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: ***17/538,990***
FILING DATE: ***November 30, 2021***
PATENT NUMBER: ***11963769***
ISSUE DATE: ***April 23, 2024***

Certified by

DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

PTO/AIA/80 (07-17)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 158174

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 158174

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: KURIN, INC.
10755 SCRIPPS POWAY PARKWAY NO. 257
SAN DIEGO, CALIFORNIA 92131

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature Bob Rogers	Date 10/15/2018
Name Bob Rogers	Telephone
Title Founder, CEO	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, 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.

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Kurin, Inc.

Application No./Patent No.: _____ Filed/Issue Date: _____

Titled: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

Kurin, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 047978, Frame 0906, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____

      The document was recorded in the United States Patent and Trademark Office at

      Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). 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 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, 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.

PTO/AIA/96 (08-12)
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/JSN/	November 26, 2021
Signature	Date
James Scott Nolan	53393
Printed or Typed Name	Title or Registration Number

[Page 2 of 2]

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.

PTO/AIA/14 (02-18)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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	UT	Country of Residence	US

Mailing Address of Inventor:

Address 1	10755 Scripps Poway, Parkway No. 257		
Address 2			
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			
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	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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	158174		
Email Address	jsnolan1@hotmail.com	Add Email	Remove Email

Application Information:

Title of the Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD		
Attorney Docket Number	KURIN2CON4	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	50	**Suggested Figure for Publication (if any)**	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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	158174		

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	16208559	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)
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

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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.

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Signature	/JSN/			Date (YYYY-MM-DD)	2021-11-26
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	KURIN2CON4
	Application Number	
Title of Invention	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD	

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application 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, 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 EQUESTRATION 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 blood sample control device comprising;

an inlet configured to receive blood from the patient;

an outlet;

a chamber connected with the inlet and having a vent that includes an air permeable blood barrier; and

a sampling channel having a distal end connected with the outlet;

a junction connected between the inlet, the chamber and the sampling channel, the junction being sized and configured such that a first portion of blood conveyed from the patient flows into the chamber to displace air therein through the air permeable blood barrier, and such that a second portion of blood is allowed to bypass the chamber and the first portion of blood at least temporarily contained therein to be directed into the sampling channel toward the outlet.

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

3. The blood sequestration device in accordance with claim 1, further comprising a housing that defines at least a part of each of the inlet, the outlet, the chamber, and the sampling channel.

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

5. The blood sequestration device in accordance with claim 2, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet, the outlet, the chamber, and the sampling channel.

6. A bodily fluid control device connected along a fluid sampling pathway that includes a patient needle or catheter and a sample collection device, the blood control device comprising:

an inlet connected with the patient needle or catheter;

an outlet connected with the sample collection device;

a diversion chamber having a vent that includes an air permeable blood barrier; and

a sampling channel having a distal end connected with the outlet;

each of the diversion chamber and the sampling channel being connected with the inlet via a junction that is sized and configured such that a first portion of the bodily fluid flows into the sequestration chamber to displace air therein through the air permeable blood barrier, and such that a second portion of the bodily fluid bypasses the diversion chamber and the first portion of the bodily fluid therein to be directed into the sampling channel toward the outlet and the sample collection device.

7. The bodily fluid control device in accordance with claim 6, further comprising a housing that at least partially houses and defines the inlet, the outlet, the sequestration chamber, and the sampling channel.

8. The bodily fluid control device in accordance with claim 6, wherein the inlet is connected with the patient needle or catheter via a first portion of the blood sampling pathway.

9. The bodily fluid control device in accordance with claim 6, wherein the outlet is connected with the sample collection device via a second portion of the blood sampling pathway.

10. The bodily fluid control device in accordance with claim 6, wherein the air permeable blood barrier includes an air permeable material that at least partially seals upon contact with blood.

11. The bodily fluid control device in accordance with claim 7, wherein the diversion chamber includes an curved channel defined in the housing.

12. The bodily fluid control device in accordance with claim 11, wherein the curved channel has a proximal end connected with the inlet, and a distal end having the vent comprising an air permeable blood barrier.

13. A bodily fluid control device comprising;

an inlet;

a junction connected with the inlet;

an outlet;

a chamber connected with the inlet via the junction, the chamber having a vent that includes an air permeable bodily fluid barrier that at least partially seals upon contact with a first portion of the bodily fluid; and

a housing that houses and defines the inlet, the outlet, and the chamber,

the chamber and the junction being configured to direct the first portion of bodily fluid from the inlet into the chamber toward the air permeable bodily fluid barrier and to displace air in the chamber, whereupon at least partially sealing of the air permeable bodily fluid barrier enables at least temporary containment of the first portion of bodily fluid in the chamber, and enables a second portion of bodily fluid from the inlet to bypass the chamber via the junction and be directed toward the outlet.

14. The bodily fluid control device in accordance with claim 13, wherein the air permeable bodily fluid barrier includes an air permeable material that seals upon contact with the bodily fluid.

15. The bodily fluid control device in accordance with claim 13, wherein the chamber includes a channel defined in the housing.

16. The bodily fluid control device in accordance with claim 13, further comprising a sampling pathway connected with the inlet via the junction, and wherein the sampling pathway conveys the second portion of bodily fluid from the inlet to the outlet.

17. The bodily fluid control device in accordance with claim 13, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet, the outlet, and the chamber.

18. The bodily fluid control device in accordance with claim 13, further comprising a sampling channel having a proximal end connected with the junction and a distal end connected with the outlet.

19. The blood control device in accordance with claim 16, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet, the outlet, the chamber, and the sampling pathway.

20. The blood control device in accordance with claim 18, wherein the housing comprises a bottom member mated with a top member, each of the bottom member and the top member defining a part of each of the inlet, the outlet, the chamber, and the sampling channel, and wherein proximate the junction the chamber has a cross-section that is larger than a cross-section of the sampling channel.

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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD
First Named Inventor/Applicant Name:	Bobby E. Rogers
Filer:	James Scott Nolan/KETHYA TEUK
Attorney Docket Number:	KURIN2CON4

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	80	80
UTILITY SEARCH FEE	2111	1	350	350
UTILITY EXAMINATION FEE	2311	1	400	400
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**830**

Electronic Acknowledgement Receipt	
EFS ID:	44373841
Application Number:	17538990
International Application Number:	
Confirmation Number:	3420
Title of Invention:	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD
First Named Inventor/Applicant Name:	Bobby E. Rogers
Customer Number:	158174
Filer:	James Scott Nolan/KETHYA TEUK
Filer Authorized By:	James Scott Nolan
Attorney Docket Number:	KURIN2CON4
Receipt Date:	30-NOV-2021
Filing Date:	
Time Stamp:	19:59:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$830
RAM confirmation Number	E2021ATJ59534501
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Drawings-only black and white line drawings	KURIN2CON4_Drawings.pdf	774722 c50a9a125ff9e5affc8f8fd73a6cf76ad009007f	no	50
Warnings:					
Information:					
2	Oath or Declaration filed	KURIN2CON4-Declaration-from-parent.pdf	875055 a5a9fc7e858ae4d6c53c2568f29bd75bcdb63b28	no	3
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3	Power of Attorney	KURIN2CON4-POA.pdf	51058 3fba2433e17796f2b150decb5904580c446b5757	no	1
Warnings:					
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4	Assignee showing of ownership per 37 CFR 3.73	KURIN2CON4_Statement-Under-3-73c.pdf	118642 56d379465e64a18e4de3a799fb1344bb373181e6	no	3
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5	Application Data Sheet	KURIN2CON4_ADS.pdf	1308231 4372cf4396c3a2928e3dcbf7a7bedebdaa2427c0	no	9
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6		KURIN2CON4-Specification-FINAL-VERSION.pdf	273638 5ceee207432342c0a73eb2ea0ddb2463a2b599a4	yes	37

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**

	Specification		1		32
	Claims		33		36
	Abstract		37		37
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	44261 36b5789082de119721a6b1839a97b5bfbd2b0ceb	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3445607		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a 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.

