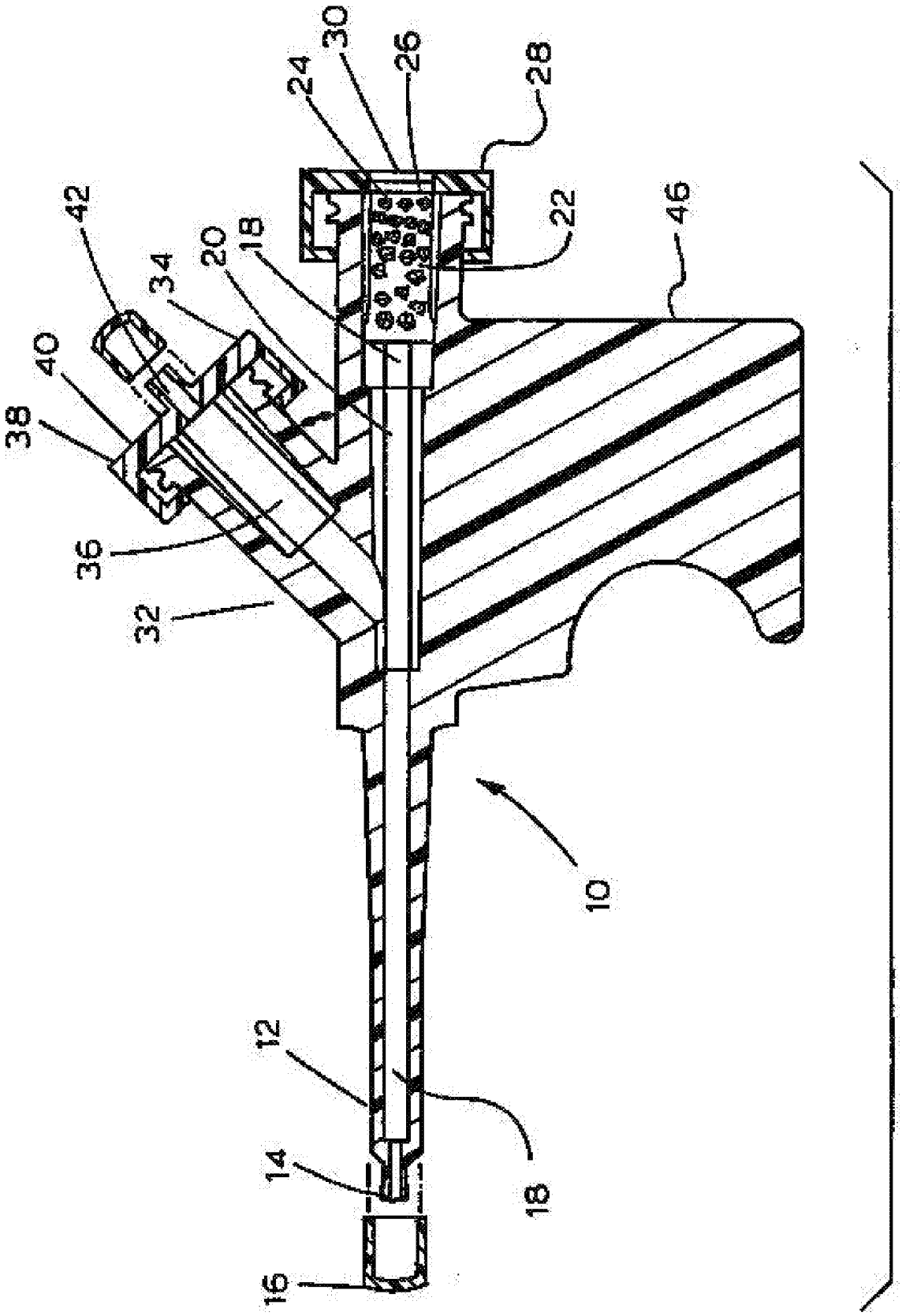


FIG. 1

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]

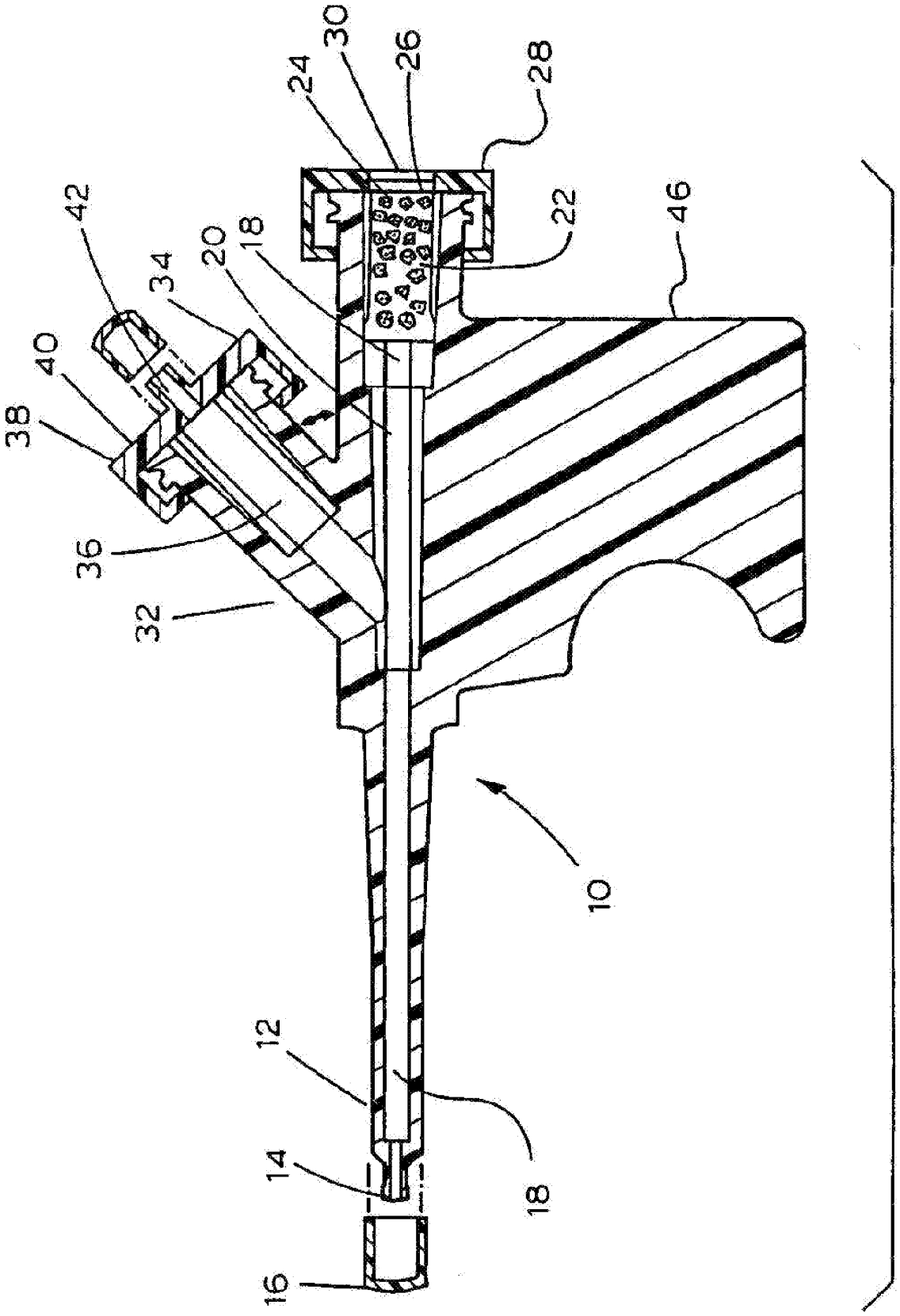


FIG. 1

[Figure 2]

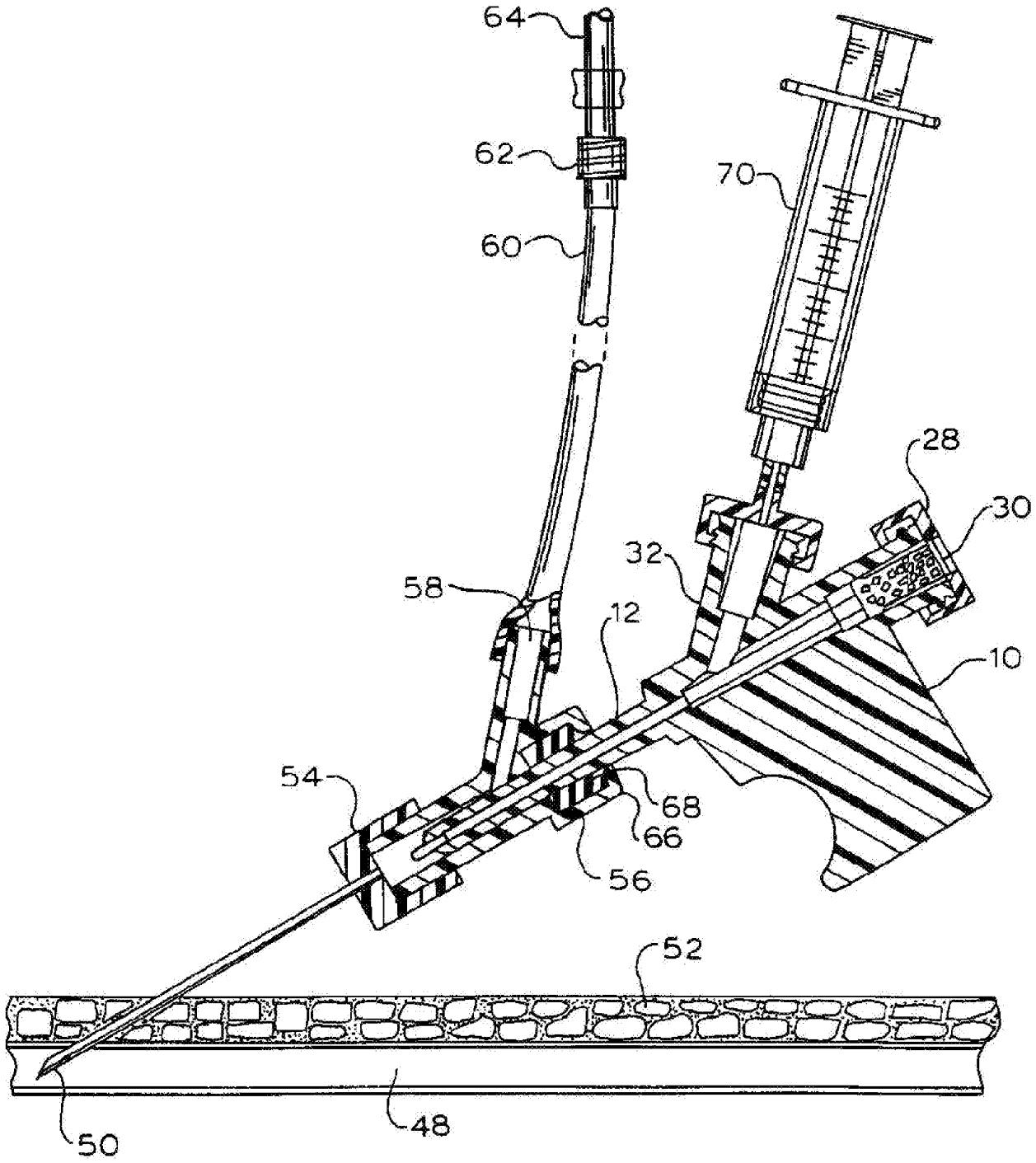


FIG. 2

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

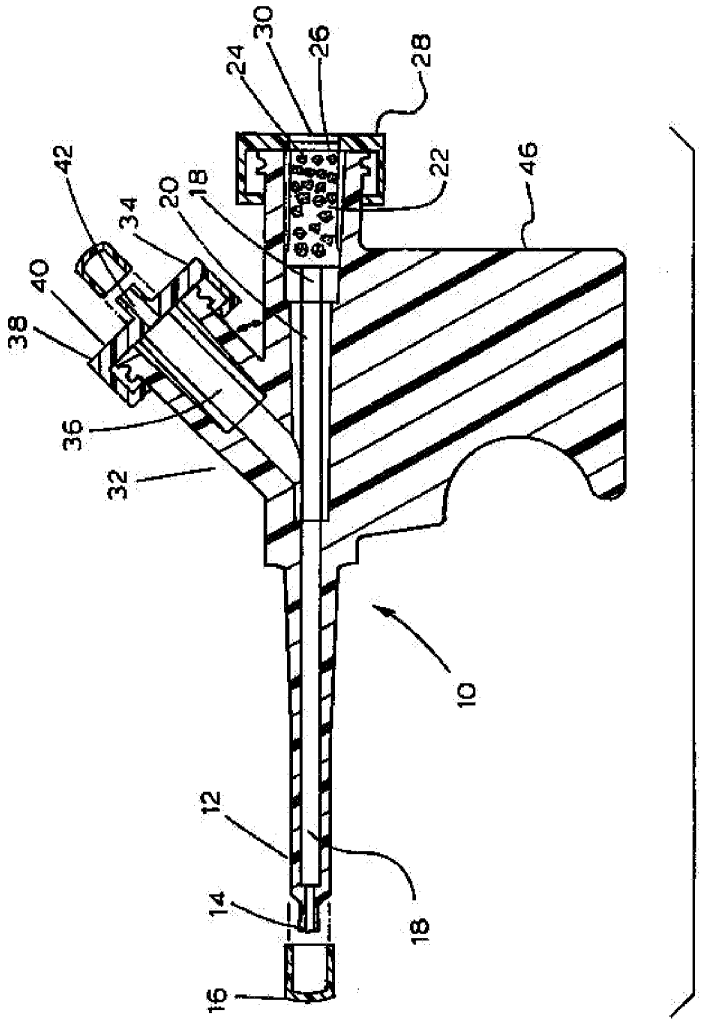


FIG. 1

Representative drawing

1 / 1 display

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(P0200)

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)

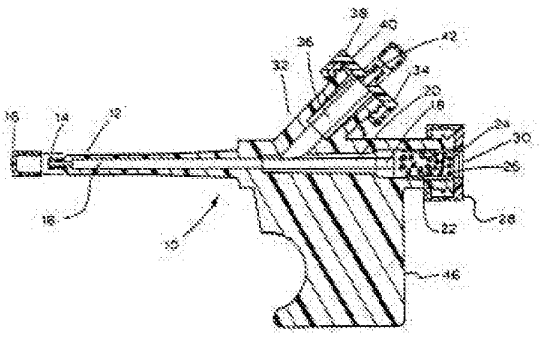
Application number: JP19950508283 19950822

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.



(19)日本国特許庁（ＪＰ）　(12) **公表特許公報**（Ａ）　(11)特許出願公表番号

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(43)公表日　平成９年(1997)５月13日

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(21)出願番号　特願平8－508283
(86)(22)出願日　平成７年(1995)８月22日
(85)翻訳文提出日　平成８年(1996)４月10日
(86)国際出願番号　ＰＣＴ／ＵＳ９５／１０７０２
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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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(74)代理人　弁理士　赤岡　迪夫　(外１名)

(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。

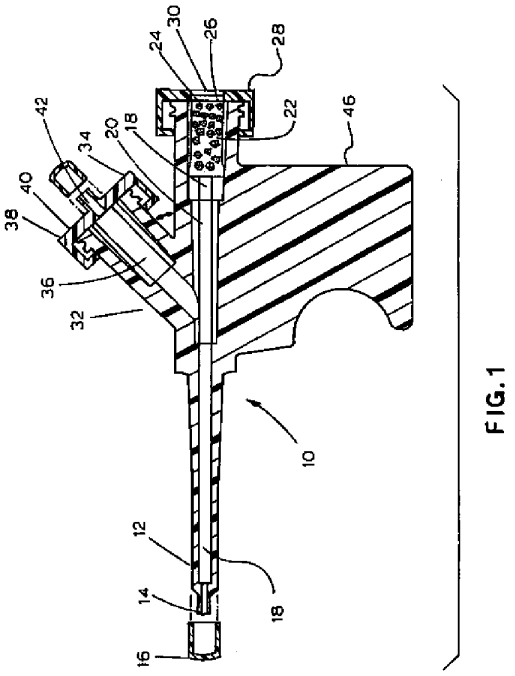


FIG. 1

【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】

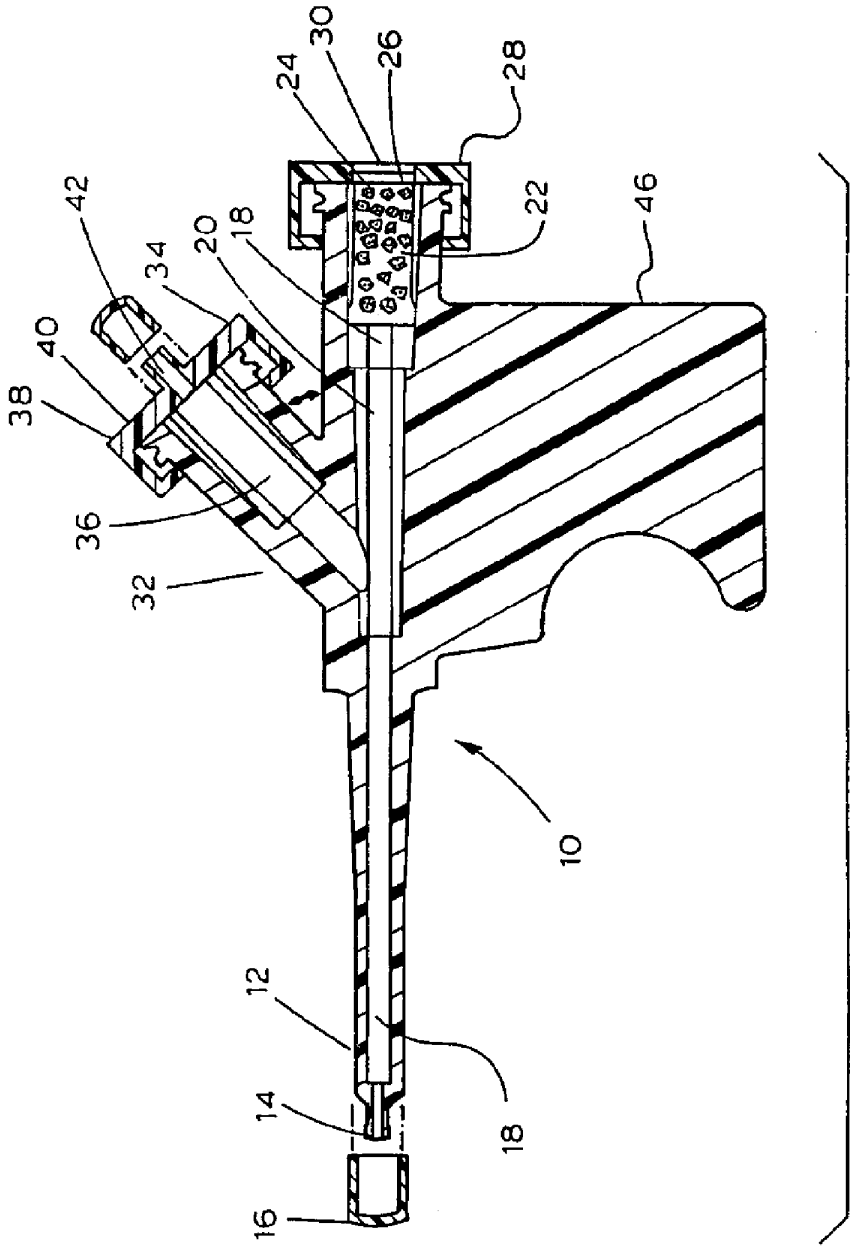


FIG. 1

【図２】

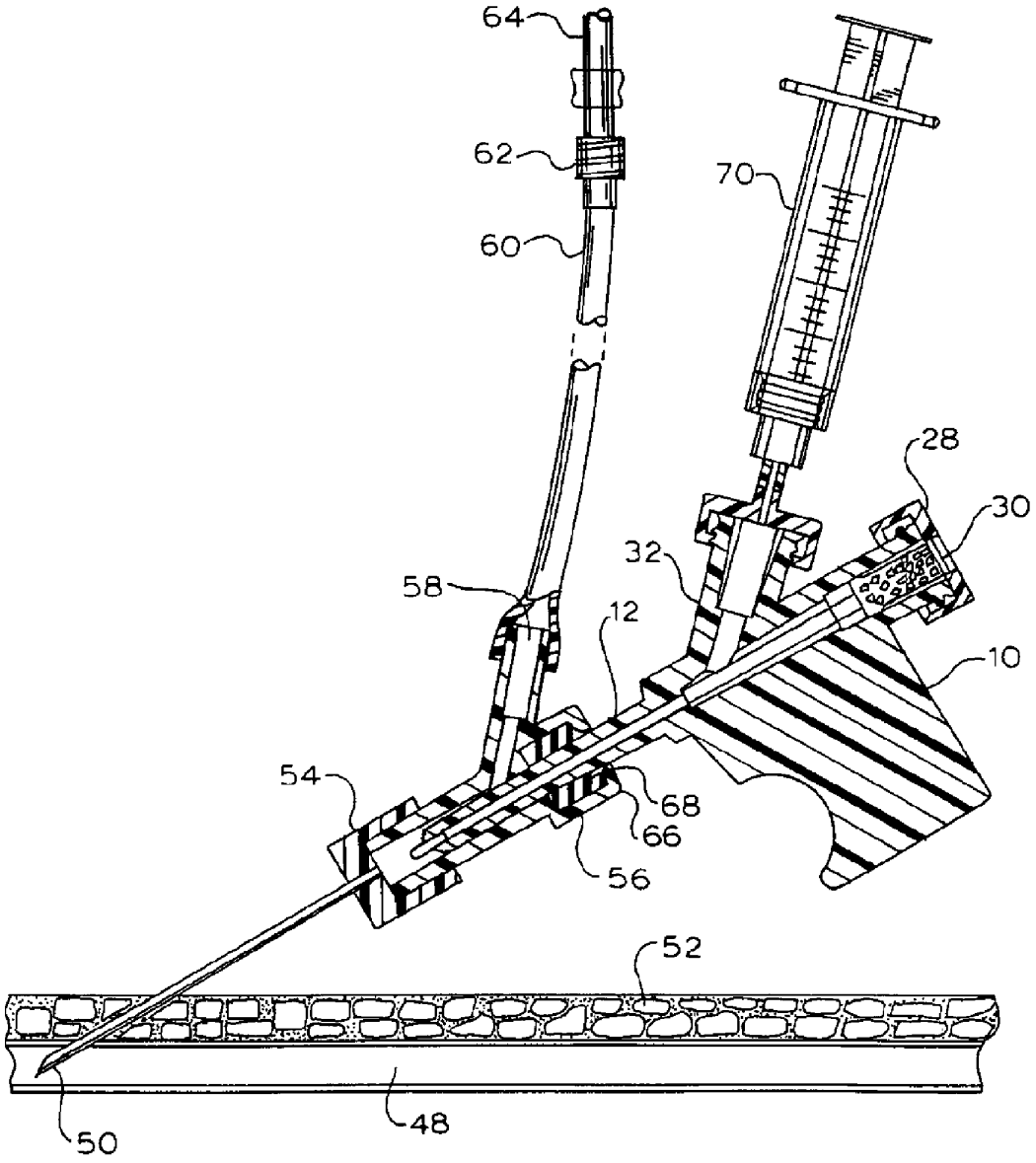


FIG. 2

【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
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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		

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)*

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]

13 PALGEN3 SCHUMACHER & KTUIN ·...."·· · ·· * ··*

[0002]

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22 Aug 1999

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27 D - 40764 Langenfeld

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]

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[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]

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[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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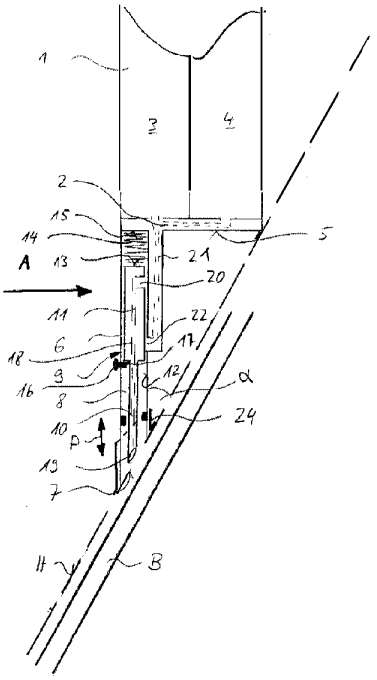
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(54) Vorrichtung zur Entnahme von Blut aus einem Blutgefäß

(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.

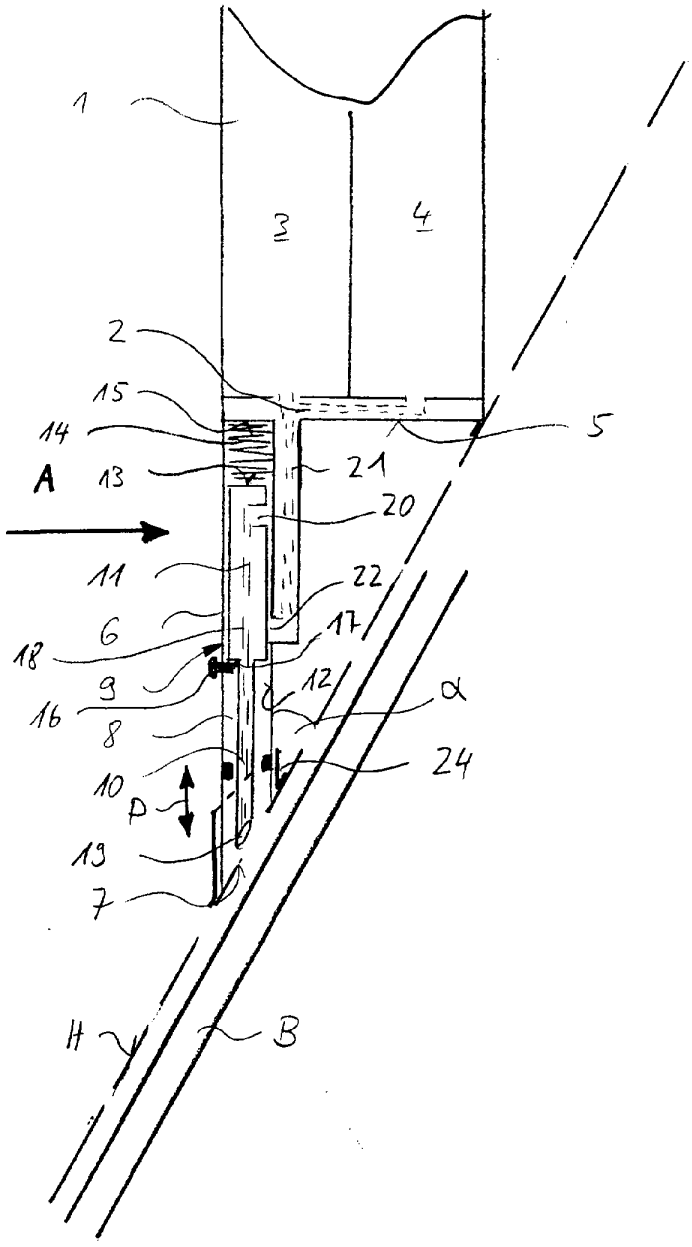
14. Vorrichtung nach einem der Ansprüche 11 bis 13, **dadurch gekennzeichnet**, daß die Anlagefläche (25) mindestens eine Aussparung (27) zur Fixierung des der Blutentnahme dienenden Blutgefäßes (B) aufweist.

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.

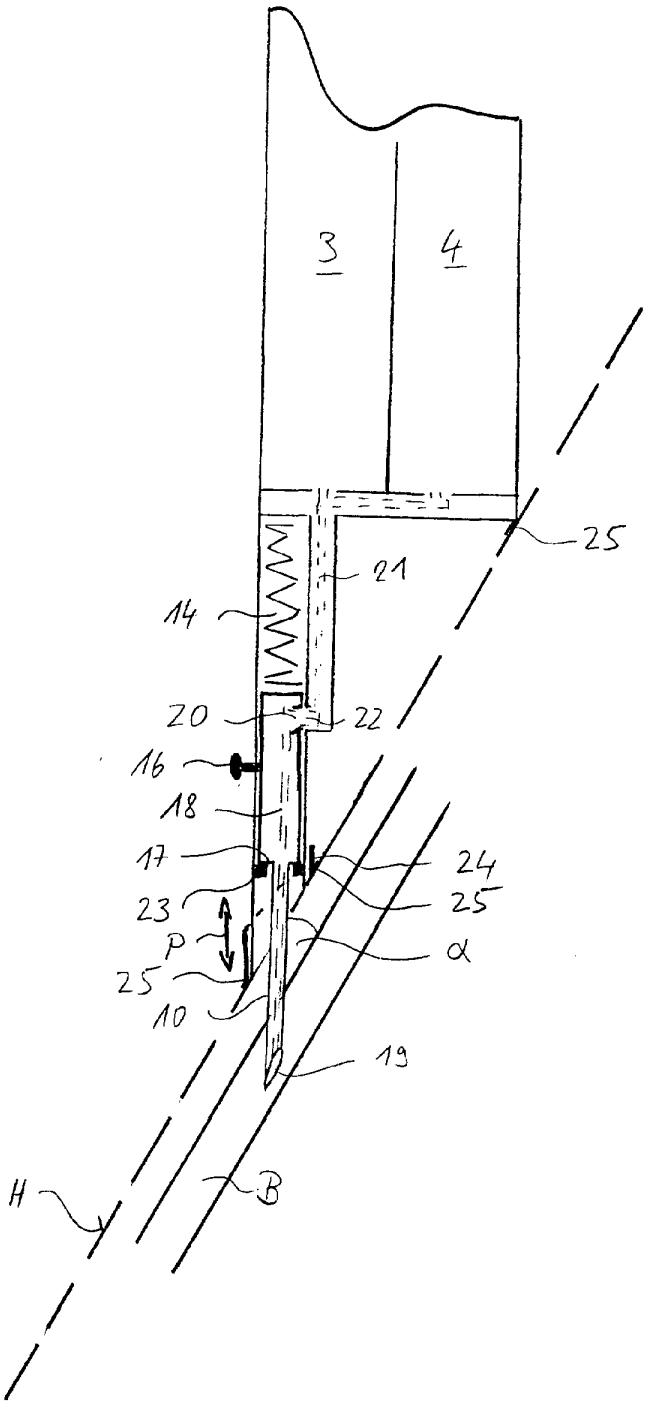
17. Vorrichtung nach Anspruch 15, **dadurch gekennzeichnet**, daß die Innenvolumina (31, 32, 33) oder die Behälter parallel miteinander kommunizieren.

Fig. 1



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Fig. 2



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Fig.3

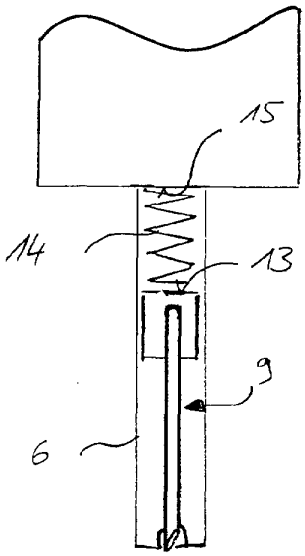
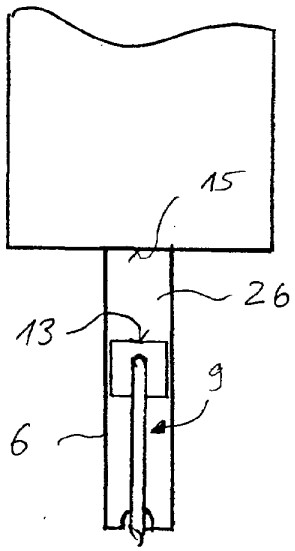


Fig.4



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Fig. 5

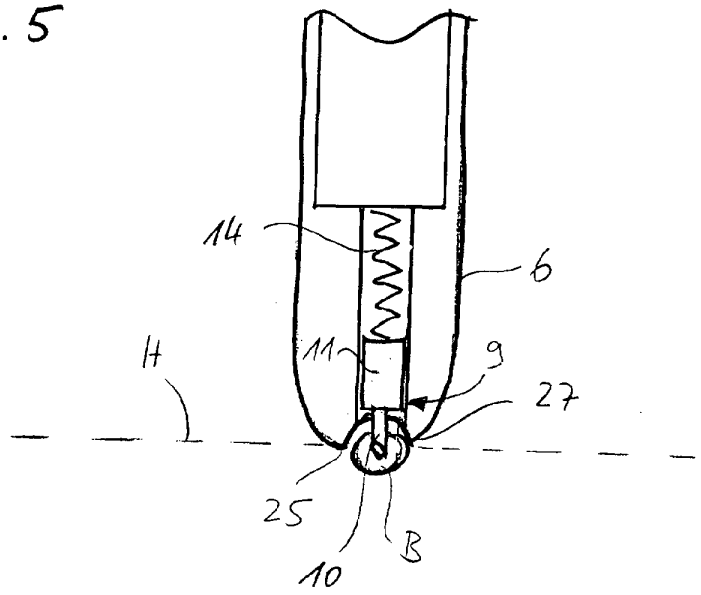
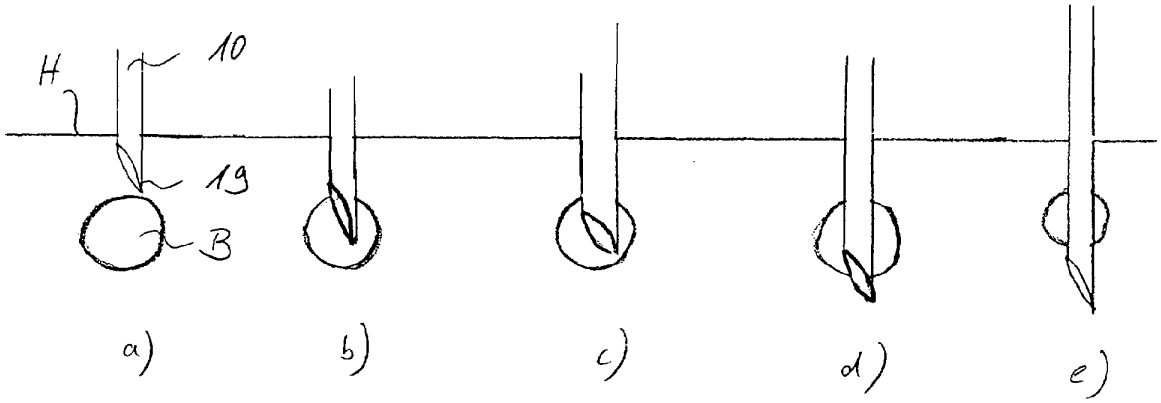