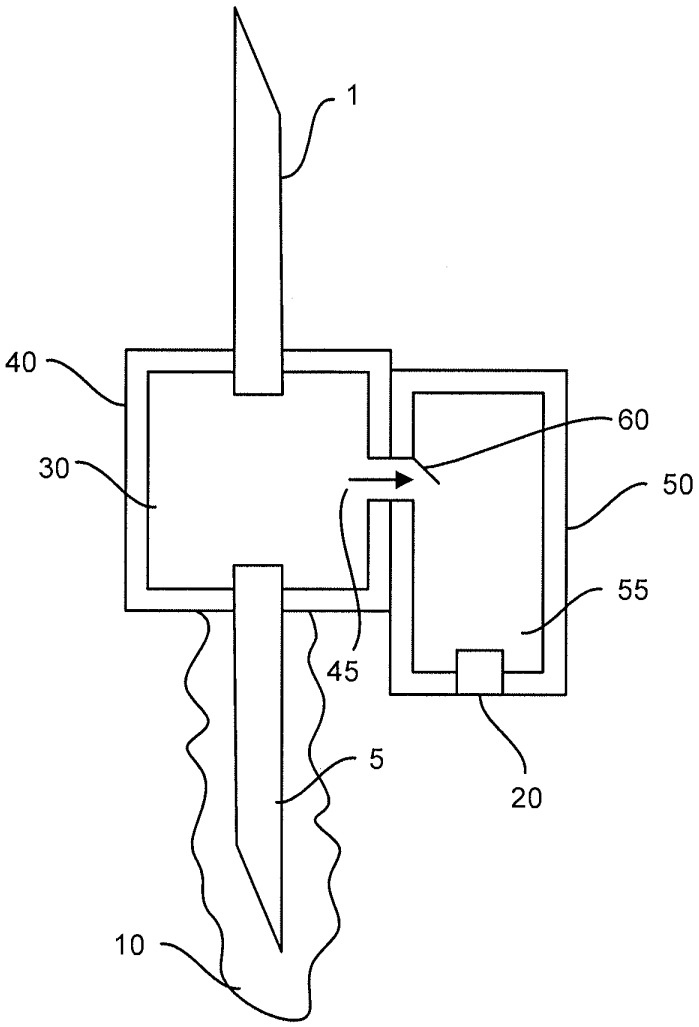


FIG. 1

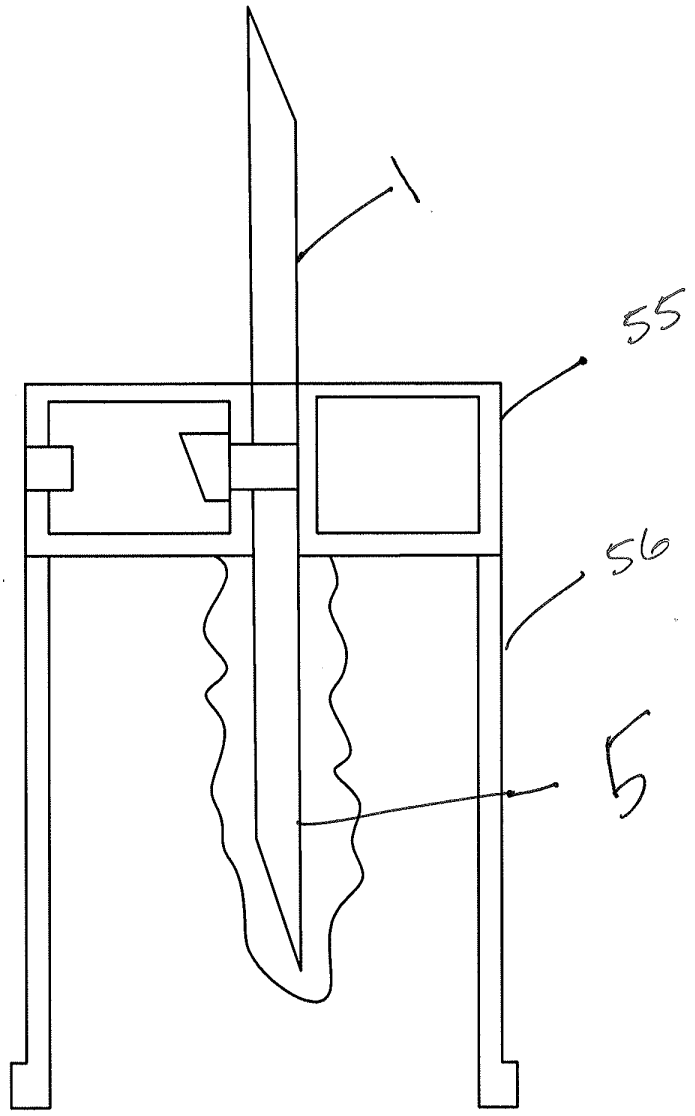


FIG. 2

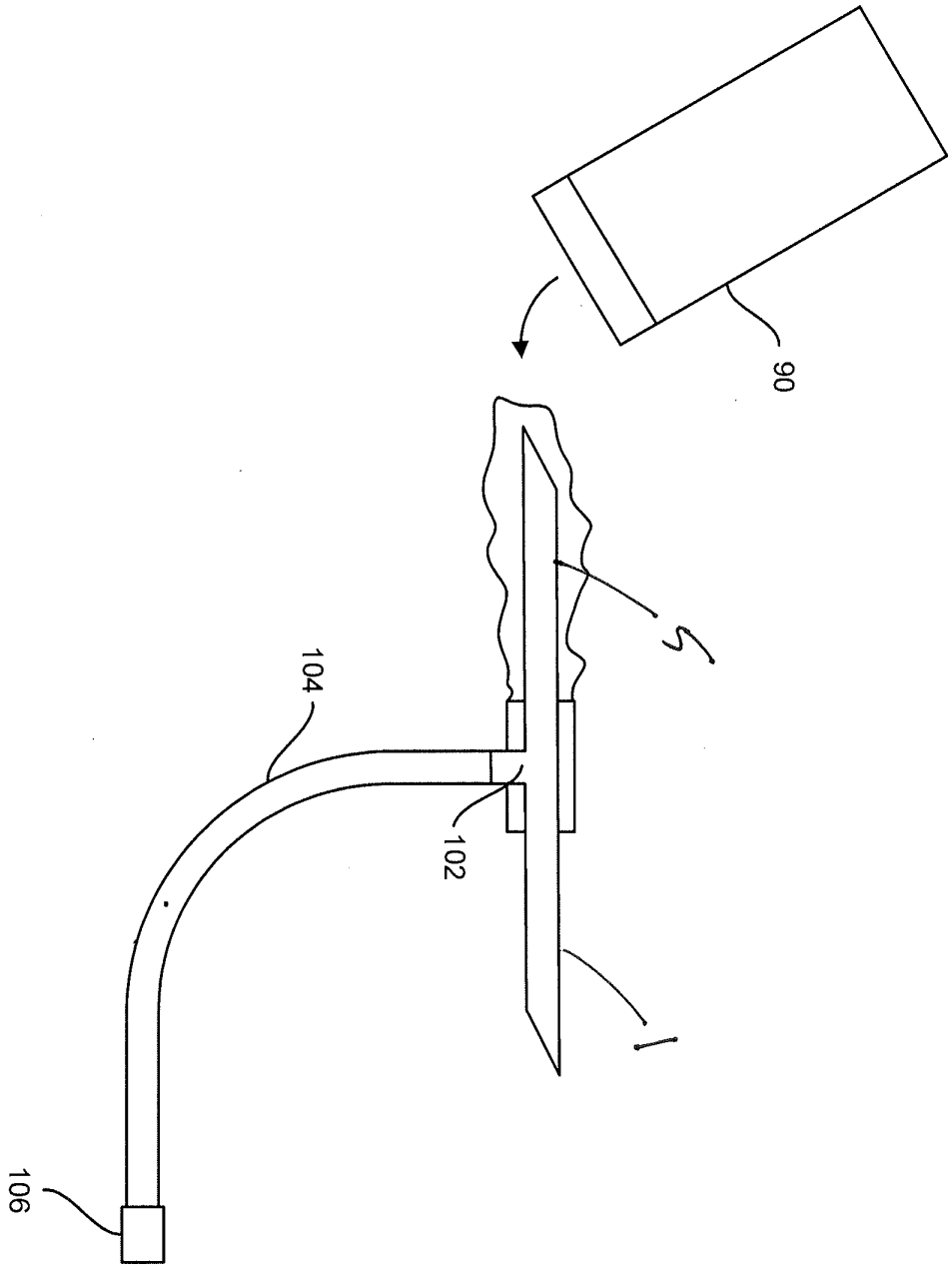


FIG. 3

FIG. 4

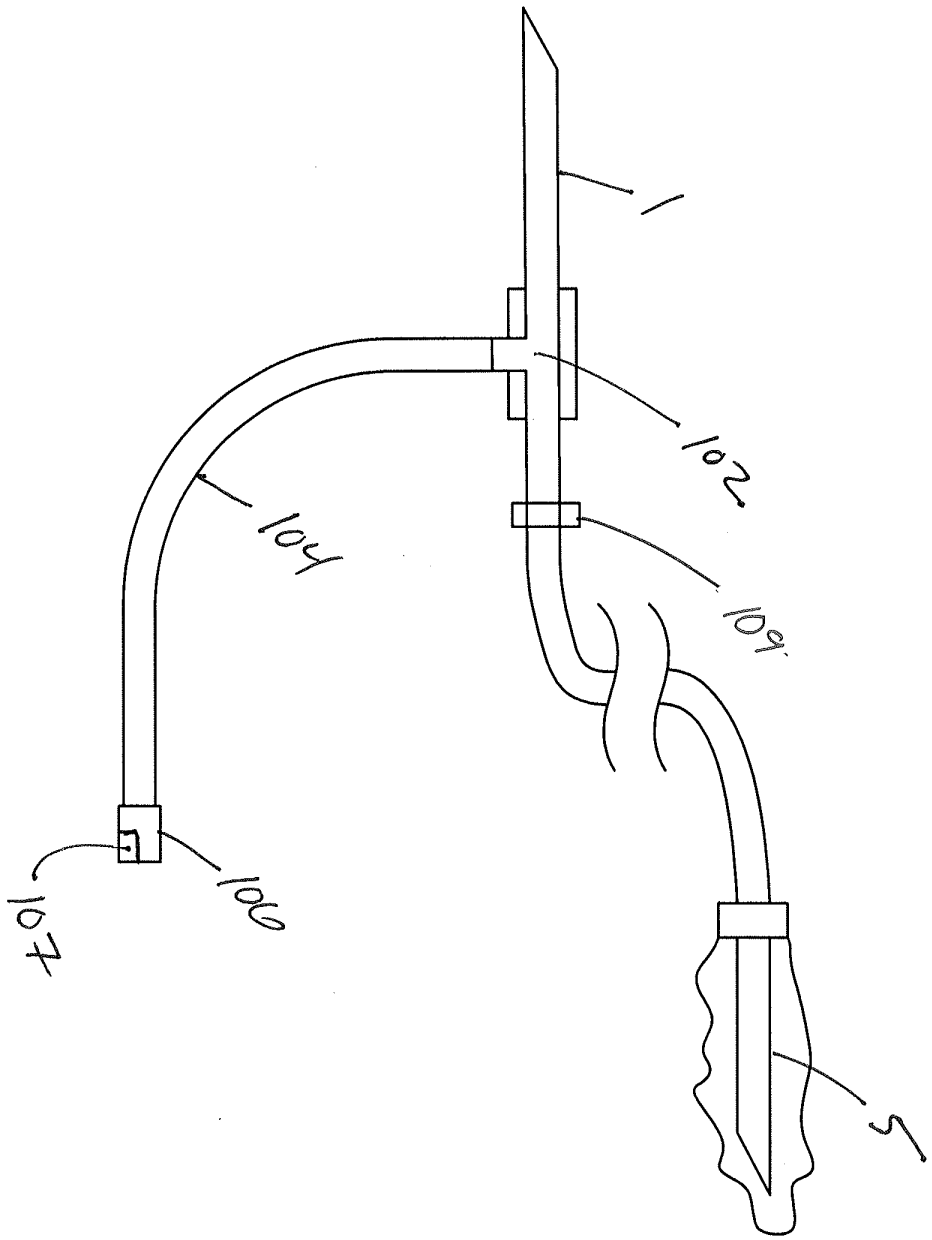


FIG. 5

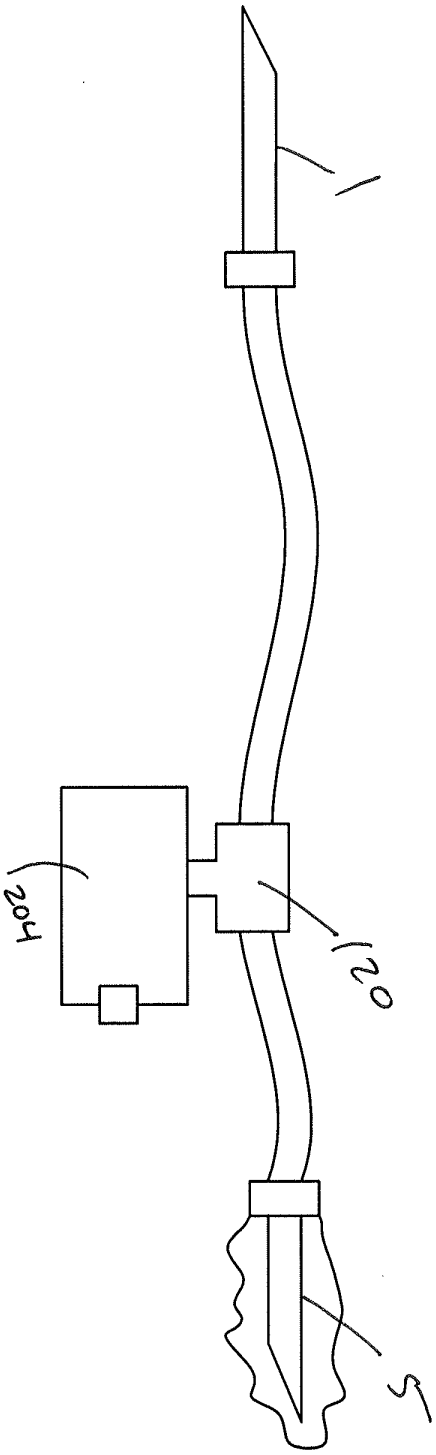
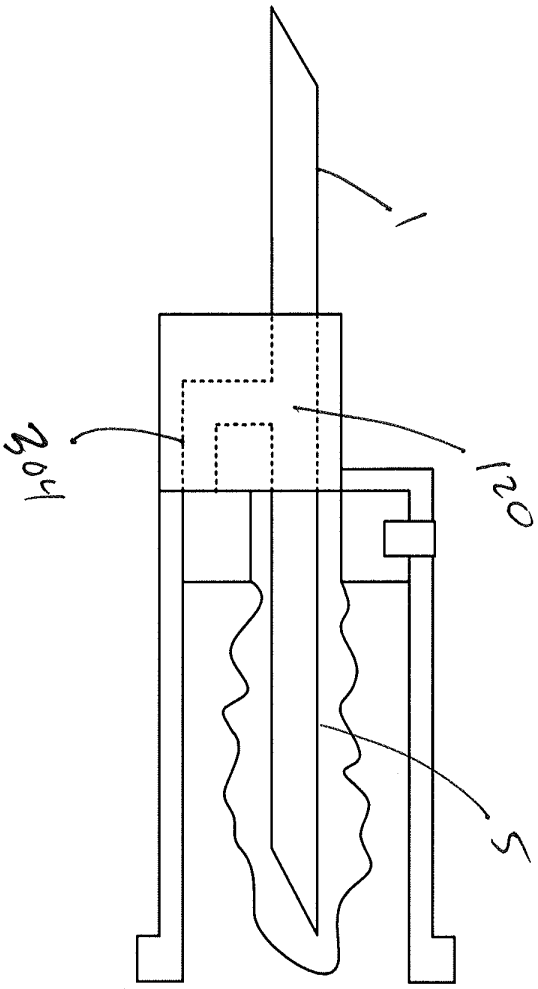


FIG. 6



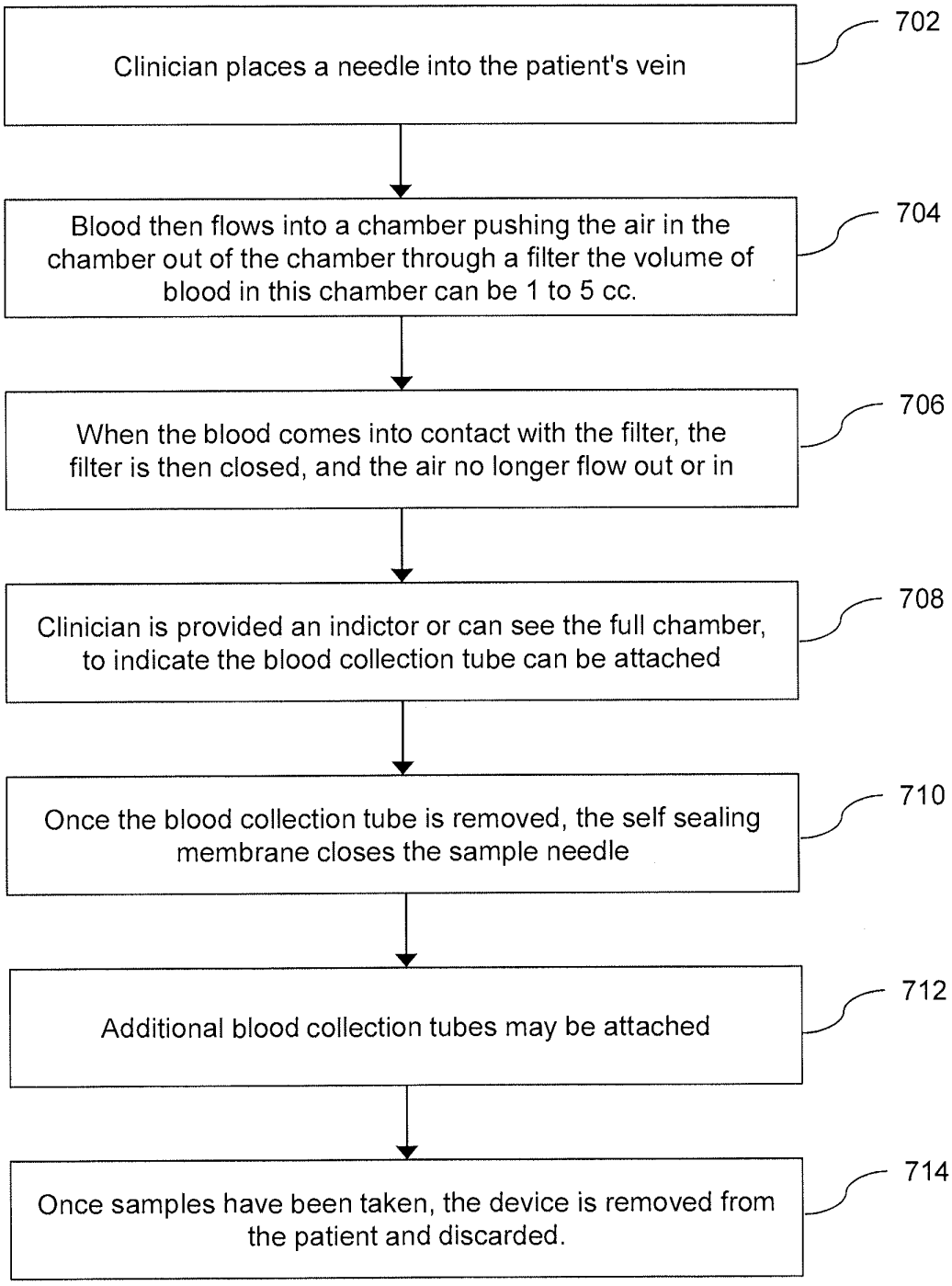

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter, the filter is then closed, and the air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