Fig. 6



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Fig. 7

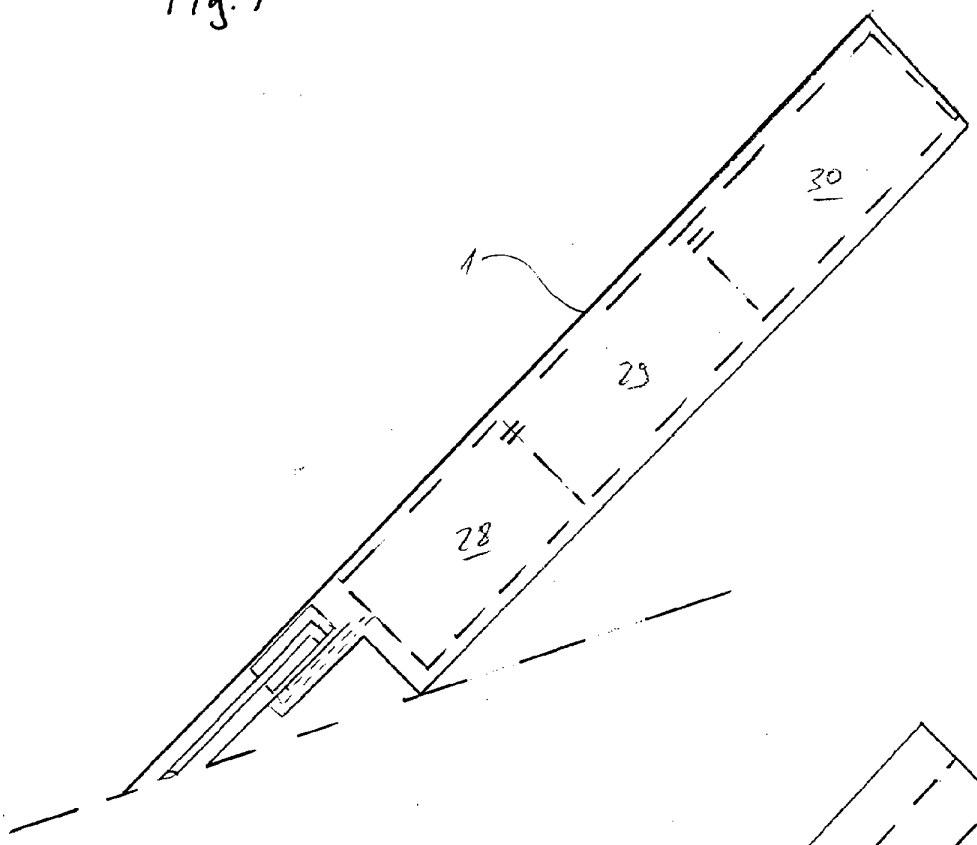
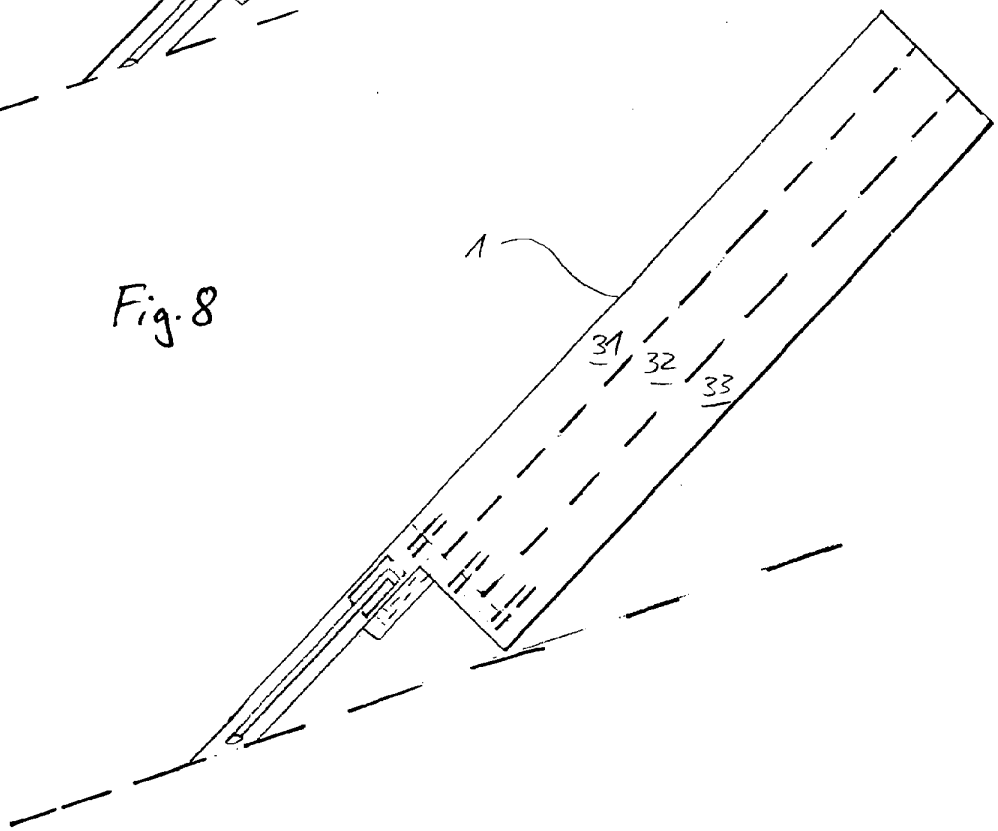
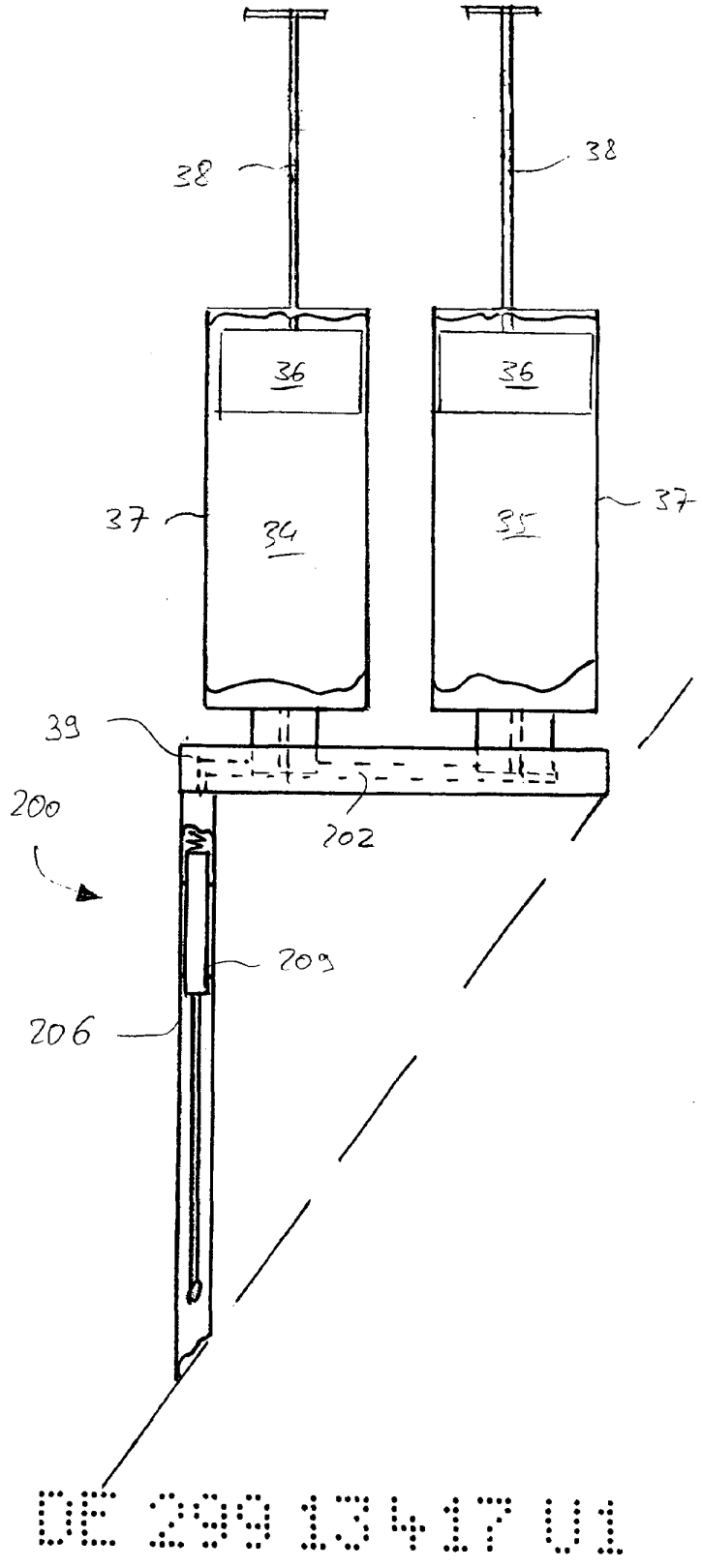


Fig. 8



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Fig. 9



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DISPOSABLE, CLOSED BLOOD SAMPLING SYSTEM FOR USE IN MEDICAL CONDUIT LINE

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Abstract of WO2008101025 (A1)

A disposable, closed fluid sampling system for use with a medical conduit line (70), especially for taking blood samples from a pressure monitoring line. The conduit line (70) has at least one fluid sampling site (100, 102) interposed between a distal segment of tubing and a proximal segment of tubing. The system includes a disposable subsystem (96) having a bypass cannula (110) adapted to engage the sampling site, a reservoir (112) for drawing a prime volume of fluid past the sampling site, and a fluid sampling container (114). A 3-way stopcock (116) may connect the reservoir, bypass cannula, and sampling vessel for controlling the sampling procedure. The bypass cannula (110) may simultaneously place the subsystem into fluid communication with an inner chamber (136) of the sampling site and exclude the proximal segment of the conduit line. Alternatively, a stopcock immediately adjacent the sampling site in the proximal segment may be utilized. A method of using the system includes attaching the disposable subsystem, opening the reservoir to the distal segment while excluding the proximal segment, drawing a prime volume of fluid into the reservoir, opening the sampling vessel to the distal segment and drawing a sample, re-infusing the prime volume into the distal segment, and removing and discarding the subsystem. The

reservoir remains attached between the prime volume draw and re-infusion and is thus "closed."

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[Continued on next page]

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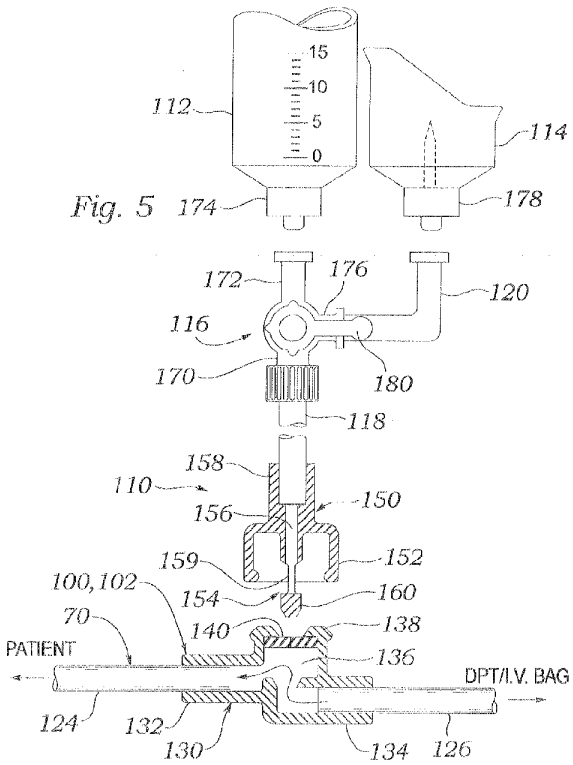


Fig. 5

(57) Abstract: A disposable, closed fluid sampling system for use with a medical conduit line (70), especially for taking blood samples from a pressure monitoring line. The conduit line (70) has at least one fluid sampling site (100, 102) interposed • between a distal segment of tubing and a proximal segment of tubing. The system includes a disposable subsystem (96) having a bypass cannula (110) adapted to engage the sampling site, a reservoir (112) for drawing a prime volume of fluid past the sampling site, and a fluid sampling container (114). A 3-way stopcock (116) may connect the reservoir, bypass cannula, and sampling vessel for controlling the sampling procedure. The bypass cannula (110) may simultaneously place the subsystem into fluid communication with an inner chamber (136) of the sampling site and exclude the proximal segment of the conduit line. Alternatively, a stopcock immediately adjacent the sampling site in the proximal segment may be utilized. A method of using the system includes attaching the disposable subsystem, opening the reservoir to the distal segment while excluding the proximal segment, drawing a prime volume of fluid into the reservoir, opening the sampling vessel to the distal segment and drawing a sample, re-infusing the prime volume into the distal segment, and removing and discarding the subsystem. The reservoir remains attached between the prime volume draw and re-infusion and is thus "closed."

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DISPOSABLE, CLOSED BLOOD SAMPLING SYSTEM FOR USE IN MEDICAL CONDUIT LINE

Field of the Invention

[0001] The present invention relates to blood sampling systems and, in particular, to a disposable blood sampling system in a medical conduit line such as a pressure monitoring line.

Background of the Invention

[0002] In a hospital setting there is always the need to monitor patient health through the evaluation of blood chemistry profile. The simplest method employed in the hospital is to use a syringe carrying a sharpened cannula at one end and insert that cannula into a vein or artery to extract a blood sample from the patient. Blood is drawn using a syringe or more easily into an evacuated vessel. Patients that are in the critical care units or the operating room sometimes require as many as twelve blood draws a day which can be quite uncomfortable. Moreover, such frequent sampling injections carry the risk to the clinician of needle sticks and blood exposure, and potentially subject the patient to airborne bacteria and viruses which can enter the bloodstream through the opening made by the sharpened cannula.

[0003] One way to obtain a blood sample is to draw the blood from a catheter that is already inserted in the patient, either in a central venous line, such as one placed in the right atrium, or in an arterial line. Typically, existing injection sites for arterial or venous drug infusion or pressure monitoring lines are used to take periodic blood samples from the patient. Conventional mechanisms for drawing blood from the lines used for infusion or pressure monitoring utilize a plurality of stopcock mechanisms that block flow from the infusion fluid supply or from the pressure column drip supply, while allowing blood to flow from the patient into a collecting syringe connected to a port formed in one of the stopcocks. Typically, a blunt cannula through a slit septum

is used to remove the danger of sticking the nurse or clinician, in a so-called "needle-less" system.

[0004] Most early systems required a two-step operation where a first sample of fluid, typically between 2-12 ml in volume for intensive care environments was withdrawn into the sampling syringe and discarded. This first sample potentially included some of the infusion fluid and thus would be an unreliable blood chemistry measurement sample. After the initial sample had been discharged, the second sample was pure blood from the artery or vein and was typically re-infused to the patient.

[0005] Of course, the possibility of discarding blood along with saline is a drawback, especially in anemic patients, and so-called closed systems that remain connected to the conduit line and preserve the initial fluid draw were developed. Examples of these can be seen in U.S. Patent No. 4,673,386 to Gordon, and more recently in U.S. Patent No. 5,961,472 to Swendson. Commercial closed systems such as the Edwards VAMP® and VAMP Plus® Venous Arterial blood Management Protection systems of Edwards Lifesciences in Irvine, CA feature a dedicated syringe-like reservoir incorporated in the tubing line from the patient that can draw fluid past a sampling port. The line continues past the reservoir to a proximal source of flushing fluid and a pressure transducer. (The standard directional nomenclature is that proximal is toward the clinician, or away from the patient, and distal is toward the patient). The clearing volume is held in the in-line reservoir, and not set aside in a syringe for discard or re-infusion later.

[0006] When a blood sample is to be taken, the flow of flushing or infusion fluid is halted by turning the handle of a reservoir stopcock valve. The nurse or clinician then withdraws an amount of fluid into the reservoir chamber and distal line sufficient to pull pure blood past one or more sampling sites and closes the reservoir stopcock. Desirably, the flow line includes a sampling site near the patient more often used in the ICU, and/or one farther away, close to the reservoir, and used in the OR when the space immediately around the patient is at a premium. To avoid needle sticks, blunt cannulas are used to draw

blood. Also, the sampling sites are desirably designed to ensure a complete flush after the sample is taken. The stopcock valve is then opened so that the volume within the reservoir can be re-infused back into the patient, and the flushing drip and pressure monitoring resumes.

[0007] In reservoir systems the nurse or technician must manipulate the reservoir, then let go of it to take the blood sample, and then grasp it again to re-infuse the prime volume, all of which is relatively inconvenient. Furthermore the continuing presence of the reservoir dangling from the pressure monitoring line is undesirable as it is only infrequently used and can become tangled with bedding or with other equipment. Finally, because the reservoir remains in place and is used multiple times, it must include a contamination shield to isolate the reservoir plunger, and such a device is costly compared to a simple syringe.

[0008] A minimum quality of system frequency response in the blood sampling/pressure monitoring systems described above is necessary for reliable blood pressure measurements. The pressure transducer typically includes a diaphragm exposed to the in-line fluid on one side and has a device for measuring deflection of the diaphragm on the other. Adding components to the flow line, such as sampling sites with elastomeric septums or a dedicated reservoir with a rubber-tipped plunger, and/or increasing the length of tubing contributes to signal degradation. Often only one sampling site is provided for the ICU or OR to avoid unduly degrading the signal response.

[0009] In view of the foregoing, there is a need for a blood sampling system, especially used in conjunction with a pressure transducer, that is more convenient and safer to use.