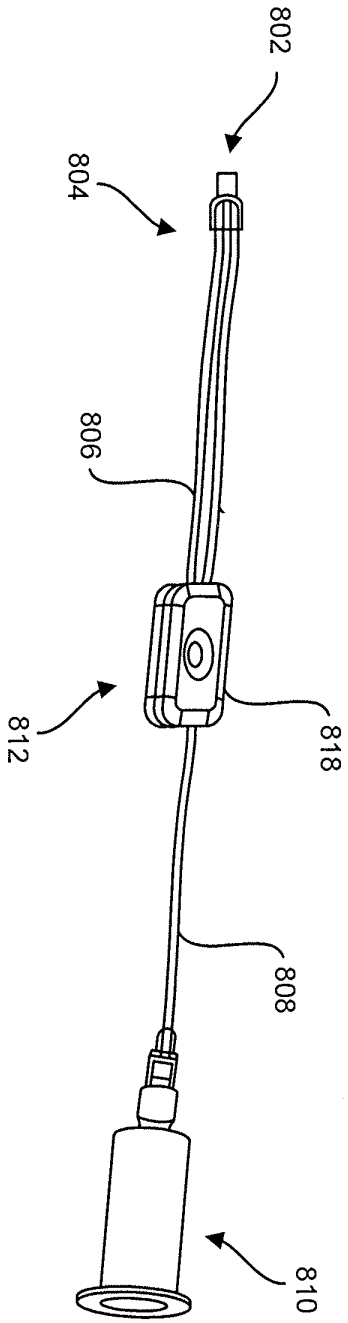


FIG. 8A

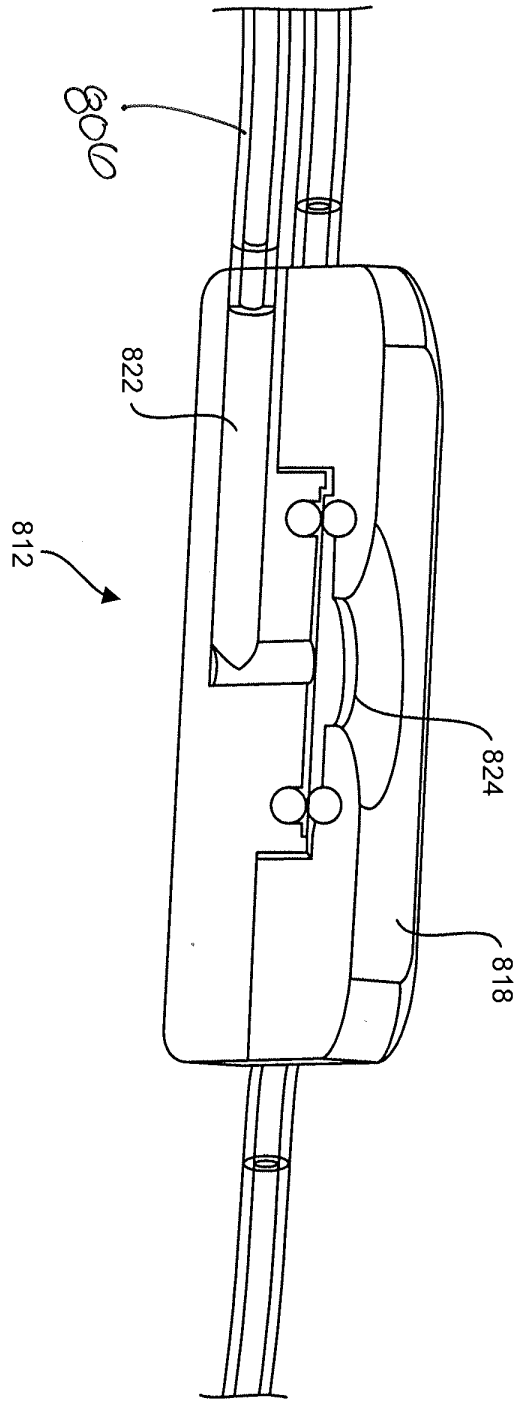


FIG. 8B

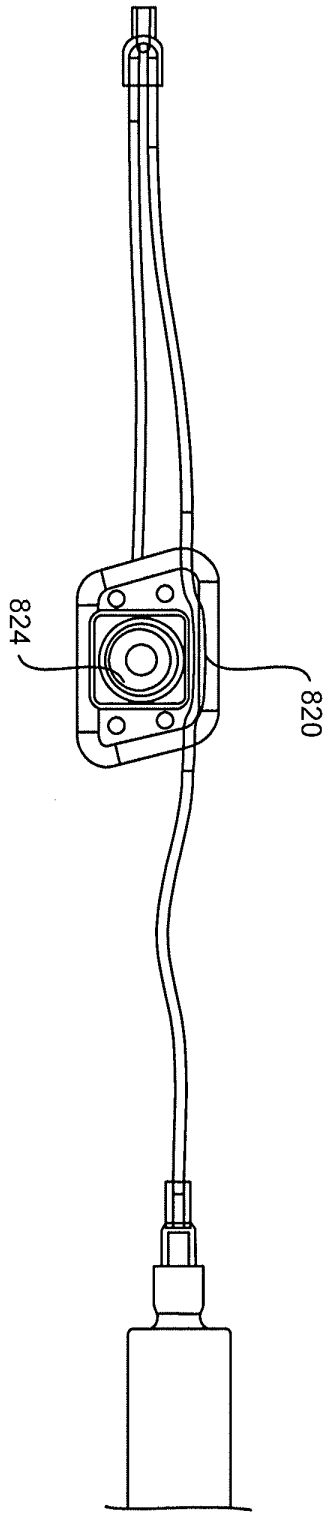
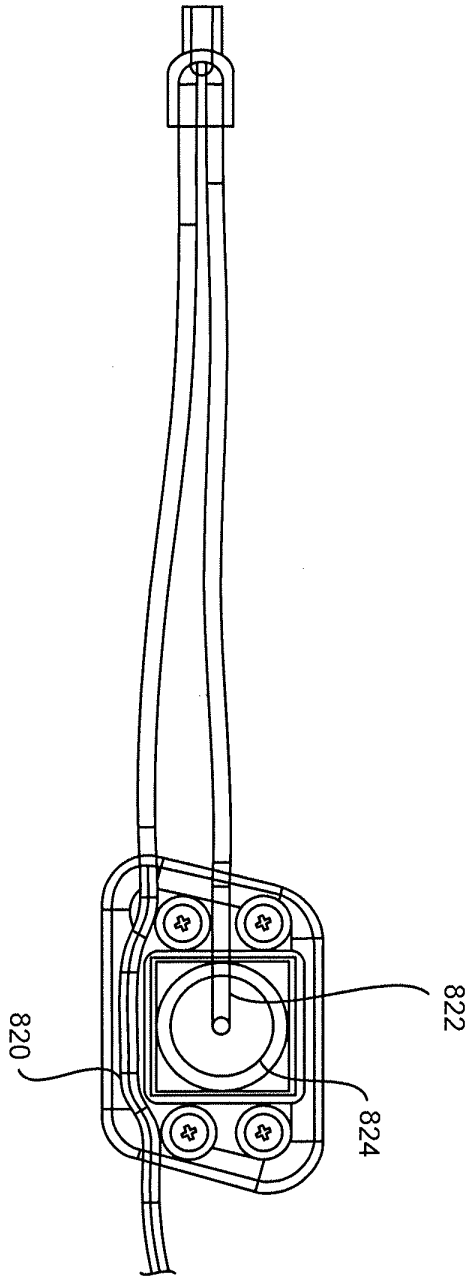


FIG. 8C

FIG. 8D



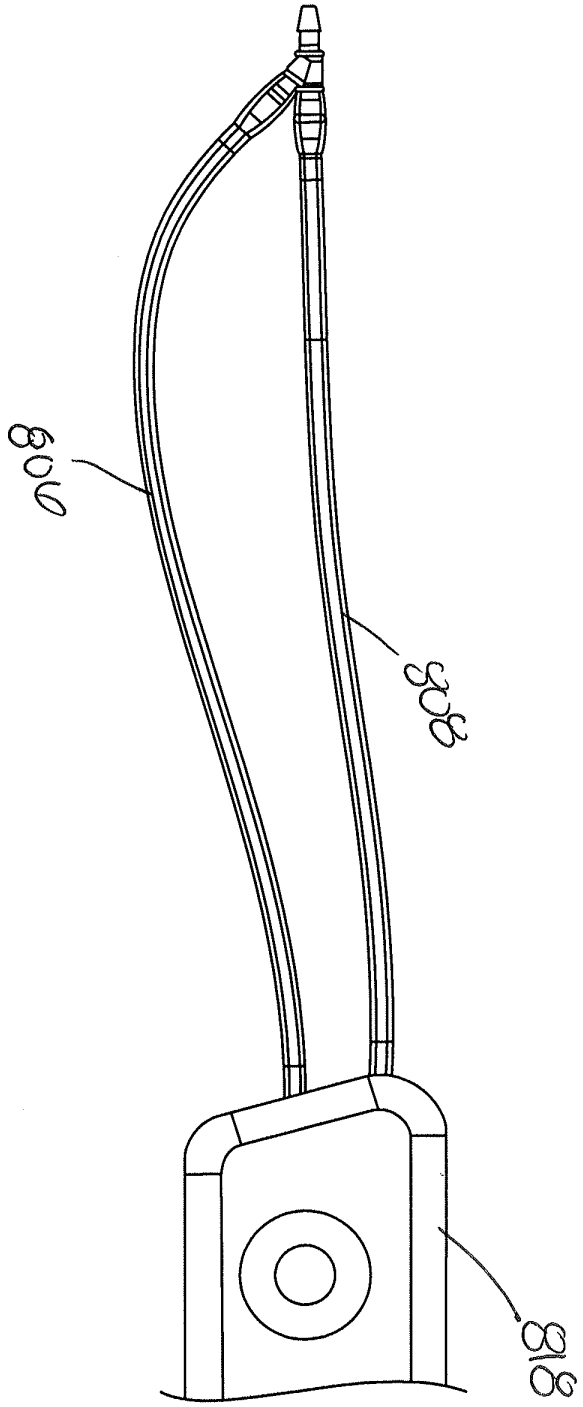
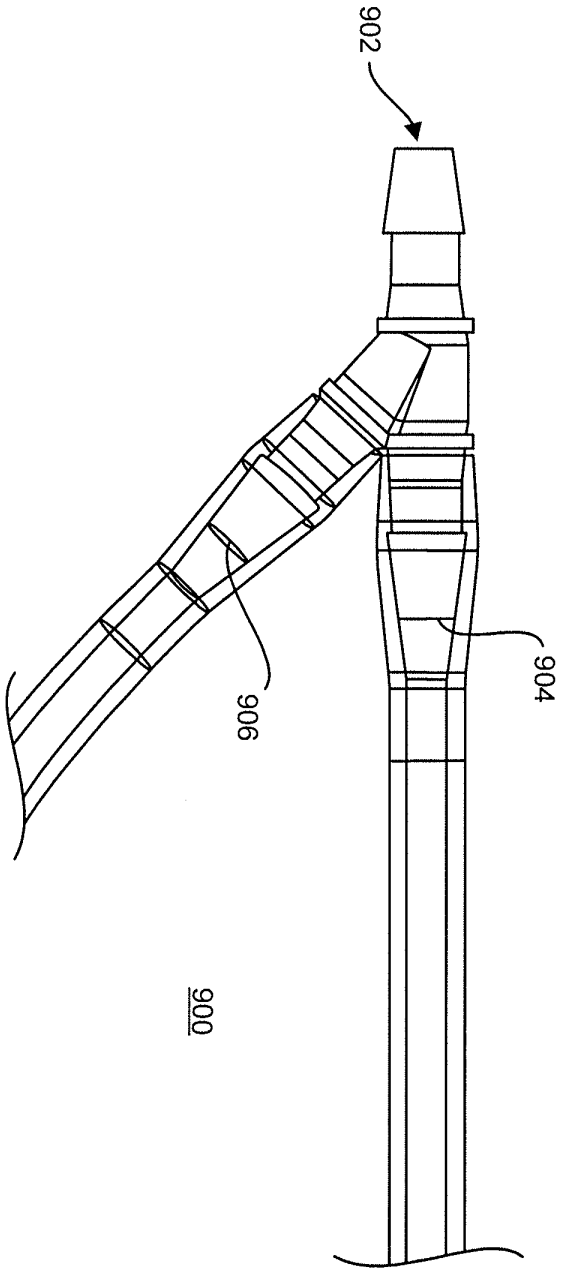


FIG. 8E

FIG. 9



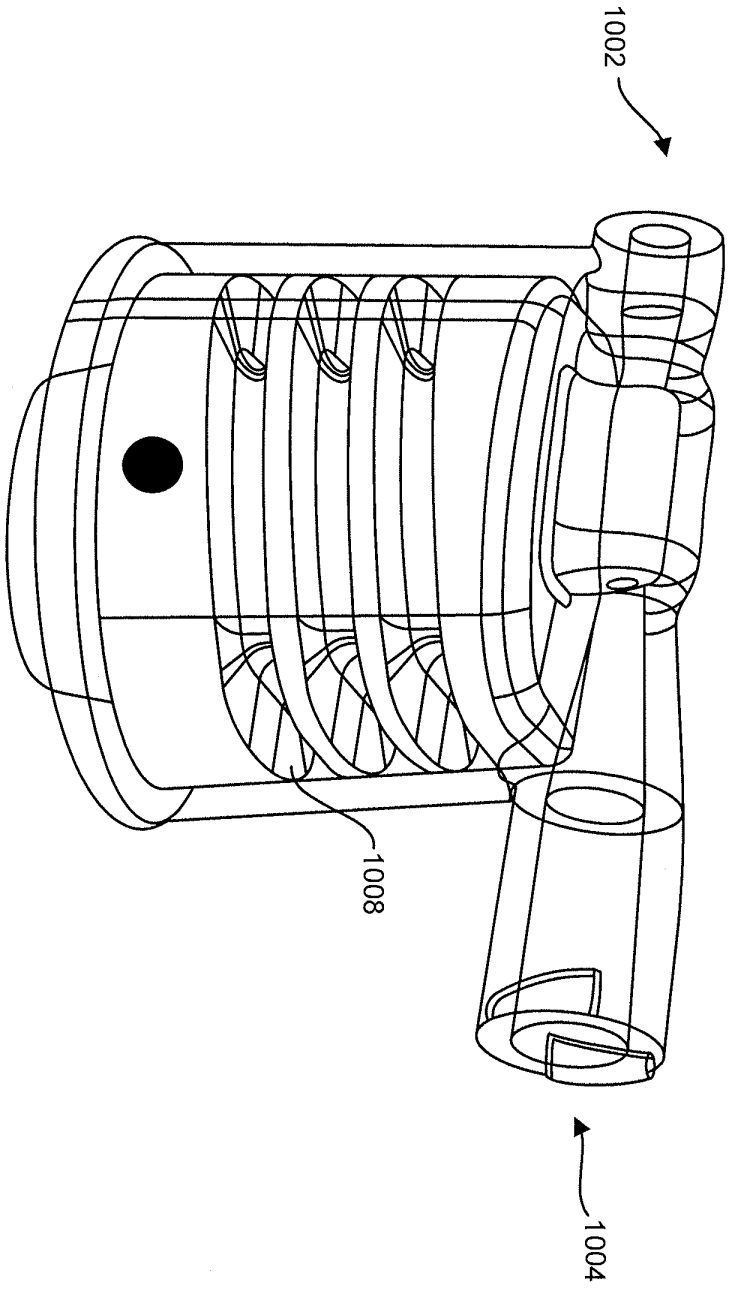


FIG. 10A

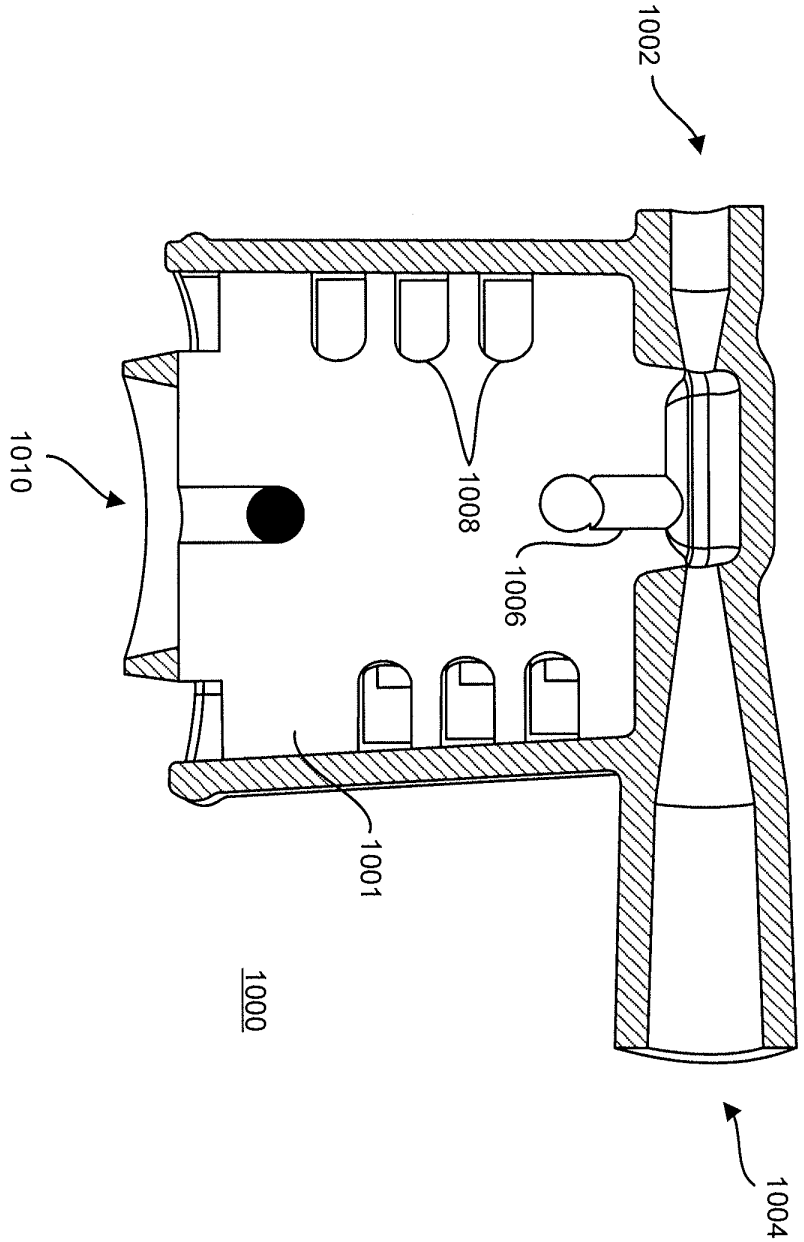


FIG. 10B

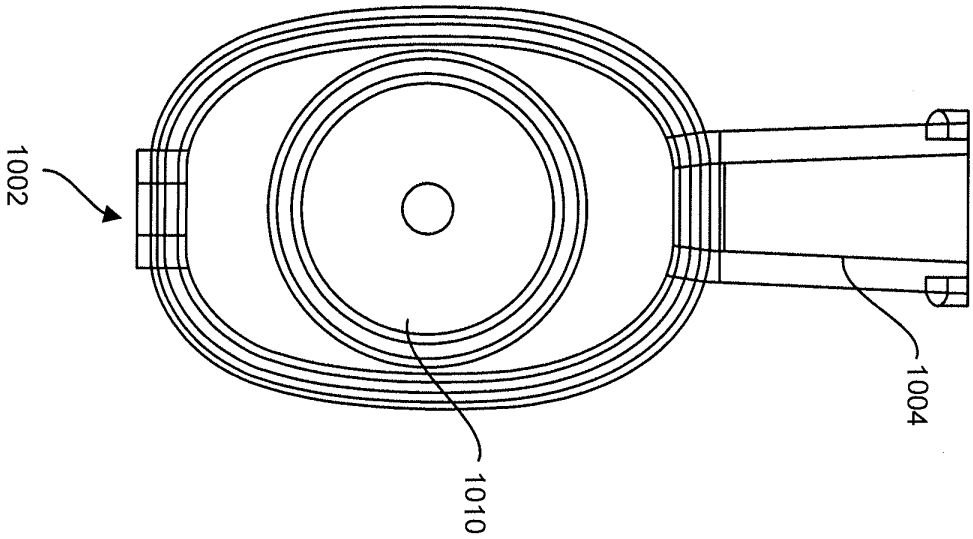


FIG. 10C

FIG. 10D

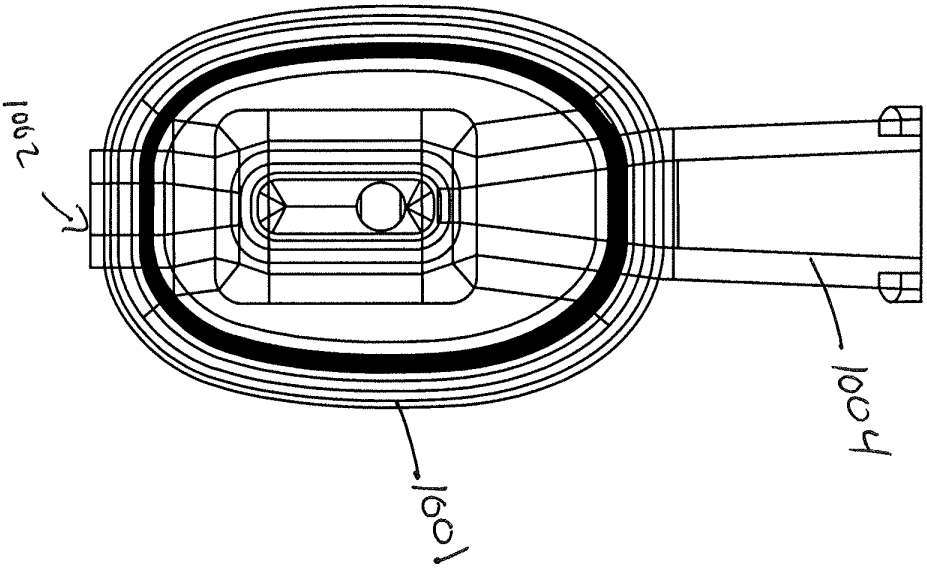
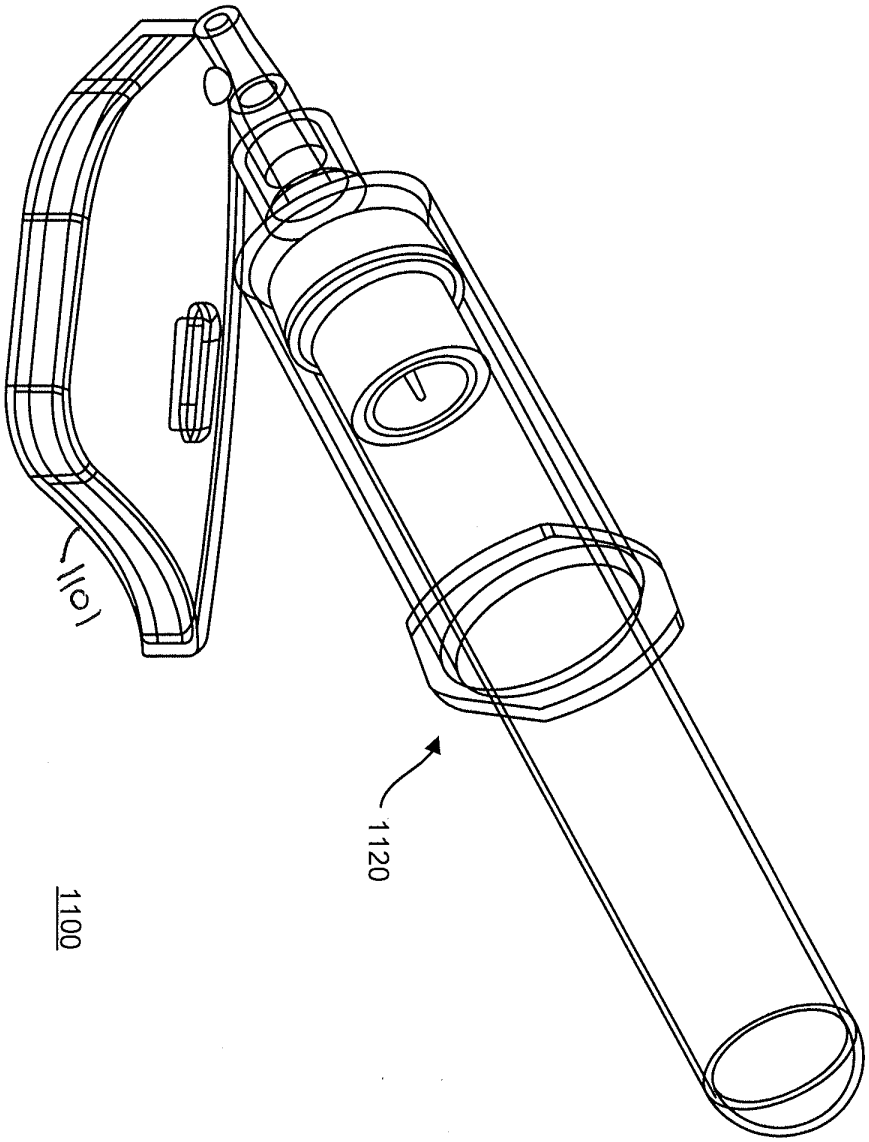