Summary of the Invention

[0010] In one aspect, the present invention provides a medical system for sampling of a fluid system of a patient for use with a conduit line. The conduit line includes a proximal segment adapted to be supplied with a

physiological fluid and a distal segment adapted to be in communication with the fluid system of a patient. A fluid sampling site in the conduit line defines a housing having a distal port connected to the distal segment and a proximal port connected to the proximal segment. Fluid may flow freely through a chamber in the housing between the proximal and distal ports, and the sampling site further defines a sampling port open to the chamber and closed from the exterior by an elastomeric seal. The medical system comprises a flowthrough bypass cannula having a body shaped to engage the sampling port. The cannula also has a bypass probe defining a throughbore and sized to pierce the elastomeric seal, project into the chamber and place the throughbore into fluid communication with the distal port of the sampling site while occluding the proximal port from the throughbore. Consequently, a fluid sample may be drawn into the bypass cannula from the distal segment of the conduit line to the exclusion of the proximal segment. In a preferred embodiment, the bypass cannula and sampling site include mating structure such that they engage with a positive snap fit.

[0011] In one embodiment, the bypass probe terminates in a tip that contacts a passageway opening in the fluid sampling site housing leading to one of the distal or proximal ports when the bypass cannula engages the sampling site, and the tip is tapered and matches the passageway opening. In another embodiment, the bypass probe terminates in a closed tip that contacts and occludes a passageway opening in the fluid sampling site housing leading to the proximal port when the bypass cannula engages the sampling site, and the bypass probe includes at least one side opening open to the chamber in the sampling site housing. The closed bypass probe tip may be at least partly compressible to enhance the seal between the tip and the passageway opening. Alternatively, the bypass probe defines a continuous tubular member and terminates in an open tip that contacts a passageway opening in the fluid sampling site housing leading to the distal port when the bypass cannula engages the sampling site. Furthermore, a sealing member may be positioned in

the passageway opening that contacts and seals against the open tip of the bypass probe to enhance the seal therebetween.

[0012] Another aspect of the present invention is a system for sampling fluid from a medical conduit line including a disposable subsystem. The system includes a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient. A fluid sampling site in the conduit line defines an internal chamber in communication with all of: a proximal port connected to the proximal segment, a distal port connected to the distal segment, and a sampling port closed by an elastomeric seal. Further has a disposable sampling subsystem for engaging the fluid sampling site. The sampling subsystem includes a bypass cannula adapted to engage the sampling port of the sampling site and simultaneously occlude the proximal port therein. The sampling subsystem also includes a stopcock having three ports, a first port in communication with the bypass cannula, a fluid reservoir connected to a second port of the stopcock, and a fluid sampling vessel in fluid communication with the third port of the stopcock. Manipulating the stopcock into a first position enables fluid communication between the first and second ports so that fluid may be drawn into the reservoir from the distal segment. Manipulating the stopcock into a second position enables fluid communication between the first and third ports so that fluid may be drawn into the fluid sampling vessel from the distal segment. The system further may include a pressure transducer connected to the proximal segment of the conduit line for sensing the pressure of the fluid system of a patient through the fluid in the conduit line. An optional component of the system is a bubble trap connected to the bypass cannula between the sampling site and reservoir that prevents bubbles from entering the sampling site from the bypass cannula.

[0013] In one embodiment, the bypass cannula includes a bypass probe terminating in a closed tip that contacts and occludes a passageway opening in the fluid sampling site housing leading to the proximal port when the bypass cannula engages the sampling site, and the bypass probe includes at least one

side opening open to the chamber in the sampling site housing. In an alternative embodiment, the bypass cannula includes a continuous tubular bypass probe terminating in an open tip that contacts a passageway opening in the fluid sampling site housing leading to the distal port when the bypass cannula engages the sampling site. A still further alternative includes a stopcock positioned adjacent the proximal port of the sampling site for occluding the proximal port when fluid is drawn into and expelled from the reservoir and drawn into the fluid sampling container.

[0014] The present invention also provides a method for sampling blood from a medical fluid conduit line using a disposable subsystem, the conduit line having a proximal segment supplied with a physiological fluid and a distal segment in communication with the blood system of a patient. The conduit line also has a fluid sampling site defining an internal chamber in communication with all of: a proximal port connected to the proximal segment, a distal port connected to the distal segment, and a sampling port closed by an elastomeric seal. The method includes the steps of:

providing a disposable sampling subsystem for engaging the fluid sampling site including a flowthrough bypass cannula having a probe, a fluid reservoir, and a fluid sampling container;

engaging the bypass cannula with the sampling site so that the probe passes through the elastomeric seal;

opening fluid communication between the bypass cannula and reservoir while closing fluid communication between the bypass cannula and fluid sampling container;

closing fluid communication between the bypass cannula and proximal segment of the conduit line and drawing fluid into the reservoir from the distal segment through the bypass cannula until blood enters the sampling site;

opening fluid communication between the bypass cannula and fluid sampling vessel while closing fluid communication between the bypass cannula and reservoir;

drawing blood into the fluid sampling vessel from the distal segment;

maintaining the bypass cannula engaged with the sampling site until a sample of blood is drawn into the fluid sampling container; and

detaching the bypass cannula from the sampling site and disposing of the sampling subsystem.

[0015] The method desirably also includes providing a pressure transducer connected to the proximal segment of the conduit line and sensing the pressure of the fluid system of a patient through the fluid in the conduit line.

[0016] In one embodiment, the disposable sampling subsystem includes a stopcock having three ports, a first port in communication with the bypass cannula, a second ports in communication with the fluid reservoir, and a third port in communication with the fluid sampling container, wherein following steps of the method are enabled by manipulating the stopcock:

opening fluid communication between the bypass cannula and reservoir while closing fluid communication between the bypass cannula and fluid sampling container; and

opening fluid communication between the bypass cannula and fluid sampling vessel while closing fluid communication between the bypass cannula and reservoir.

[0017] In one version of the method the step of opening fluid communication between the bypass cannula and reservoir while closing fluid communication between the bypass cannula and fluid sampling vessel is accomplished by the step of engaging the bypass cannula with the sampling site. The probe of the bypass cannula may have a size sufficient to contact a passageway opening leading to the proximal port of the sampling site, and exclude fluid communication between the proximal port and the distal port by, for example, occluding the passageway opening.

[0018] The method may alternatively include providing a stopcock adjacent the proximal port of the sampling site for occluding the proximal port

when fluid is drawn into and expelled from the reservoir and drawn into the fluid sampling container.

[0019] A further understanding of the nature and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings in which like parts bear like reference numerals.

Brief Description of the Drawings

[0020] Features and advantages of the present invention will become appreciated as the same become better understood with reference to the specification, claims, and appended drawings wherein:

[0021] Figures 1A-1C are schematic diagrams of blood sampling systems within dedicated closed reservoirs within pressure monitoring lines of the prior art;

[0022] Figures 2A-2B are schematic diagrams of two different configurations of a blood sampling system of one embodiment of the present invention within a pressure monitoring line;

[0023] Figure 3 illustrates a typical hospital room setup of a pressure monitoring system for a patient incorporating two fluid sampling ports of one embodiment of the present invention;

[0024] Figure 4 schematically illustrate a fluid sampling system in conjunction with the fluid sampling ports of Figure 3;

[0025] Figure 5 is an exploded sectional view of the main fluid sampling components of one embodiment of the present invention;

[0026] Figure 6 is a partial sectional view of a flowthrough bypass cannula of the fluid sampling system of one embodiment of the present invention engaged with a fluid sampling site and illustrating the occlusion of a proximal segment of the pressure monitoring line;

[0027] Figures 7A-7E are schematic views illustrating a sequence of steps involved in taking a fluid sample in accordance with one embodiment of the present invention;

[0028] Figures 8A-8C are perspective assembled and exploded views of an exemplary bypass cannula and a sampling site combination of one embodiment of the present invention;

[0029] Figure 9A is a top plan view of the bypass cannula and sampling site combination of Figures 8A-8C;

[0030] Figures 9B and 9C are vertical sectional views along orthogonal axes through the centerline of the bypass cannula and sampling site combination, taken along respective section lines shown in Figure 9A;

[0031] Figure 10 is a vertical sectional view through an alternative bypass cannula and sampling site combination of one embodiment of the present invention;

[0032] Figure 11 is a vertical sectional view through another alternative bypass cannula and sampling site combination of one embodiment of the present invention;

[0033] Figures 12A and 12B illustrates a still further alternative bypass cannula and sampling site combination, as well as an exemplary bubble trap that may be used therewith; and

[0034] Figure 13 is an alternative disposable fluid sampling system of one embodiment of the present invention that permits fluid to be drawn into and expelled from a removable reservoir to and from a distal segment of a conduit line while occluding a proximal segment.

Detailed Description of the Preferred Embodiments

[0035] The present invention provides an improved blood sampling system, desirably for use in a pressure monitoring line. As mentioned above, continuous or periodic blood pressure monitoring is a common and extremely useful tool in the intensive care or operating room. However, it should be mentioned that the apparatuses and methods described herein could be utilized in conjunction with any fluid system of a patient which would benefit from pressure monitoring. For instance, intracranial pressures could be monitored and cerebrospinal fluid samples taken by placing the system described herein in

fluid communication with an intraventricular catheter. Therefore, the appended claims cover the sampling and monitoring of any fluid system within a patient unless otherwise specified. Additionally, certain aspects of the present invention may be useful for taking fluid samples in conduit lines connected to the patient that do not include pressure monitoring, such as from existing injection lines for arterial or venous drug infusion.

[0036] The present invention comprises an improved sampling system especially useful for sampling blood in the operating room (OR), intensive care unit (ICU) or critical care unit (CCU). The system is closed as some in prior systems, for example the VAMP Plus® Venous Arterial blood Management Protection system available from Edwards Lifesciences of Irvine, CA, because the prime volume drawn in to a reservoir may be returned to the patient. However, one embodiment of the present invention also provides an option of discarding the prime volume, and does not include a "dedicated" in-line reservoir.

[0037] Figures 1A-1C are schematic diagrams of closed blood sampling systems within pressure monitoring lines of the prior art. As explained above, a "closed" system typically features a dedicated in-line reservoir (i.e., one that remains connected), therefore avoiding "breaking" (or opening) the conduit line to pull the pure blood across the sampling site. This eliminates any potential contamination of the blood or contamination of the environment from the blood, such as if a removable syringe was used and set aside for later re-infusion. The systems illustrated in Figures 1A-1C all include a dedicated reservoir 20 mounted within a fluid conduit line or tubing connected to a fluid system of the patient P, much like the VAMP Plus® Venous Arterial blood Management Protection system available from Edwards Lifesciences.

[0038] Figure 1A illustrates a pressure monitoring system where the placement of the reservoir 20 defines a distal segment 22 and a proximal segment 24 of the conduit line. The conduit line is primarily medical grade pressure tubing. The system includes a disposable pressure transducer (DPT) 26 in the proximal segment 24 which measures pressure pulses within the fluid

column in the conduit line derived from a patient to which the distal segment 22 connects. Although not shown, the distal end of the distal segment 22 typically includes a luer connector which engages a mating luer connector on an in-dwelling catheter or cannula placed in a vein or artery of the patient. In this manner, the pulse and blood pressure of the patient transmits through the fluid column within the conduit line to the pressure transducer 26.

[0039] Pressure lines such as shown in Figure 1A typically make use of relatively stiff tubing primed with a suitable physiological fluid such as saline or 5% dextrose solution from a supply bag 30 (denoted "I.V.") as a pressure column. For adults, a bag pressurized with air surrounds the fluid supply bag to maintain a constant pressure differential in the line urging fluid toward the patient through a restrictor orifice. The slow drip of physiological fluid, as indicated by the flow arrows in Figure 1A, flushes the line to prevent clotting. Some transducers such as the TruWave® Disposable Pressure Transducer from Edwards Lifesciences include a flush device that also can be used for sending transient pressure waves through the line. A Snap-Tab™ device of the TruWave® is a rubber tab which when pulled and then released sends a square wave through the pressure column to check the inherent frequency response of the entire system, which includes the tubing and any components attached thereto.

[0040] When the pressure line is also used for fluid sampling it features at least one and preferably two sampling sites 32, 34 in the proximal segment 24. A proximal sampling site 32 is located near the reservoir 20, often 5 or 6 feet (152-178 cm) from the patient. The distal sampling site 34 is located close to the distal end of the conduit line. The operators (clinicians) who draw blood samples can be generally categorized in two groups: 1) OR nurses and anesthesiologists, and 2) CCU or ICU nurses. Each grouping has different requirements regarding position of the sampling sites. In the OR, access near the patient is limited; therefore the preferred sampling site location is near the IV pole, so the proximal sampling site 32 is preferred. On the other hand, in the

CCU or ICU nurses prefer to take blood as close to the patient as possible, so the distal sampling site 34 is preferred.

[0041] Figure 1B shows one step in operation of the sampling system wherein a prime volume of fluid has been drawn into the reservoir 20 from the distal segment 22 of the conduit line. The reservoir 20 has sufficient capacity to draw all of the saline and mixed saline and blood into its chamber such that pure blood extends from the patient past one or both of the sampling sites 32, 34. In the illustrated embodiment, enough prime volume has been drawn into the reservoir 20 such that a sample can be taken at the proximal sampling site 32, as indicated by the schematic sampling syringe 36, though of course a sample could be taken at the distal site 34. Prior to taking the sample, a stopcock 38 between the reservoir 20 and sampling site 32 is closed to prevent drawing any fluid into the sampling syringe 36 from the reservoir 20, thus insuring an undiluted sample. After taking a sample, the nurse withdraws the syringe 36 from the sample site 32, opens the stopcock 38, and depresses the plunger of the reservoir 20 so that the entire prime volume infuses back to the patient.

[0042] Figure 1C illustrates an alternative pressure monitoring/fluid sampling conduit line wherein a dedicated reservoir 20 is located close to the patient and there is only one sampling site 40. This system functions in a similar manner to the one described above, but is typically only used in the CCU or ICU because of the proximity of the sampling site 40 to the patient, which would get in the way in the OR.

[0043] Figures 2A and 2B are schematic views of a pressure monitoring/fluid sampling system of one embodiment of the present invention. As in the prior art systems, a conduit line 50 extends between an injection site in a vein or artery of the patient to a source of physiological fluid 52. A pressure transducer 54 connects to the fluid column within the conduit line 50 near the proximal end, and the system includes a proximal sampling site 56 and a distal sampling site 58, desirably at the same locations as those shown in Figure 1A.

[0044] The system of Figures 2A and 2B does not include a dedicated in-line reservoir or stopcock as described above. Instead, a removable fluid

sampling subsystem 60 is designed to engage either of the sampling sites 56, 58, but does not remain attached to the conduit line when not in use. Figure 2A illustrates engagement of the subsystem 60 with the proximal sampling site 56, while Figure 2B shows the subsystem 60 engaged with the distal sampling site 58. In this manner, the pressure monitoring function of the system is improved by removal of the dedicated reservoir 20 and stopcock 38 shown in Figures 1A-1C. That is, any reduction in signal fidelity caused by those dedicated components is removed. Also, elimination of an in-line reservoir dangling from the conduit line removes that potential cause of tangling with bedclothes or other such items. Furthermore, the fluid sampling aspect of the system is flexible such as that seen in Figure 1A, with both proximal and distal sampling sites provided for use in different hospital settings, depending on need.

[0045] Exemplary details of the components of the system of Figures 2A-2B will be described below, however the system enables a method for sampling fluid from a medical pressure monitoring conduit line without a dedicated reservoir, though with the closed functionality of such a reservoir, and greatly improved convenience. In essence, the system enables as-needed fluid sampling from the pressure monitoring line by temporary attachment of a fluid reservoir to one of the sampling sites, occlusion of fluid communication between the reservoir and the conduit line proximal to the sampling site, withdrawal of a prime volume from the distal segment into the reservoir, taking of a blood sample, re-introduction of the prime volume into the conduit line, and removal of the fluid reservoir from the conduit line.

[0046] Figure 3 illustrates an exemplary pressure monitoring system in a typical hospital room environment and connected to a patient P. The system shown in Figure 3 is absent the detachable/disposable blood sampling subsystem 60 of Figure 2, and therefore possesses a fairly low profile in the clinical setting which greatly enhances convenience when no blood sample is being taken. The pressure monitoring system comprises a conduit line 70 having a distal segment toward the patient and a proximal segment away from the patient. (As will be clear below, the terms proximal and distal segments will

be used relative to either of two blood sampling sites.) The distal segment may terminate in a male luer connector 72 for attaching to a female luer connector (not shown) of an injection site, or other conduit leading to the patient.

[0047] As mentioned above, the exemplary blood sampling system advantageously works in conjunction with the pressure monitoring system. The proximal segment of the conduit line terminates in a female luer connector 74 attached to a stopcock (not shown) of a pressure transducer 78, such as a TruWave™ Disposable Pressure Transducer available from Edwards Lifesciences of Irvine, CA. The pressure transducer 78 removably mounts to a bracket 80 which, in turn, may be secured to a conventional pole support 82 with the reservoir in a vertical orientation. A supply of flush solution 84 connects to a flush port 86 of the transducer 78 via tubing 88. Typically for adults, the flush solution 84 comprises a bag of physiological fluid such as saline surrounded by a pressurized sleeve that squeezes the fluid and forces it through the tubing 88. In addition, an infusion fluid supply (not shown) may be provided in communication with an infusion port of the stopcock 76. The pressure transducer 78 is thus placed in fluid communication with the arterial or venous system of the patient through the conduit line 70, and preferably includes a cable 92 and plug to connect to a suitable display monitor 94.