FIG. 11A



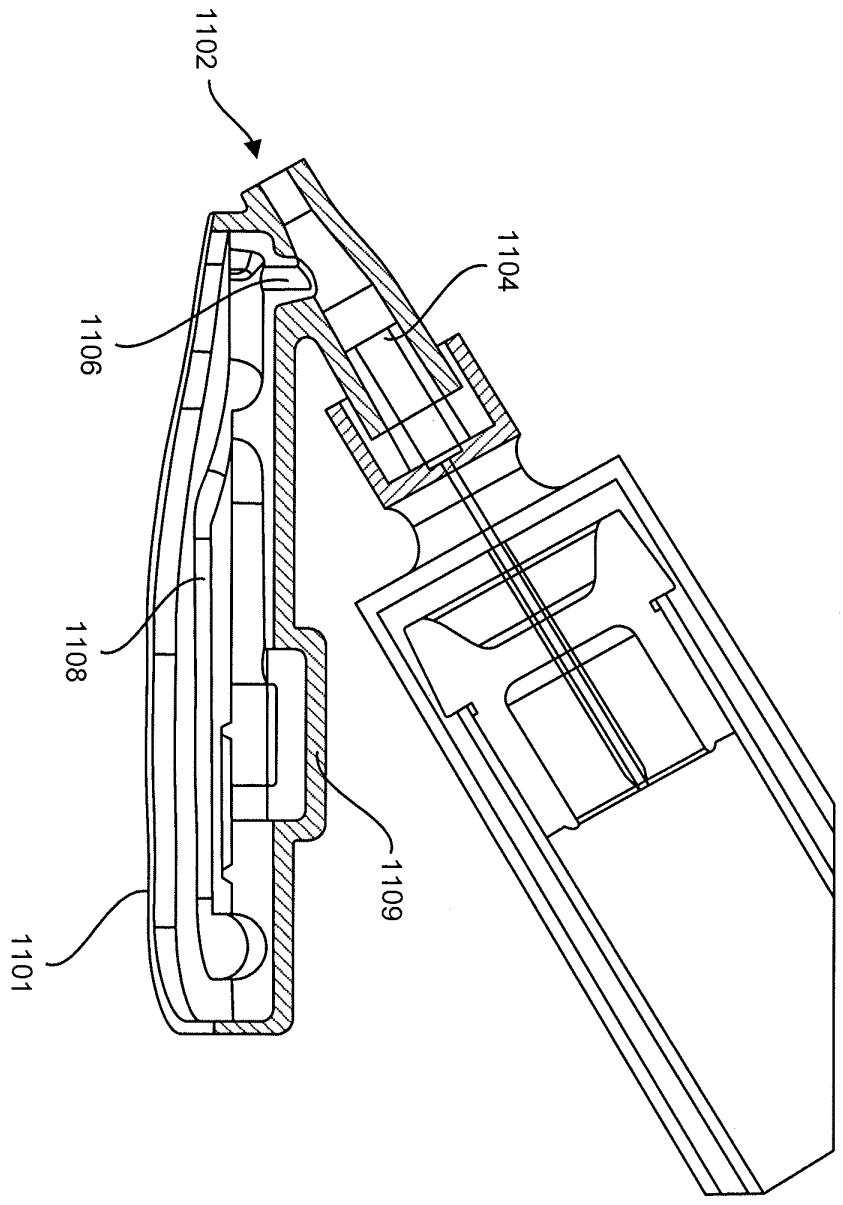


FIG. 11B

FIG. 11C

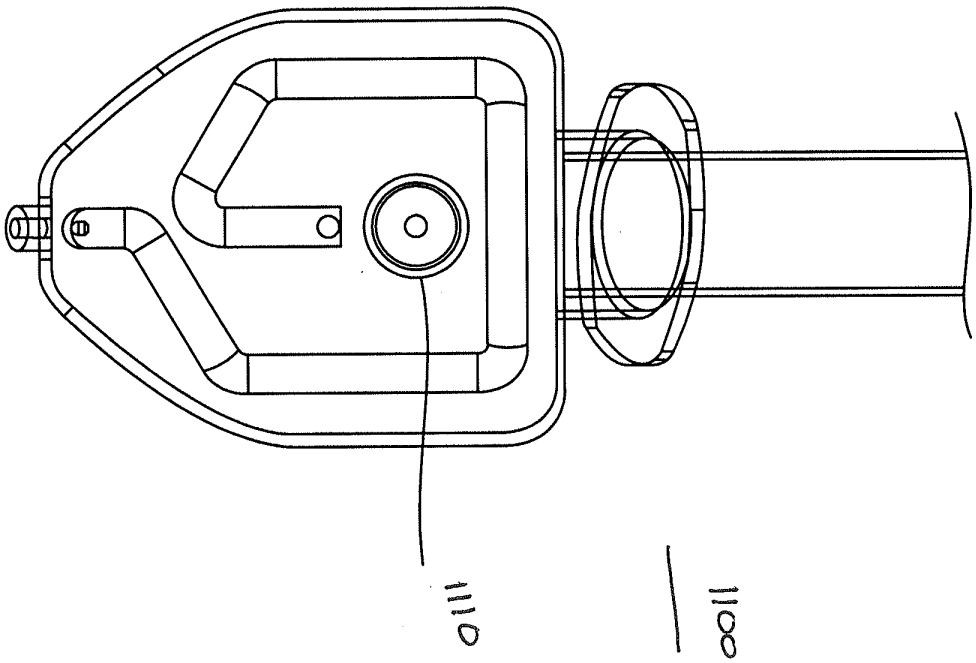


FIG. 11D

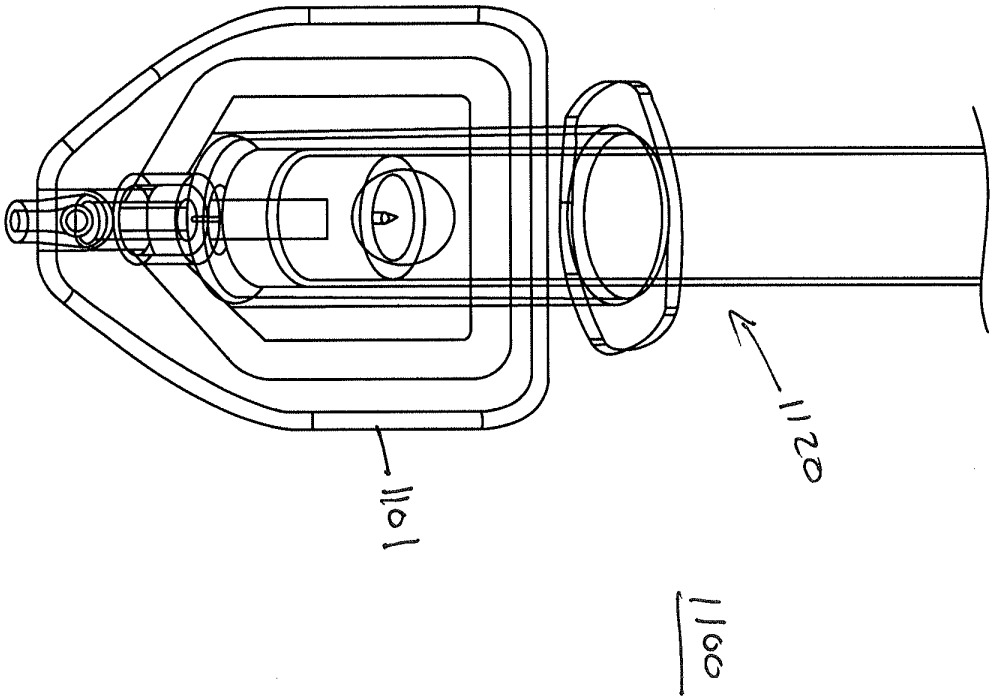
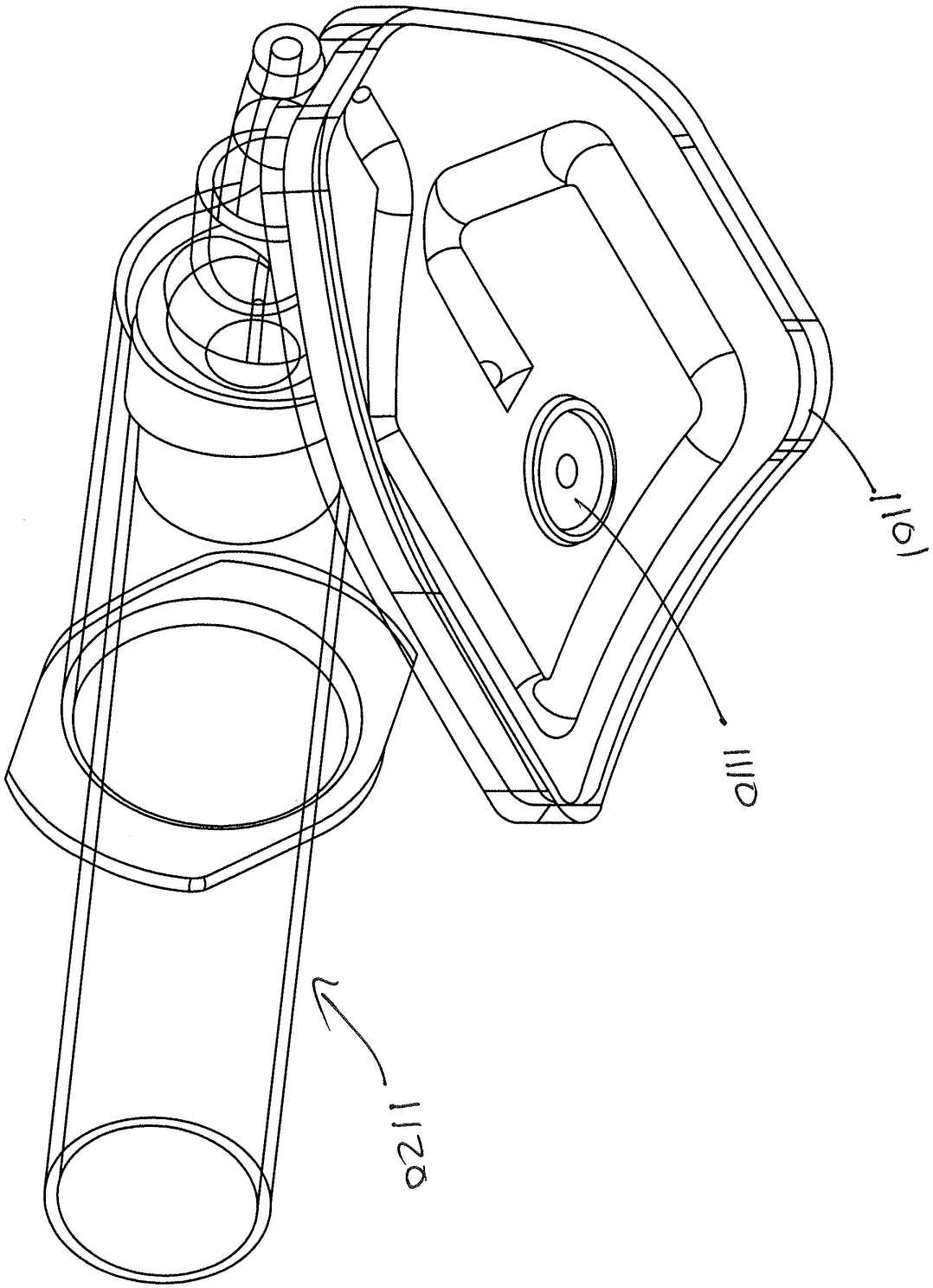