[0048] The blood sampling system 96 shown in Figure 4 comprises at least one and desirably both proximal and distal fluid sampling sites 100, 102 in the conduit line (also seen in Figure 3). Each sampling site 100, 102 defines a flow passage, preferably Z-shaped, adjacent a pre-slit septum (described below). With this configuration, a minimal amount of flush volume is needed to clear the line after sampling. The septum preferably comprises a split elastomeric disc which accepts a blunt cannula and reseals after each sample is drawn, reducing the potential for contamination and eliminating the danger of needle sticks. A similar sampling site is described in U.S. Patent No. 5,135,489 to Jepson, et al.

[0049] Figure 4 further illustrates an exploded packaged sterile kit that includes the aforementioned blood sampling subsystem 60 and integrates a

blood sampling collection vessel with a pull-back reservoir. This is a single use, disposable accessory used to sample blood at either the proximal (OR) sampling site 100 or distal (ICU/CCU) sampling site 102. The kit desirably consists of the following elements:

- Bypass cannula - 110
- Pull-back reservoir (shown as a simple syringe) - 112
- Sample collection vessel (Syringe or Vacutainer®) - 114
- 3-position valve, or stop-cock -116
- Short tube segment - 118
- Elbow - 120
- Sterile packaging - 122

[0050] Because the sterile kit described above works in conjunction with one of the two sampling sites 100, 102, and samples blood that is present in the conduit line 70, all of these components together make up the fluid sampling system 96 of one embodiment of the present invention. However, it should be understood that some of the elements above, such as the elbow 120, are optional.

[0051] Figure 4 best illustrates the disposable nature of most of the blood sampling system 96. Indeed, all of the disposable components of the system 96 are provided in the sterile package 122 for use at one of the two sample sites, and are then detached from the conduit line 70 and discarded. As mentioned, this greatly enhances the convenience of the system by eliminating the dedicated, in-line reservoir. However, as will be clear, the system remains closed during the sampling process and provides all of the safety benefits of a conventional dedicated reservoir. Moreover, as will be seen in greater detail below, the disposable components provided in the sterile package 122 are relatively simple, inexpensively produced items, which reduces the cost of the system even if multiple sterile packages 122 are used. Furthermore, because the reservoir 112 does not remain connected with conduit line 70, there is no need for a contamination sleeve or other special design to prevent blood stagnation.

[0052] Figure 5 is a close-up partial sectional view of an exemplary fluid sampling system 96 of one embodiment of the present invention. As mentioned, one of the two sampling sites 100, 102 within the conduit line 70 forms a part of the system 96. In the illustrated embodiment, the distal or patient segment 124 is to the left, while a proximal or pressure transducer/I.V. segment 126 is to the right. The sampling site 100, 102 is shown as a conventional "Z-site," so named because of the Z-shaped path taken by the fluid drip therethrough, as indicated. The sampling site 100, 102 includes a rigid housing 130 having a distal port 132 connected to the distal segment 124 and a proximal port 134 connected to the proximal segment 126, wherein fluid may flow freely through an inner chamber 136 in the housing between the proximal and distal ports. The sampling site 100, 102 further defines a sampling port 138 opening into the chamber 136 that is closed by an elastomeric septum or seal 140.

[0053] It should be emphasized at this point that although a particular blood sampling site (i.e., a Z-site configuration) is illustrated and described as a component of the blood sampling system, other in-line sampling sites could also be used. That is, the disposable blood sampling subsystem 60 described above may be designed to interact with other sampling sites than those illustrated. The disposable subsystem 60 is intended to be used with any flowthrough sampling site which includes a rigid housing having distal and proximal ports for connecting the sampling site within a fluid conduit line, and a sampling port to which the subsystem connects. The proximal, distal, and sampling ports all open to an internal chamber, and the sampling port is typically closed by an elastomeric seal or septum. As mentioned above, U.S. Patent No. 5,135,489 to Jepson, et al. exemplifies this type of sampling site, though another similar sampling site which could be used is disclosed in U.S. Patent No. 5,417,673 to Gordon.

[0054] As seen in Figure 5, the flowthrough bypass cannula 110 includes a generally tubular rigid body 150 defining a front fitting 152 shaped to engage the sampling port 138, and a bypass probe 154 that pierces the

elastomeric seal 140, projects into the chamber 136 and occludes the proximal port 134 of the sampling site. The bypass cannula 110 further defines a central throughbore 156 in communication with a rear fitting 158 opposite the front fitting 152. The throughbore 156 extends part way along the bypass probe 154 and opens within the front fitting 152 at at least one side passage 159. The terminal end of the probe 154 possesses an enlarged head or plug 160. The probe 154 may be configured in a number of ways, as will be seen, but includes a terminal end that mates with the opening to a passageway leading to one of the ports of the sampling site 100, 102, as seen in Figure 6. The exemplary probe 154 further includes at least one opening such as the side passage 159 providing fluid communication between the throughbore 156 and the chamber 136 of the sampling site. The probe 154 therefore may be configured as a tubular member having a solid terminal end at plug 160, and diametrically opposed side passages 159 just before the plug.

[0055] The front fitting 152 is illustrated as a female cap member that fits over the male sampling port 138 of the sampling site 100, 102. In this regard, opposed flanges or ribs (not numbered) ensure an interference or snap fit and positive coupling of the bypass cannula 110 to the sampling site. Of course, other arrangements such as a threaded (e.g., luer) coupling may be provided. One desirable feature of the system is to maintain a good seal between the plug 160 and passage within the sampling site 100, 102. This can be accomplished between various materials (rigid or compressible) using mechanical pressure by way of a snap fit or a threaded engagement between the bypass cannula 110 to the sampling site 100, 102. Any such connection desirably provides constant mechanical force and accommodates tolerance variations typical of manufacturing processes.

[0056] The stopcock 116 connects to the rear fitting 158 of the bypass cannula 110. In this regard, the stopcock 116 may attach directly to the fitting 158, or via the intermediate tubing segment 118. A transparent tubing segment 118 is preferably utilized so that the clinician can monitor the formation of any bubbles within the aspirated fluid created by the suction of the reservoir 112.

The short tubing segment 118 is included as a safety precaution against air bubble infusion. Because the syringe-type reservoir 112, bypass cannula 110, and tubing 118 are often not purged of air prior to sampling, an air pocket between the reservoir plunger and fluid may form during the draw back step. In the unlikely event of trapped air bubbles, they will be visible in the short (between 3 and 8 inches) tubing segment 118. In such a situation, the user would simply disconnect and dispose of the entire subsystem 60.

[0057] The stopcock 116 defines three ports: a first port 170 in communication with the rear fitting 158 of the bypass cannula, a second port 172 adapted to mate with a coupling 174 on the reservoir 112, and a third port 176 adapted to couple to one end of the elbow 120. The elbow 120 in turn includes a fitting on its opposite end that mates with a coupling 178 on the sample collection vessel 114. A handle 180 of the stopcock 116 may be manipulated into three positions to provide fluid communication between any two of the three ports, to the exclusion of the other. Again, the engagement of the various ports and connected elements may be through luer fittings, snap fittings, or the like. The use of standard luer connection fittings enables the users to substitute standardized components if they so choose

[0058] Figure 6 illustrates a slightly modified flowthrough bypass cannula 190 engaged with a sampling site 100, 102. The bypass probe 194 is shown piercing the elastomeric seal 140 of the sampling site to enter the chamber 136. The tapered distal end 192 of the bypass probe 194 seats against a similarly tapered internal opening (not numbered) to the proximal port 134 of the sampling site. Because of one or more side openings 196 in the bypass probe 194, an inner throughbore (not shown) of the bypass cannula 190 opens to the chamber 136 within the sampling site. Inner threads on a front fitting 198 of the bypass cannula 190 mate with external threads formed on the sampling port 138 of the sampling site.

[0059] Operation of the fluid sampling system of one embodiment of the present invention will now be described with reference to the exemplary

structures shown in Figures 5 and 6, and the schematic sequence of events shown in Figures 7A-7E.

[0060] First, the fluid sampling subsystem 60 is removed from the sterile package 122 (Figure 4) and the appropriate components are connected with the bypass cannula 110, 190 engaging the sampling port 138 of the sampling site 100, 102 (Figure 7A). As seen in Figure 6, this causes the bypass probe 154, 194 to pass through the elastomeric septum 140 into the chamber 136. The length of the probe 194 and its configuration is such that its distal tip 192 engages and occludes the opening to the proximal port 134 of the sampling site. The single step of engaging the cannula 110 to the sampling site 100, 102 places the reservoir 112 into fluid communication with the distal segment 124 of the conduit line and simultaneously blocks flow between the proximal segment 126 and the sampling site chamber 136.

[0061] The step of engaging the bypass cannula 110, 190 with the sampling site 100, 102 is desirably accomplished with the handle 180 of the stopcock 116 in a position that blocks fluid flow through the stopcock; that is, the first port 170 is closed. After secure engagement of the bypass cannula 110, 190 with the sampling site, the clinician manipulates the stopcock handle 180 into a position that permits fluid flow from the sampling site through the bypass cannula 110, 190 and to the reservoir 112; that is, the first port 170 communicates with the second port 172.

[0062] Retraction of a plunger of the reservoir 112 creates a negative pressure differential such that a fluid sample from the distal segment 124 is drawn into the chamber 136 and into the reservoir 112 (Figure 7B). The reservoir 112 has a sufficient volume, typically 5-15 ml, to draw blood from the patient P past both sampling sites 100, 102. If blood is being taken from distal sampling site 100 in the ICU/CCU, the prime volume is typically about 5 ml, whereas if blood is taken from the proximal sampling site 102 in the OR, the prime volume is typically about 12 ml. Please note that the syringe-type reservoir 112 could be used, or another manual draw type reservoir, or even mechanically-assisted fluid draw device.

[0063] Once all of the saline and mixed saline and blood has been pulled into the reservoir 112, the clinician can then take a sample of undiluted blood from the site 100, 102. To do so, he/she manipulates the stopcock handle 180 into a position that blocks flow to the reservoir 112 and permits flow between the bypass cannula 110 and the third port 176 leading to the elbow 120 and sample collection vessel 114. As indicated in Figure 7C, a sample of blood is then drawn into the collection vessel 114 through action of a plunger, or as soon as the stopcock handle 180 opens the flow, if the collection vessel is an evacuated container (e.g., Vacutainer®). The sample collection vessel 114 is designed to be detached from the elbow 120 or directly from the stopcock 116 for remote analysis of the blood therein. It should be understood that in one use of the disposable blood sampling subsystem 60 more than one sample may be taken by simply engaging more than one collection vessel 114 in sequence.

[0064] After the desired sample is taken, the stopcock handle 180 is again manipulated into a position that closes off the third port 176 and opens flow between the first and second ports 170, 172 (i.e., between the sampling site 100, 102 and reservoir 112). Subsequently, the blood and other fluids drawn into the reservoir 112 during the sample priming operation are re-infused by depressing the reservoir plunger (Figure 7D) into the distal segment 124, and ultimately back to the patient. It should be noted that during this re-infusion step the bypass probe 154, 194 remains occluding the proximal port 134 of the sampling site so that fluid from the reservoir 112 does not travel into the proximal segment 126 toward the pressure transducer.

[0065] It is important to understand that the sampling system 96 provides a closed reservoir 112 since the priming volume that ensures a pure sample of blood reaches the sampling site 100, 102 remains within the system 96 and is re-infused into the patient without removal of the reservoir. That is, because the reservoir 112 as a part of the sampling subsystem 60 remains connected to the sampling site 100, 102 during the entire process until re-infusion, the conduit line is not "broken," meaning the reservoir is not detached between drawing the prime volume and re-infusing it. Of course, as mentioned

above, if the clinician notices bubbles have formed within the reservoir 112 or adjacent tubing, the subsystem 60 can be removed from the sampling site 100, 102 without re-infusing the prime volume, which is then also discarded. This is a significant advantage over earlier "dedicated" reservoirs which could not be removed and had to be operated with great care to prevent formation of bubbles.

[0066] Finally, as indicated in Figure 7E, after obtaining a blood sample the clinician detaches the fluid sampling subsystem 60 from the sampling site 100, 102 and discards it. Again, this is preferred over dedicated reservoirs which can get tangled with sheets and such.

[0067] The reader will now appreciate certain benefits of the improved fluid sampling system as follows:

- The pull back reservoir 112 desirably comprises a simple inexpensive syringe. Because this is a single use device no contamination shield is required.
- Elimination of the pull back reservoir from the pressure monitoring system eliminates the chances of air bubbles, residual blood, and makes priming and initial set-up much easier.
- By eliminating the reservoir from the pressure monitoring system there is no impact to the pressure wave form fidelity.
- The pull back reservoir is no longer integrated into the tubing system. This eliminates the tangling or snagging with the patients bedding or other equipment. Elimination of the reservoir makes for a much cleaner, or less cluttered, system.
- Blood pressure monitoring kits can be configured with two Z-sites so that both ICU and OR clinicians can have easy access to blood samples. A single "universal" blood pressure monitoring kit can serve both the ICU and the OR user.
- Products that are currently available require the user to first manipulate the reservoir, and valve. They then have to reposition their hands to take a sample from the Z-site. Then they have to reposition their hands back to the reservoir and

valve. This sequence requires the user to reposition three times. The advantage of the present system is that all sampling activities happen with one single user positioning.

- Because the reservoir is only used once there is no need for a complex design, nor is there a need for a contamination shield. A standard syringe can be incorporated into the kit configuration thereby providing a low cost sampling system.

[0068] The bypass function (i.e., excluding the proximal segment) of the sampling system of the present invention can be achieved in a number of ways. Figures 8A-8C and 9A-9E illustrate in great detail an alternative exemplary sampling site 200 and bypass cannula 202. The sampling site 200 is shown exploded in Figure 8C and features a main body 204 adapted to project upward from a base plate 206. The base plate 206 includes slots for securing it with tape, for example, to a base surface. The main body 204 is desirably rigid molded plastic having a central column 208 with a closed bottom and a sampling port 210 opening upward. A proximal port 212 projects horizontally from one side of the column 208, while a distal port 214 projects horizontally in the opposite direction but offset vertically. The main body 204 mounts on top of a tubular flange 216 on the base plate 206 via an intermediate O-ring 218. As seen in the sectional views of Figures 9B and 9C, a plug member 220 extends upward into a countersunk bore in the base plate 206 to contact the underside of the main body 204. Desirably, the main body 204 and the plug member 220 are attached via adhesive, or other similar expedient.

[0069] The bypass cannula 202 is similar to those described above and includes a front fitting 230 bifurcated into a pair of fingers or skirts 232. The front fitting 230 positively engages the sampling port 210 of the sampling site 200, while a rear fitting 234 projects upward. The vertical gaps between the bifurcated skirts 232 receive the outwardly projecting proximal and distal ports 212, 214.

[0070] With reference to Figures 9B and 9C, the bypass cannula 202 further includes a bypass probe 240 aligned along a central axis defining a throughbore 242 therein and terminating in an open and tapered distal tip 244. When the bypass cannula 202 couples to the sampling site 200, the bypass probe 240 projects through an elastomeric septum 246 provided at the opening of the sampling port 210. The length of the bypass probe 240 is sufficient so that the tapered tip 244 extends into a central chamber of the sampling site main body 204 and into engagement with a similarly tapered opening (not numbered) that communicates with a passageway opening leading to the distal port 214. Upon engagement between the bypass cannula 202 and sampling site 200, the throughbore in the bypass probe 240 and rear fitting 234 is placed in fluid communication with the passageway through the distal port 214, to the exclusion of the proximal port 212. That is, instead of forming the bypass probe 240 with a solid distal end and side openings as before, it is a continuous tubular member open only at its distal end, so that engagement of the passageway opening with the distal port 214 excludes communication between the proximal port 212 and the throughbore 242.

[0071] The bifurcated skirts 232 of the bypass cannula 202 extend axially farther than the length of the bypass probe 240. The bypass cannula 202 therefore includes the safety feature of a blunt-tipped probe 240 which is also protected from undesirable contact or damage by the generally parallel and laterally adjacent skirts 232. The skirts 232 each have on their lowermost ends small internal depressions that receive similarly-shaped teeth 250 on the tubular flange 216 of the sampling site 200. Furthermore, the external shape of the central column 208 of the sampling site main body 204 is slightly conical, though the skirts 232 are not and they are slightly outwardly biased upon engagement with the main body 204. Engaging the bypass cannula 202 onto the sampling site 200 involves pressing the cannula downward such that the probe 240 extends through the elastomeric septum 246 and the bifurcated skirts 232 flex outward until the lower depressions are engaged with the teeth 250. Desirably, the engagement provides an audible "snap," and the coupling is

made more secure by the frictional contact of the skirts 232 against the intermediate O-ring 218. Once the bypass cannula 202 and sampling site 200 are fully engaged, the tapered tip 244 of the bypass probe 240 accurately seats within the tapered opening in the sampling site main body 204. The procedure for taking a fluid sample using the combined bypass cannula 202 and sampling site 200 is similar to that described above.

[0072] Figure 10 illustrates an alternative bypass cannula 260 and sampling site 262 combination of one embodiment of the present invention which is very similar to that shown in Figures 8-9. As before, the sampling site 262 includes a main body 264 defining an internal chamber opening at a distal port 266, a proximal port 268, and a sampling port 270. An elastomeric seal or septum 272 occludes the sampling port 270 until the bypass cannula 260 engages the sampling site 262 and a bypass probe 274 projects therethrough. As above, the bypass probe 274 has a tapered tip, but instead of fitting into a tapered seat within the main body 264, it expands within and contacts the bore of a tubular sealing member 276. The sealing member 276 is made of a compressible material such as silicone rubber which provides good sealing contact against the bypass probe 274. It will thus be apparent that engagement of the bypass cannula 260 over the sampling site 262 enables a fluid flow between the bypass cannula throughbore and the distal port 266, thus bypassing the proximal port 268.