FIG. 11E



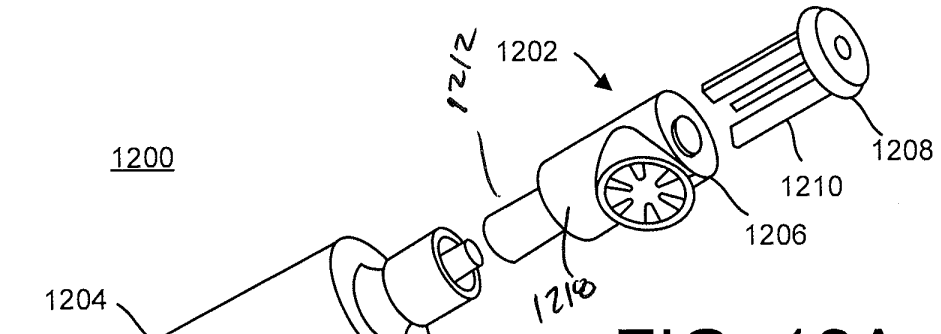


FIG. 12A

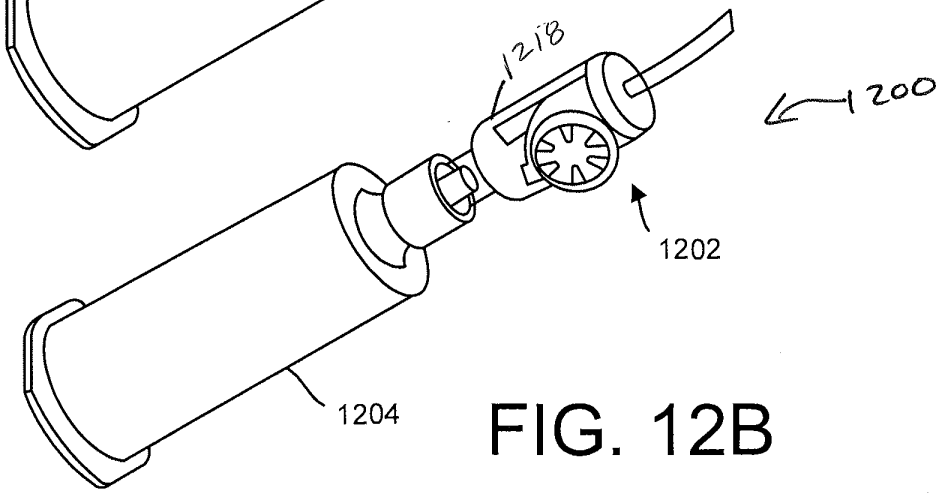


FIG. 12B

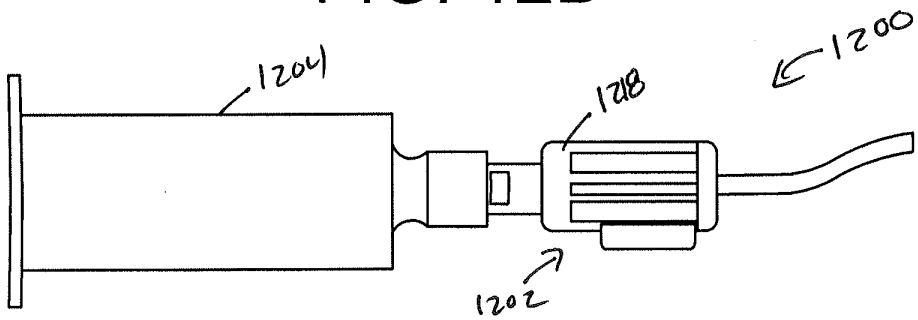


FIG. 12C

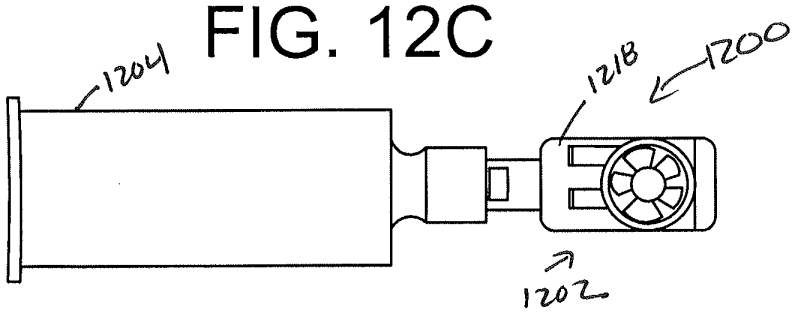