[0073] Figure 11 illustrates another alternative bypass cannula 280 and sampling site 282 combination of one embodiment of the present invention which is similar to that shown in Figure 5. As before, the sampling site 282 includes a main body 284 defining an internal chamber opening at a distal port 286, a proximal port 288, and a sampling port 290. An elastomeric seal or septum 292 occludes the sampling port 290 until the bypass cannula 280 engages the sampling site 282 and a bypass probe 294 projects therethrough. As with the embodiment of Figure 5, the bypass probe 294 terminates in an enlarged and tapered tip 296. The tip 296 acts as a plug to contact and occlude a passageway leading to the proximal port 288. One or more side openings 298

provided in the bypass probe 294 enable fluid communication between the internal chamber of the main body 284 and the throughbore of the bypass cannula 280. It will thus be apparent that engagement of the bypass cannula 280 over the sampling site 282 enables a fluid flow between the bypass cannula throughbore and the distal port 286, to the exclusion of the proximal port 288. To further enhance the ability of the bypass probe 294 to plug the opening to the proximal port 288, the tapered tip 296 may be supplemented with an elastomeric head or other compressible coating.

[0074] Figures 12A and 12B illustrate a still further alternative bypass cannula 300 and sampling site 302 combination, as well as an exemplary bubble trap 304 that may be used therewith. The bypass cannula 300 has a threaded front fitting 306 adapted to mate with a threaded sampling port 308 of the sampling site 302. As before, the bypass cannula 300 includes a bypass probe 310 sized to extend through an elastomeric seal or septum 312 into engagement with a passage leading to a distal port 314 of the sampling site 302. The bypass probe 310 is similar to the bypass probe 240 of Figures 8 and 9 in that it is a continuous tube having a central throughbore 316. The engagement of bypass cannula 300 with the sampling site 302 therefore connects the throughbore of the cannula with the distal port 314 and a distal segment 318 of a conduit line leading to a patient, and excludes a proximal port 320 and a proximal segment 322 from the flow path.

[0075] The bypass cannula 300 connects through the bubble trap 304 to a 3-way stopcock 330, and from there to a reservoir 332 and elbow conduit 334. Although not shown, a sampling collection vessel may be connected to the opposite end of the elbow conduit 334. Indeed, the system functions in a similar manner to those described above, with the exception of the interposition of the bubble trap 304.

[0076] With reference to Figure 12B, the bubble trap 304 includes a generally tubular outer body 340 having a conical lower end 342 and defining a float chamber 344 therewith. The lower end 342 opens into the central throughbore 316 of the bypass probe 310. A ball valve 346 floats on any fluid

within the chamber 344, and nests within a similarly shaped inner surface at the bottom of the float chamber 344. A flow separator 348 projects downward from an upper cap 350 of the bubble trap 304. Passages around the flow separator 348 leading to an upper throughbore 352 within the cap 350. The upper cap 350 receives the optional flexible tubing 354 leading to the 3-way stopcock 330.

[0077] In use, fluid drawn into the reservoir 332 passes upward through the bubble trap 304 without hindrance. Bubbles that may form from the suction created by the reservoir 332 rise to the fluid surface layer within the chamber 344 and pop. Upon re-infusion from the reservoir 332, the fluid passes downward through the bubble trap 304, bypass cannula 300, and into the distal port 314 and distal segment 318 of the conduit line. Once the fluid level within the chamber 344 lowers enough, the ball valve 346 contacts the shaped inner surface of the float chamber 344 to prevent any air or bubbles being passed into the conduit line.

[0078] Figure 13 is an alternative disposable fluid sampling system 360 of one embodiment of the present invention that again permits fluid to be drawn into and expelled from a removable reservoir 362 to and from a distal segment 364 of a conduit line while occluding a proximal segment 366. Although not shown, the distal and proximal segments 364, 366 desirably formed a part of a pressure monitoring conduit line where the distal segment 364 communicates with a fluid system of the patient and proximal segment 366 connects to a disposable pressure transducer (DPT) and an intravenous (I.V.) drip. The fluid sampling system 360 resembles somewhat that shown in Figure 5, wherein a disposable subsystem comprises the reservoir 362, a 3-way stopcock 370, an optional length of flexible tubing 372, a flowthrough bypass cannula 374, an optional elbow conduit 376, and a sample collection vessel 378. The bypass cannula 374 engages a sampling port 380 of the sampling site 382 positioned in the conduit line between the distal segment 364 and proximal segment 366.

[0079] In contrast to the earlier-described embodiments, a hollow probe 390 on the bypass cannula 374 has a length sufficient to extend through a slit septum 392 within the sampling port 382 into an inner chamber 394 of the

sampling site 382, but not long enough to engage any passageway openings therein. Instead, the probe 390 extends just passed the septum 392 into the inner chamber 394 and remains in fluid communication with both the distal segment 364 and proximal segment 366. In other words, the probe 390 does not in itself provide the bypass function described above.

[0080] The fluid sampling system 360 further includes a 2-way stopcock 400 positioned adjacent to the sampling site 382 in the proximal segment 366 of the conduit line. Alternatively, the 2-way stopcock 400 could be incorporated into the sampling site 382, although such a design is relatively more expensive to manufacture. The stopcock 400 provides the bypass function of the fluid sampling system.

[0081] In use, the clinician manipulates the stopcock 400 to disconnect the proximal segment 366 of the conduit line from the sampling site 32. The disposable subsystem is removed from its sterile package (e.g., the sterile package 122 of Figure 4) and the appropriate components are connected with the bypass cannula 374 engaging the sampling port 380 of the sampling site 382. The probe 390 passes through the elastomeric septum 392 into the chamber 394.

[0082] The step of engaging the bypass cannula 374 with the sampling site 382 occurs while the stopcock 370 blocks fluid flow therethrough. After secure engagement of the bypass cannula 374 with the sampling site 382, the clinician manipulates the stopcock 370 into a position that permits fluid flow from the distal segment 364 and sampling site 382 through the bypass cannula 374 and to the reservoir 362. Retraction of a plunger (not shown) of the reservoir 362 creates a negative pressure differential such that a fluid sample from the distal segment 364 is drawn into the chamber 394 and into the reservoir 362.

[0083] Once all of the saline and mixed saline and blood has been pulled into the reservoir 362, the clinician can then take a sample of undiluted blood from the site 382. To do so, he/she manipulates the stopcock 370 into a position

that blocks flow to the reservoir 362 and permits flow between the bypass cannula 374 and the elbow conduit 376 and sample collection vessel 378.

[0084] After the desired sample is taken, the clinician again manipulates the stopcock 370 into a position that closes off the elbow conduit 376 and opens flow between the reservoir 362 and sampling site 382. Blood and other fluids drawn into the reservoir 362 during the sample priming operation are re-infused by depressing the reservoir plunger into the distal segment 364, and ultimately back to the patient. It should be noted that during this re-infusion step the stopcock 400 remains closed so that fluid re-infused from the reservoir 362 does not travel into the proximal segment 366 toward the DPT. After re-infusion of the prime volume the clinician manipulates the stopcock 370 to close off the communication between the sampling port 380 and reservoir 362 and removes and discards the disposable subsystem by disconnecting the bypass cannula 374 from the sampling site 382. The clinician opens the stopcock 400 and the "normal" operation of the conduit line resumes, such as a flushing drip and pressure monitoring.

[0085] Again, the sampling system 360 provides a closed reservoir 362 since the priming volume that ensures a pure sample of blood reaches the sampling site 382 remains within the system and is re-infused into the patient without removal of the reservoir. That is, because the reservoir 362 as a part of the disposable subsystem remains connected to the sampling site 382 during the entire process until re-infusion, the conduit line is not "broken," meaning the reservoir is not detached between drawing the prime volume and re-infusing it. Of course, as mentioned above, if the clinician notices bubbles have formed within the reservoir 362 or adjacent tubing, the disposable subsystem can be removed from the sampling site 382 without re-infusing the prime volume, which is then also discarded.

[0086] The system 360 of Figure 13 functions in a similar manner as the earlier-described embodiments, in that the sampling subsystem including the fluid draw reservoir is removable and disposable. Moreover, the reservoir is closed because it remains in place during the fluid draw and re-infusion.

However, if bubbles are detected in the reservoir or intermediate tubing the fluid draw can be discarded which is not possible with a dedicated reservoir. All of the systems of the present invention provide a removable/disposable closed reservoir that can be isolated from the proximal or upstream segment of the conduit line.

[0087] In contrast to the earlier-described embodiments of the present invention, the bypass feature of the fluid sampling system 360 is enabled by the proximal stopcock 400 rather than by simple engagement of a bypass cannula with the sampling site. One advantage with such a system is the elimination of the need for special components such as the bypass probes described above, and therefore there is an attendant reduction in manufacturing costs. A potential drawback, however, is the possibility of including some saline in the blood sample taken because of the spacing between the stopcock 400 and the sampling site 382. That is, the reservoir 362 draws most of the saline and mixed saline and blood therein, though some saline or diluted blood may remain in the passages that are not in the direct line of reservoir flow. Also, because a second stopcock 400 is included, the system 360 is less elegant and not as simple to use.

[0088] While the invention has been described in its preferred embodiments, it is to be understood that the words which have been used are words of description and not of limitation. Therefore, changes may be made within the appended claims without departing from the true scope of the invention.

WHAT IS CLAIMED IS:

1. A medical system for sampling of a fluid system of a patient for use with a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with the fluid system of a patient, and a fluid sampling site in the conduit line, the sampling site including a housing having a distal port connected to the distal segment and a proximal port connected to the proximal segment, wherein fluid may flow freely through a chamber in the housing between the proximal and distal ports, the sampling site further defining a sampling port open to the chamber and closed from the exterior by an elastomeric seal, the medical system comprising:

a flowthrough bypass cannula having a body shaped to engage the sampling port and a bypass probe having a throughbore and being sized to pierce the elastomeric seal, project into the chamber and place the throughbore into fluid communication with the distal port of the sampling site while occluding the proximal port from the throughbore, wherein a fluid sample may be drawn into the bypass cannula from the distal segment of the conduit line to the exclusion of the proximal segment.

2. The system of claim 1, wherein the bypass probe terminates in a tip that contacts a passageway opening in the fluid sampling site housing leading to one of the distal or proximal ports when the bypass cannula engages the sampling site, and the tip is tapered and matches the passageway opening.

3. The system of claim 1, wherein the bypass probe terminates in a closed tip that contacts and occludes a passageway opening in the fluid sampling site housing leading to the proximal port when the bypass cannula engages the sampling site, and the bypass probe includes at least one side opening open to the chamber in the sampling site housing.

4. The system of claim 3, wherein the bypass probe tip is at least partly compressible.

5. The system of claim 1, wherein the bypass probe defines a continuous tubular member and terminates in an open tip that contacts a passageway opening in the fluid sampling site housing leading to the distal port when the bypass cannula engages the sampling site.

6. The system of claim 5, further including a sealing member positioned in the passageway opening that contacts and seals against the open tip of the bypass probe.

7. The system of claim 1, wherein the bypass cannula and sampling site include mating structure such that they engage with a positive snap fit.

8. A system for sampling fluid from a medical conduit line including a disposable subsystem, comprising:

a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

a fluid sampling site in the conduit line having an internal chamber in communication with all of: a proximal port connected to the proximal segment, a distal port connected to the distal segment, and a sampling port closed by an elastomeric seal;

a disposable sampling subsystem for engaging the fluid sampling site including:

a bypass cannula adapted to engage the sampling port of the sampling site and simultaneously occlude the proximal port therein;

a stopcock having three ports, a first port in communication with the bypass cannula;

a fluid reservoir connected to a second port of the stopcock;

a fluid sampling vessel in fluid communication with the third port of the stopcock;

wherein in a first position the stopcock enables fluid communication between the first and second ports so that fluid may be drawn into the reservoir from the distal segment, and in a second position the stopcock enables fluid communication between the first and third ports so that fluid may be drawn into the fluid sampling vessel from the distal segment.

9. The system of claim 8, further including:

a pressure transducer connected to the proximal segment of the conduit line for sensing the pressure of the fluid system of a patient through the fluid in the conduit line.

10. The system of claim 8, wherein the bypass cannula includes a bypass probe terminating in a closed tip that contacts and occludes a passageway opening in the fluid sampling site housing leading to the proximal port when the bypass cannula engages the sampling site, and the bypass probe includes at least one side opening open to the chamber in the sampling site housing.

11. The system of claim 8, wherein the bypass cannula includes a continuous tubular bypass probe terminating in an open tip that contacts a passageway opening in the fluid sampling site housing leading to the distal port when the bypass cannula engages the sampling site.

12. The system of claim 8, wherein the system further includes a stopcock positioned adjacent the proximal port of the sampling site for occluding the proximal port when fluid is drawn into and expelled from the reservoir and drawn into the fluid sampling container.

13. The system of claim 8, further including:

a bubble trap connected to the bypass cannula between the sampling site and reservoir that prevents bubbles from entering the sampling site from the bypass cannula.

14. A method for sampling blood from a medical fluid conduit line using a disposable subsystem, the conduit line having a proximal segment supplied with a physiological fluid and a distal segment in communication with the blood system of a patient, the conduit line also having a fluid sampling site defining an internal chamber in communication with all of: a proximal port connected to the proximal segment, a distal port connected to the distal segment, and a sampling port closed by an elastomeric seal, the method comprising:

providing a disposable sampling subsystem for engaging the fluid sampling site including a flowthrough bypass cannula having a probe, a fluid reservoir, and a fluid sampling container;

engaging the bypass cannula with the sampling site so that the probe passes through the elastomeric seal;

opening fluid communication between the bypass cannula and reservoir while closing fluid communication between the bypass cannula and fluid sampling container;

closing fluid communication between the bypass cannula and proximal segment of the conduit line and drawing fluid into the reservoir from the distal segment through the bypass cannula until blood enters the sampling site;

opening fluid communication between the bypass cannula and fluid sampling vessel while closing fluid communication between the bypass cannula and reservoir;

drawing blood into the fluid sampling vessel from the distal segment;

maintaining the bypass cannula engaged with the sampling site until a sample of blood is drawn into the fluid sampling container; and

detaching the bypass cannula from the sampling site and disposing of the sampling subsystem.

15. The method of claim 14, wherein the disposable sampling subsystem further includes a stopcock having three ports, a first port in communication with the bypass cannula, a second ports in communication with the fluid reservoir, and a third port in communication with the fluid sampling container, wherein following steps of the method are enabled by manipulating the stopcock:

opening fluid communication between the bypass cannula and reservoir while closing fluid communication between the bypass cannula and fluid sampling container; and

opening fluid communication between the bypass cannula and fluid sampling vessel while closing fluid communication between the bypass cannula and reservoir.

16. The method of claim 14, further including:

providing a pressure transducer connected to the proximal segment of the conduit line and sensing the pressure of the fluid system of a patient through the fluid in the conduit line.

17. The method of claim 14, wherein the step of opening fluid communication between the bypass cannula and reservoir while closing fluid

communication between the bypass cannula and fluid sampling vessel is accomplished by the step of engaging the bypass cannula with the sampling site.

18. The method of claim 17, wherein the probe of the bypass cannula has a size sufficient to contact and occlude a passageway opening leading to the proximal port of the sampling site.

19. The method of claim 17, wherein the probe of the bypass cannula has a size sufficient to contact a passageway opening leading to the distal port of the sampling site and exclude fluid communication between the proximal port and the distal port.

20. The method of claim 14, wherein the method further includes providing a stopcock adjacent the proximal port of the sampling site for occluding the proximal port when fluid is drawn into and expelled from the reservoir and drawn into the fluid sampling container.

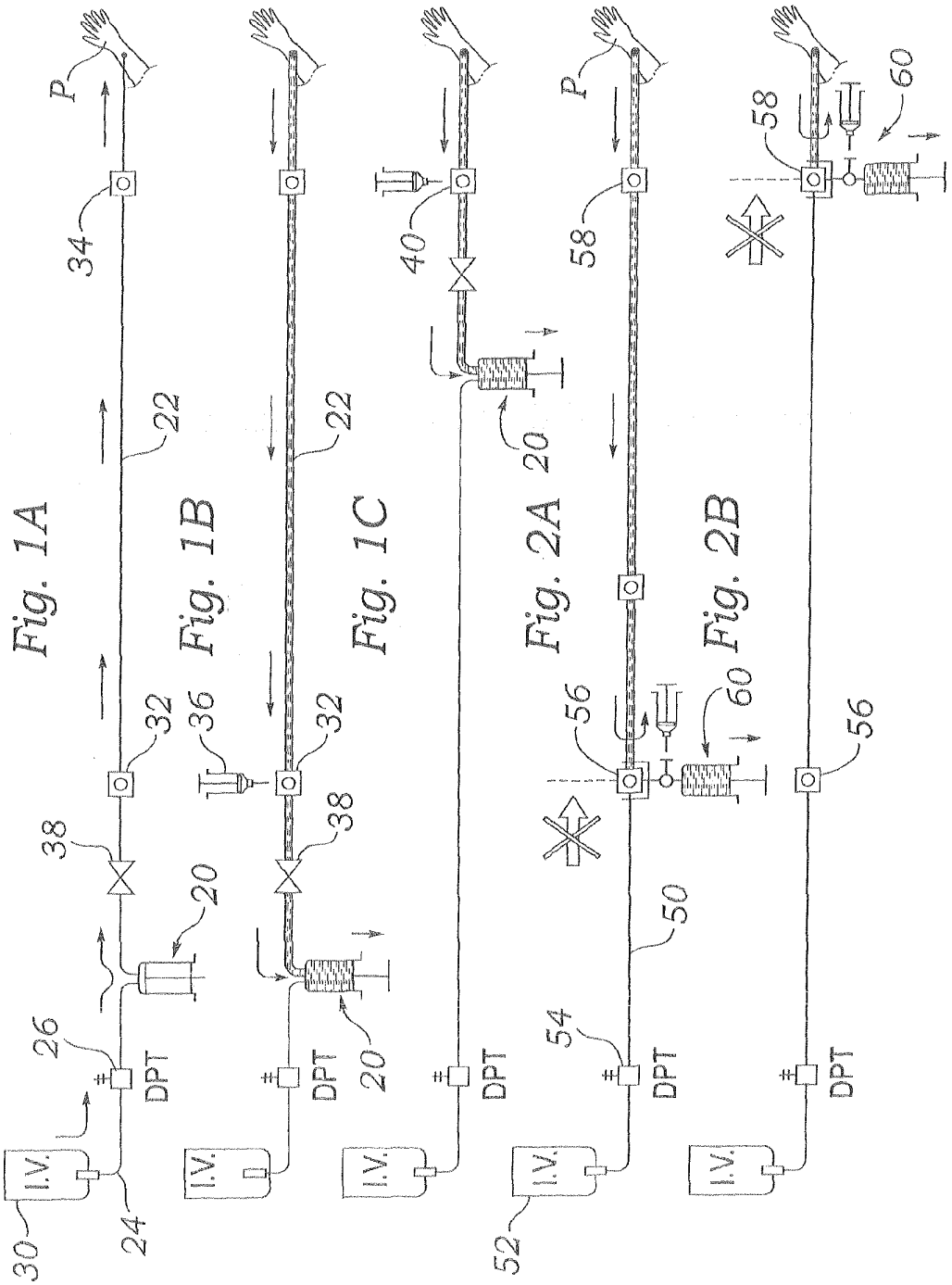
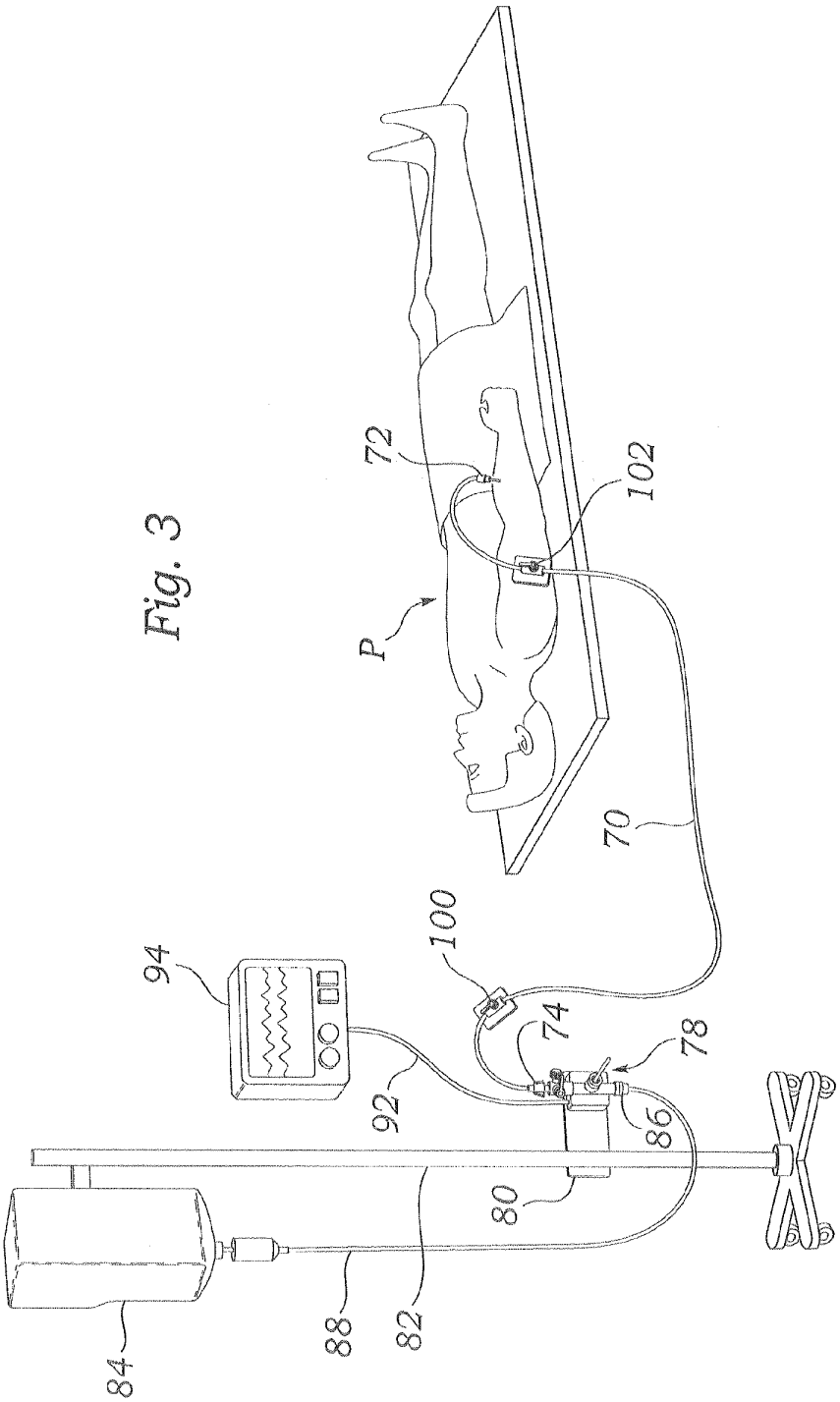

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Fig. 1A
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Fig. 2B

Fig. 3



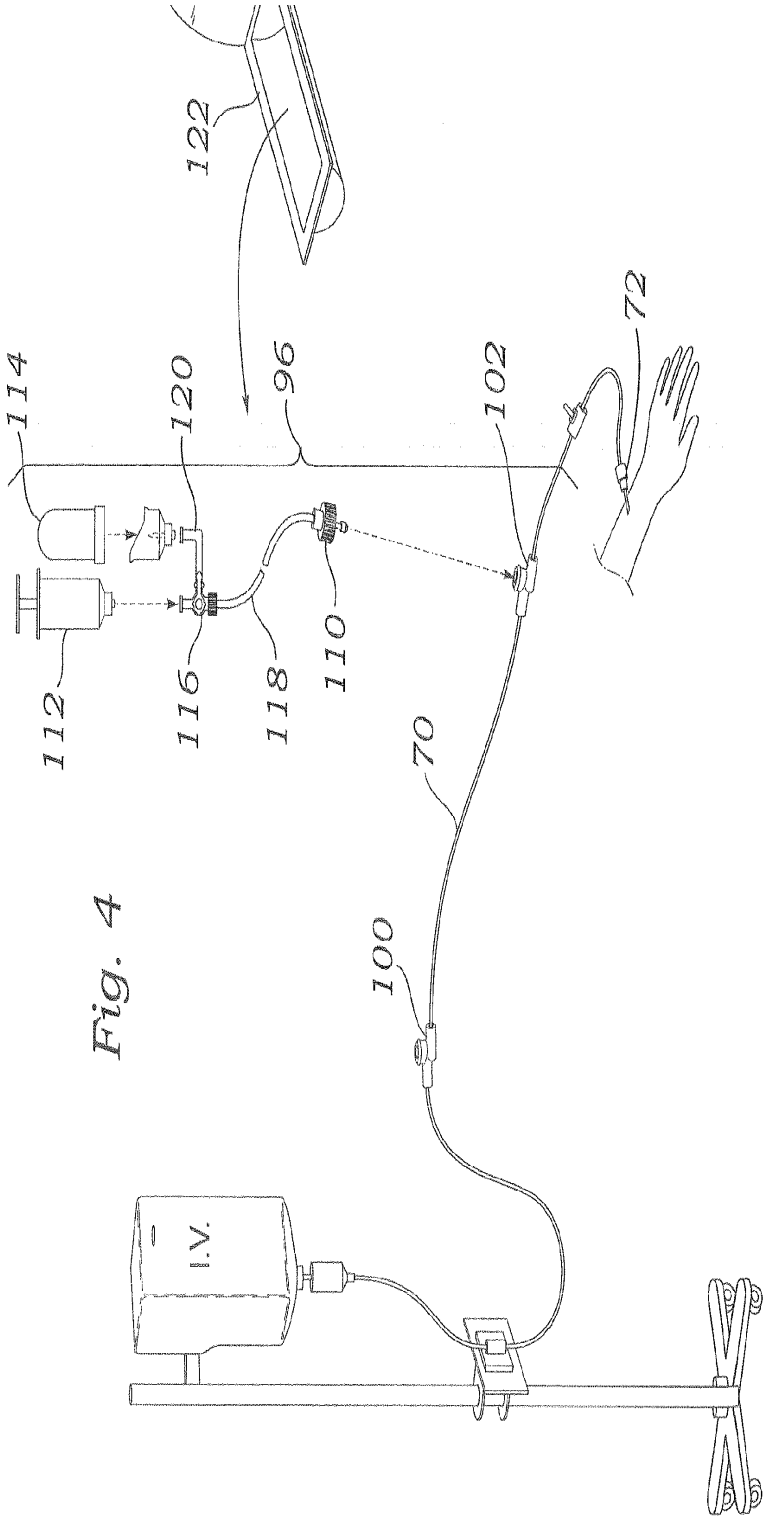


Fig. 4

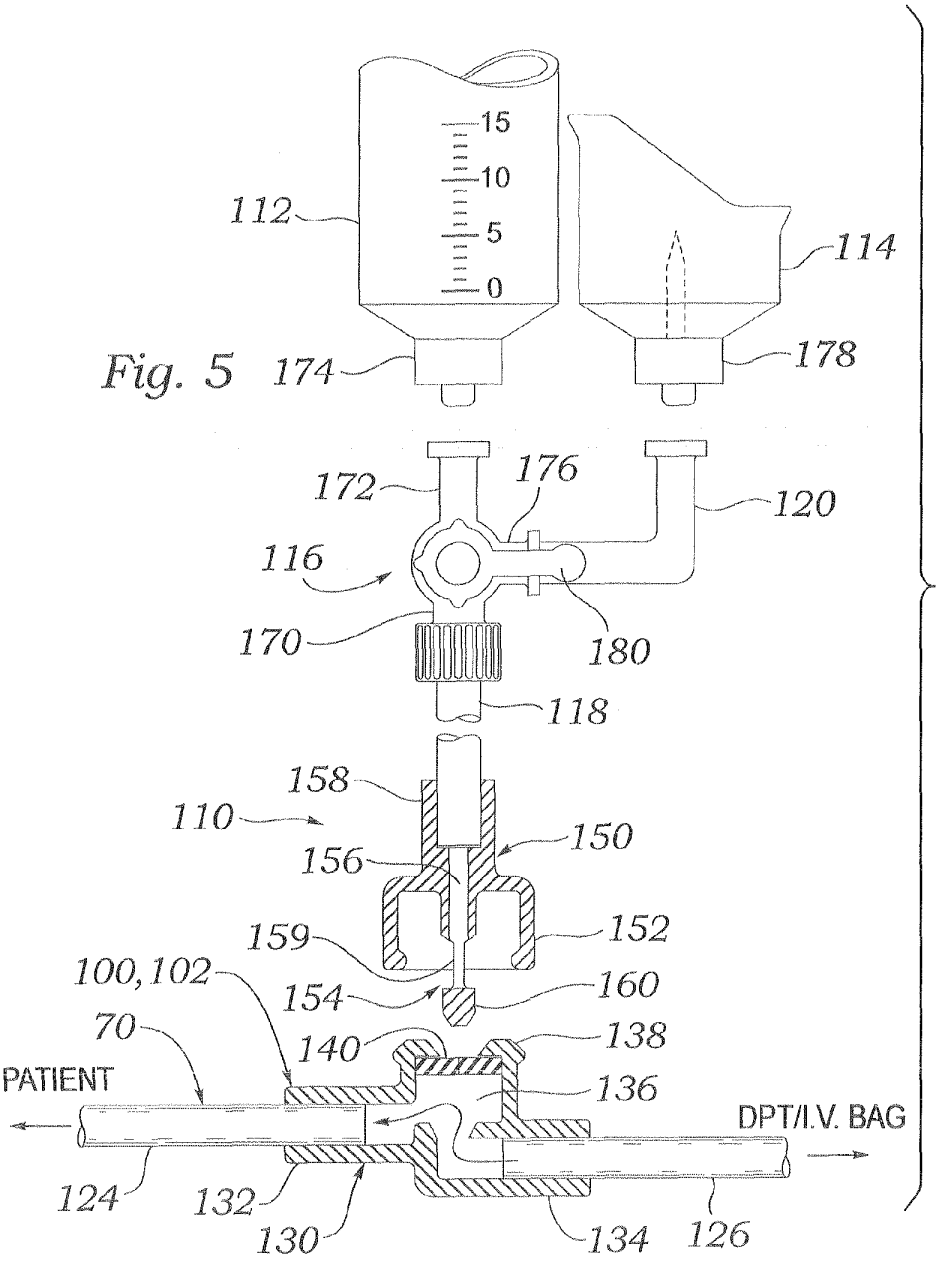

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Fig. 5

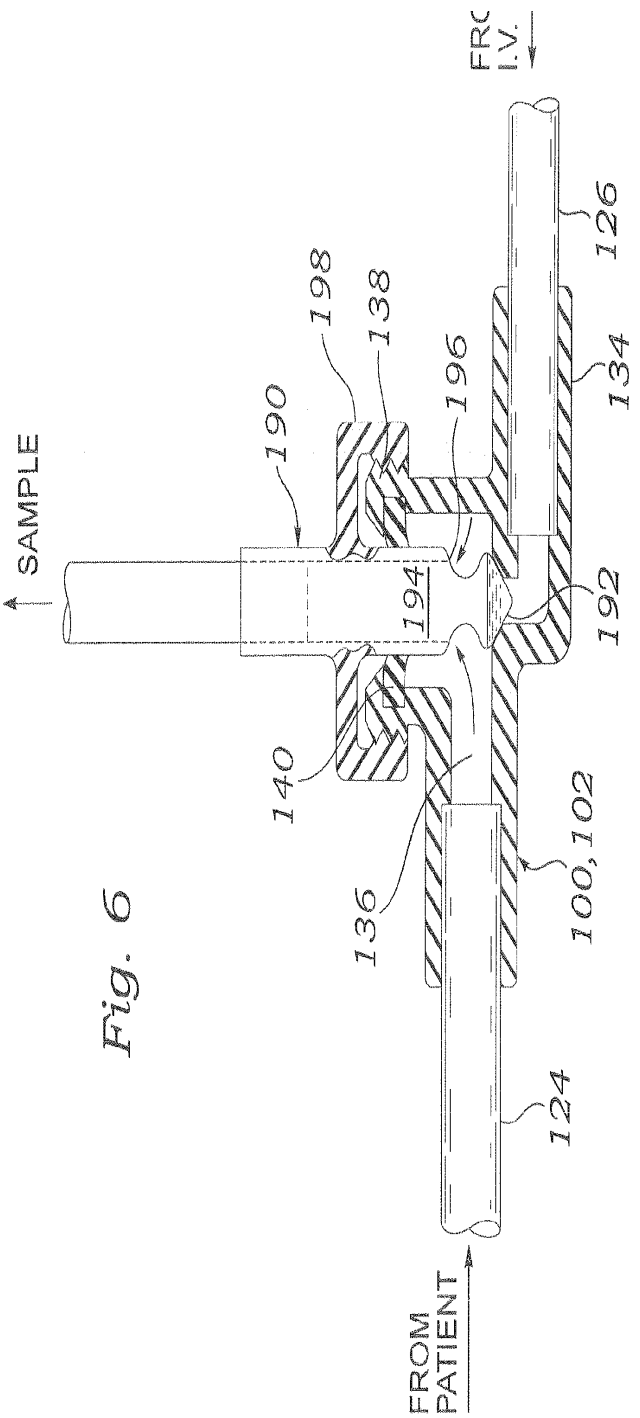

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Fig. 6

Fig. 7A

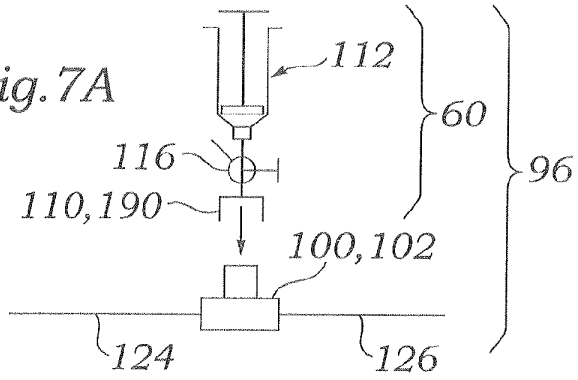


Fig. 7B

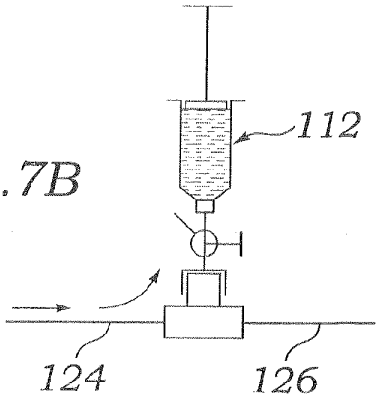


Fig. 7C

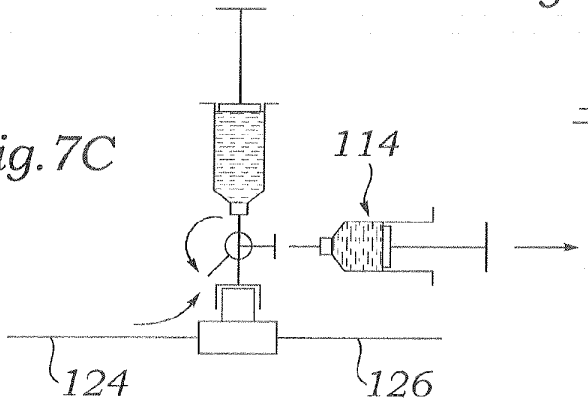


Fig. 7D

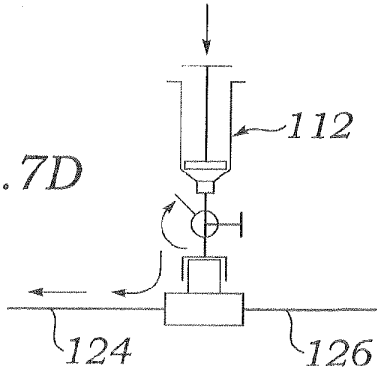
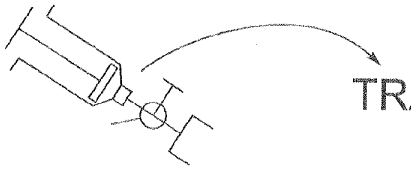


Fig. 7E



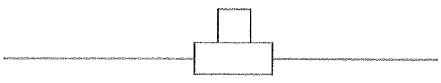


Fig.9A

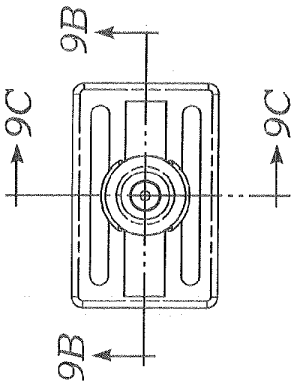


Fig.8B

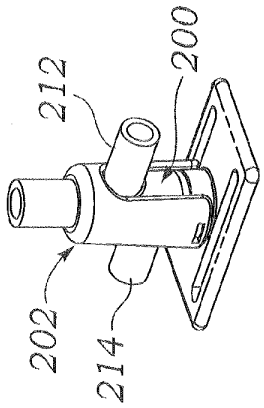


Fig.8A

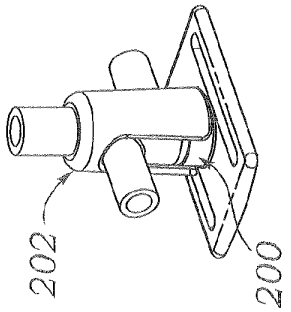


Fig.9C

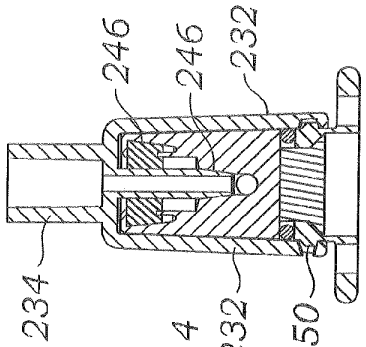


Fig.9B

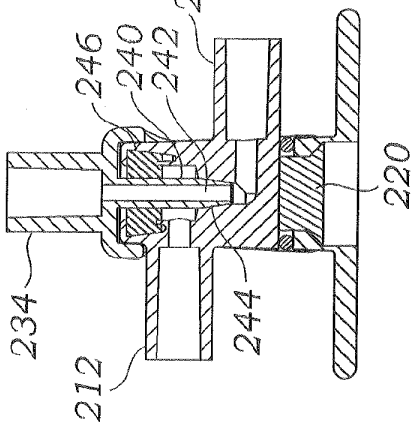


Fig.8C

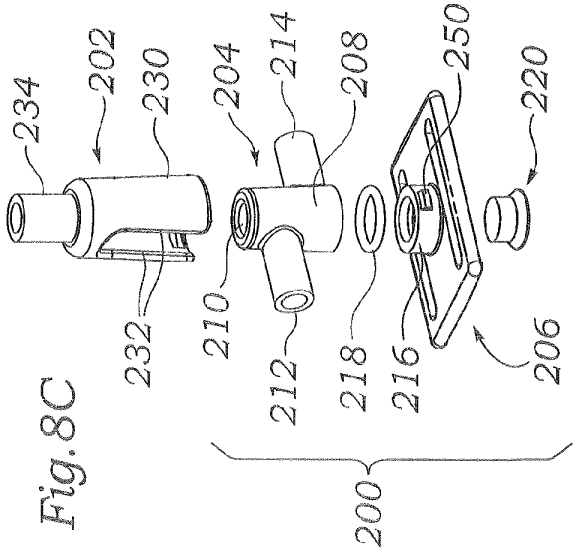


Fig. 10

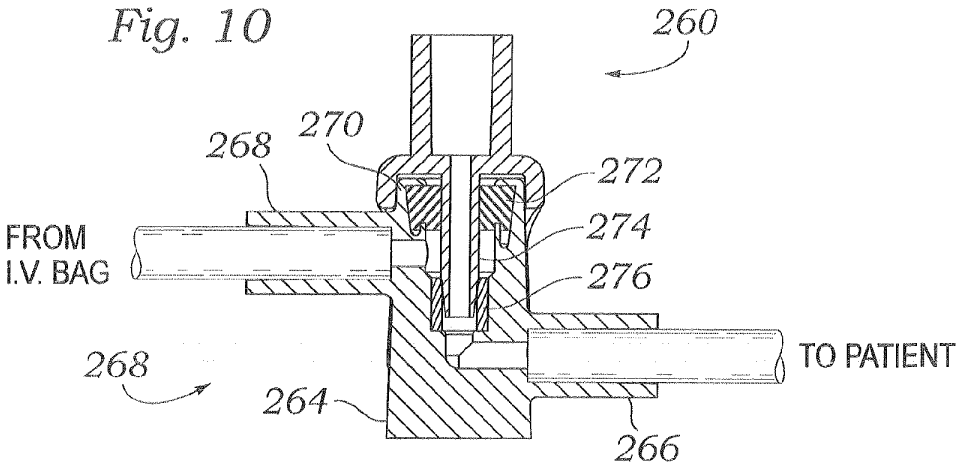

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Fig. 11

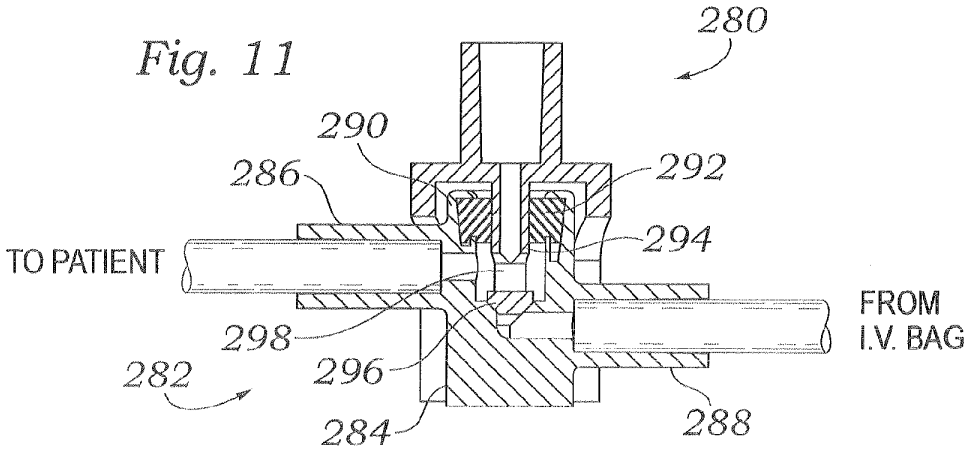

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Fig. 12A

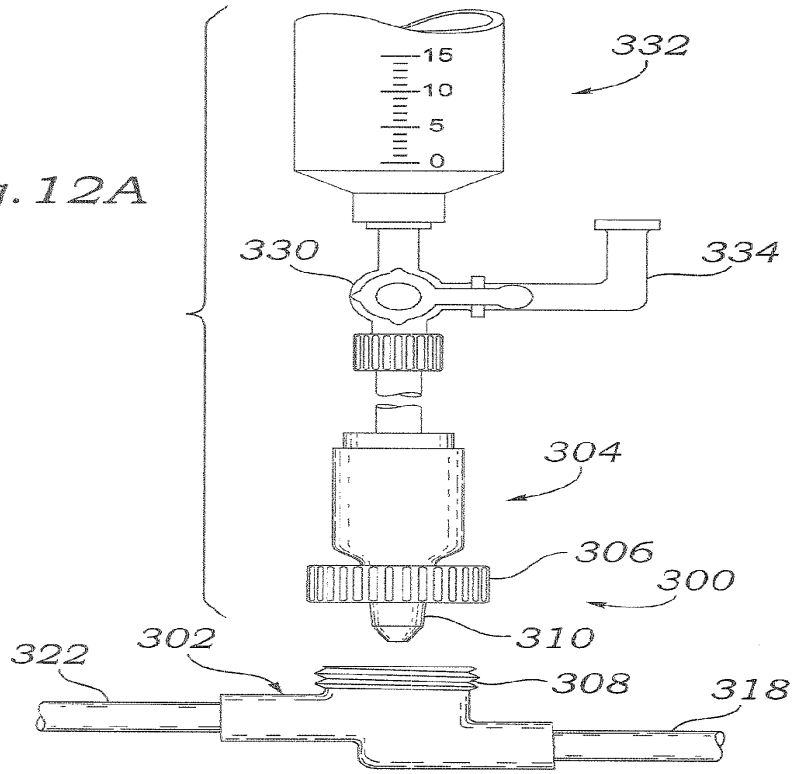
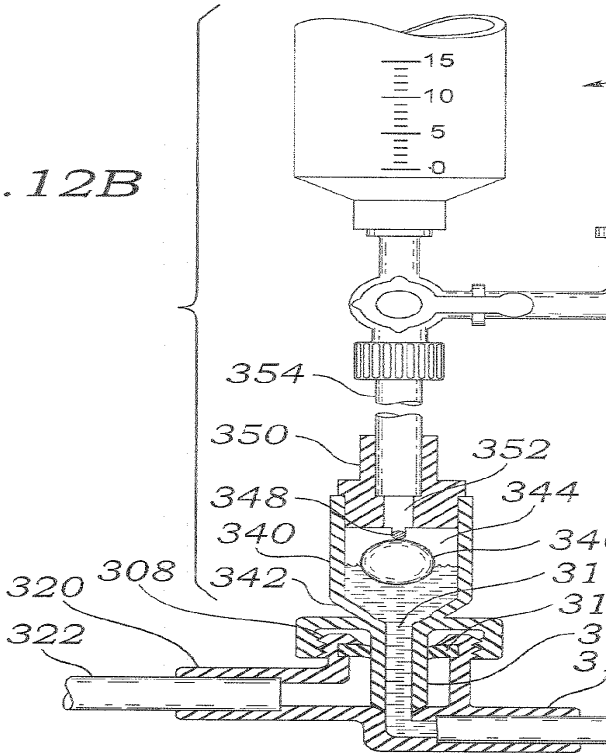


Fig. 12B



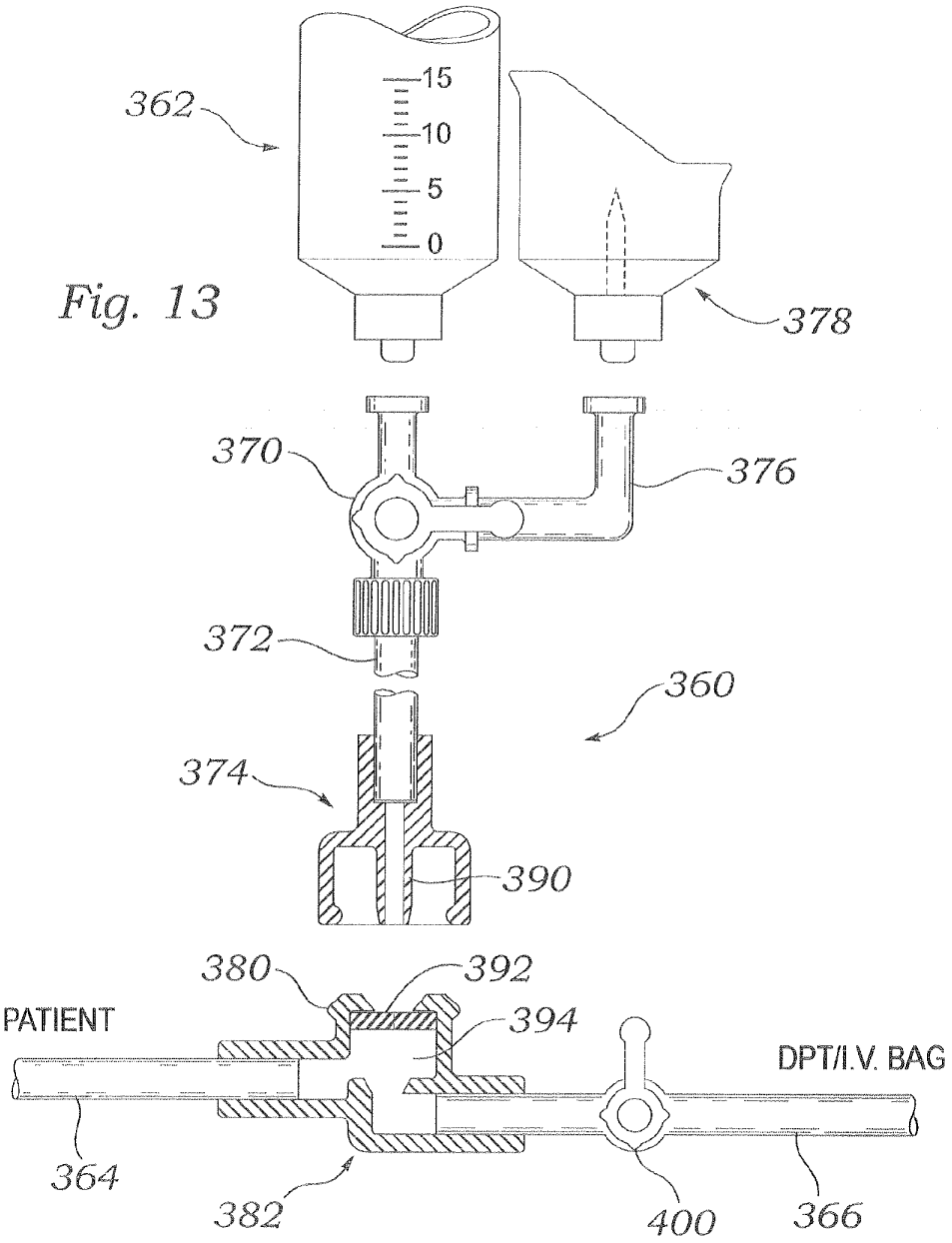

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Fig. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/053871

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61M39/04 A61M39/02
ADD. A61M1/02

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 A61M

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 637 455 A (SIEMENS ELEMA AB [SE]) 8 February 1995 (1995-02-08) column 1, lines 21,22 column 3, line 56 - column 4, line 4 column 4, line 47 - column 5, line 18; figures 1,3,12	1-7 8-13
X	EP 0 240 590 A (INTERMEDICAT GMBH [CH]) 14 October 1987 (1987-10-14) column 7, lines 11-32; figure 4	1
X	US 5 348 542 A (ELLIS DAVID W [US]) 20 September 1994 (1994-09-20) column 2, line 57 - column 3, line 9; figure 1	1
	-/--	

[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 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
4 July 2008	14/07/2008

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	Böttcher, Stephanie

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/053871

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 287 265 B1 (GLEASON CINDY L [US]) 11 September 2001 (2001-09-11) column 6, line 16 - column 7, line 32; figure 7	8-13

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/053871

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. [X] Claims Nos.: 14-20
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgeryThe sampling of blood requires a surgical step, namely the withdrawal of blood from a patient's blood vessel.

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:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an 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 reportcovers 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.:

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/US2008/053871

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0637455 A	08-02-1995	JP 7051386 A	28-02-1995
		US 5549582 A	27-08-1996
EP 0240590 A	14-10-1987	AT 66622 T	15-09-1991
		DE 3681158 D1	02-10-1991
		JP 1708152 C	11-11-1992
		JP 3062113 B	24-09-1991
		JP 62243563 A	24-10-1987
		US 4819684 A	11-04-1989
US 5348542 A	20-09-1994	NONE	
US 6287265 B1	11-09-2001	NONE	

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

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

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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

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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
		US 2012330187 A1	27-12-2012
JP H08257018 A	08-10-1996	NONE	
US 4416290 A	22-11-1983	NONE	
US 3648684 A	14-03-1972	NONE	
EP 1665986 A1	07-06-2006	BR PI0505336 A	11-07-2006
		EP 1665986 A1	07-06-2006
		JP 4914601 B2	11-04-2012
		JP 2006150083 A	15-06-2006
		US 2006129064 A1	15-06-2006
US 4056101 A	01-11-1977	NONE	
US 2013317391 A1	28-11-2013	US 2013317391 A1	28-11-2013
		US 2015099996 A1	09-04-2015
		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)