FIG. 12D

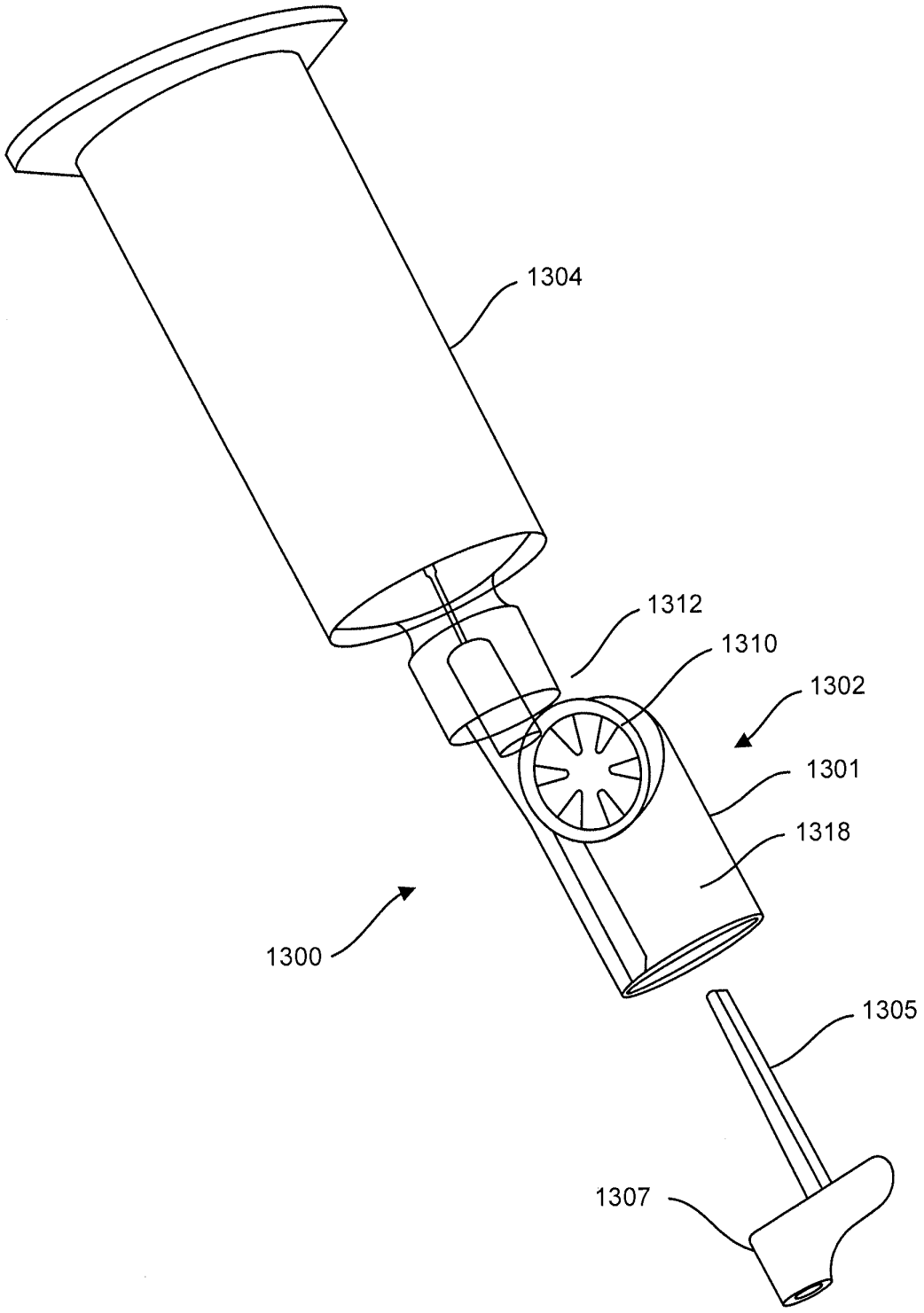


FIG. 13A

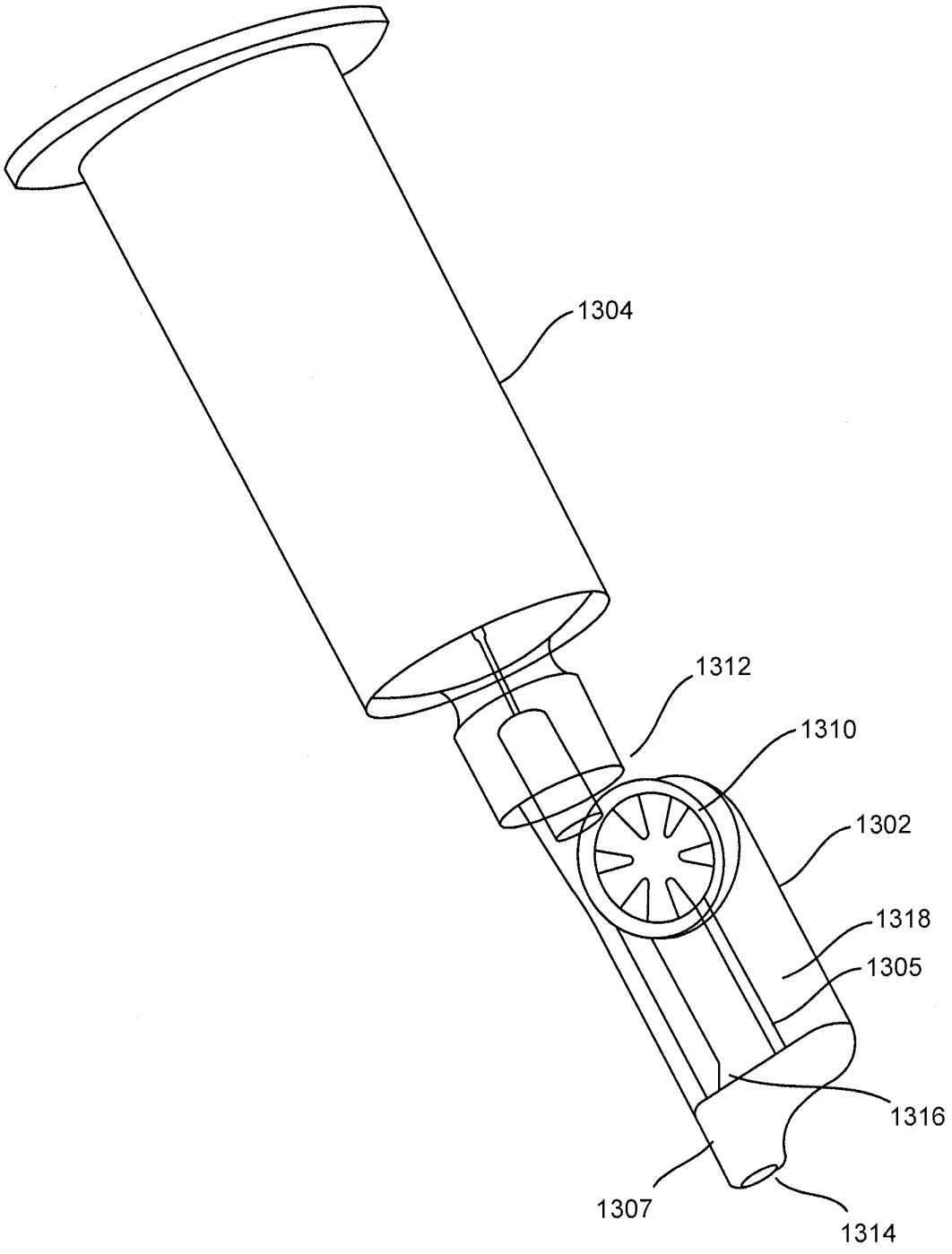


FIG. 13B

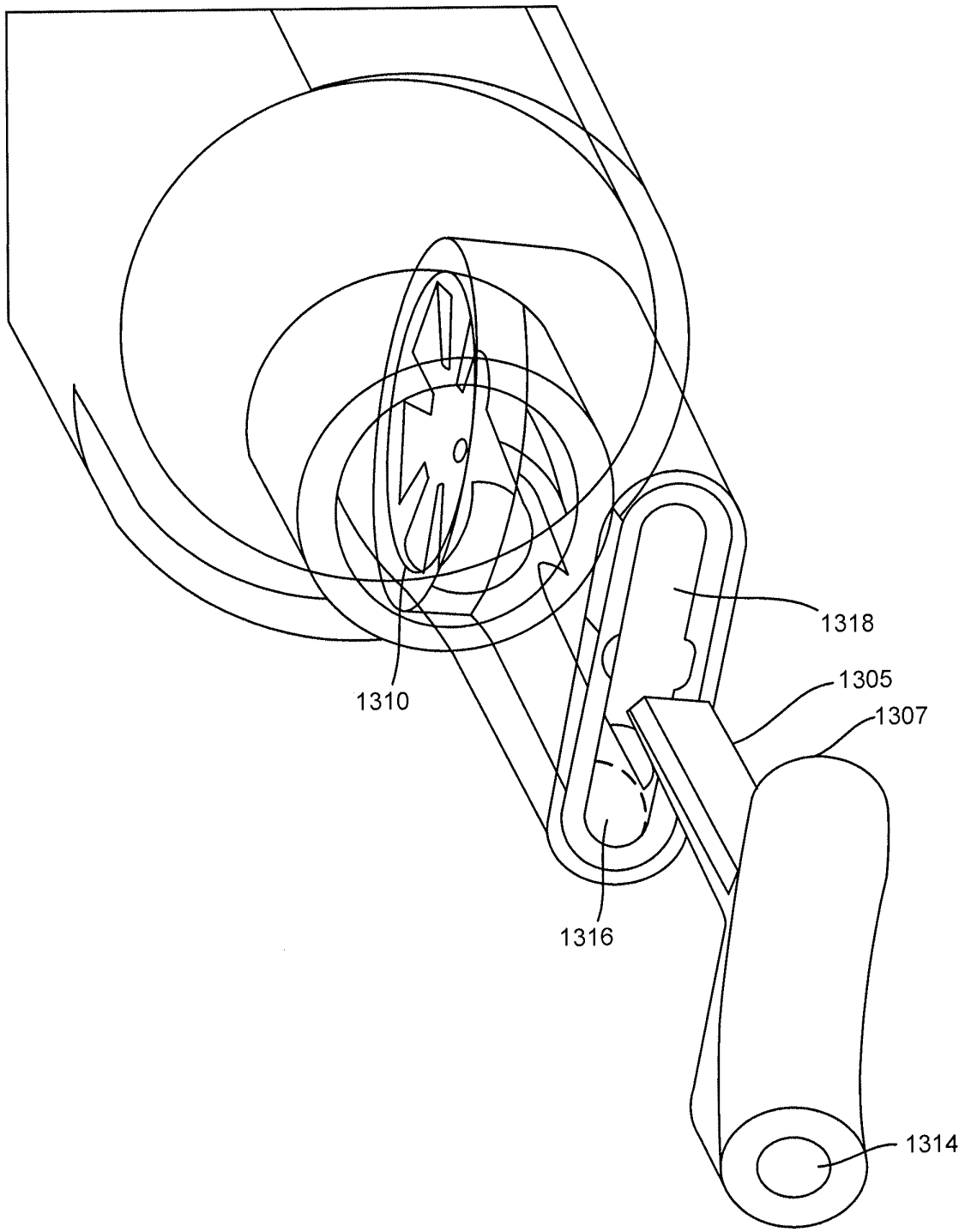


FIG. 13C

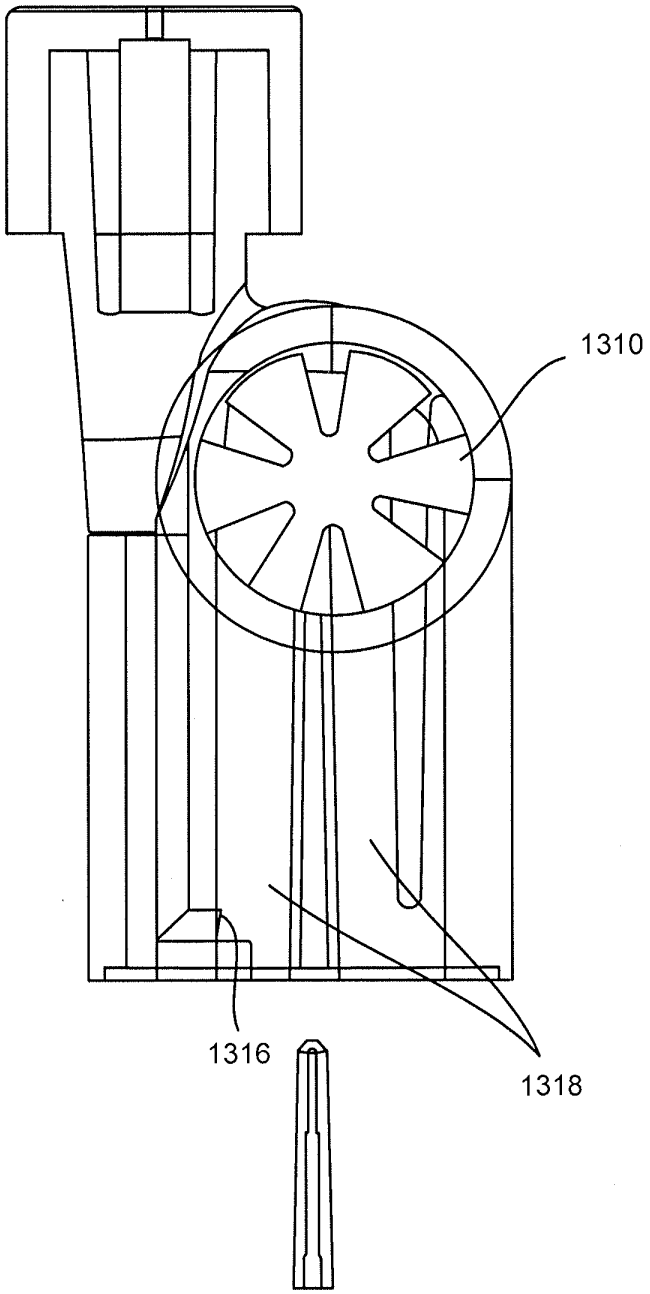


FIG. 13D

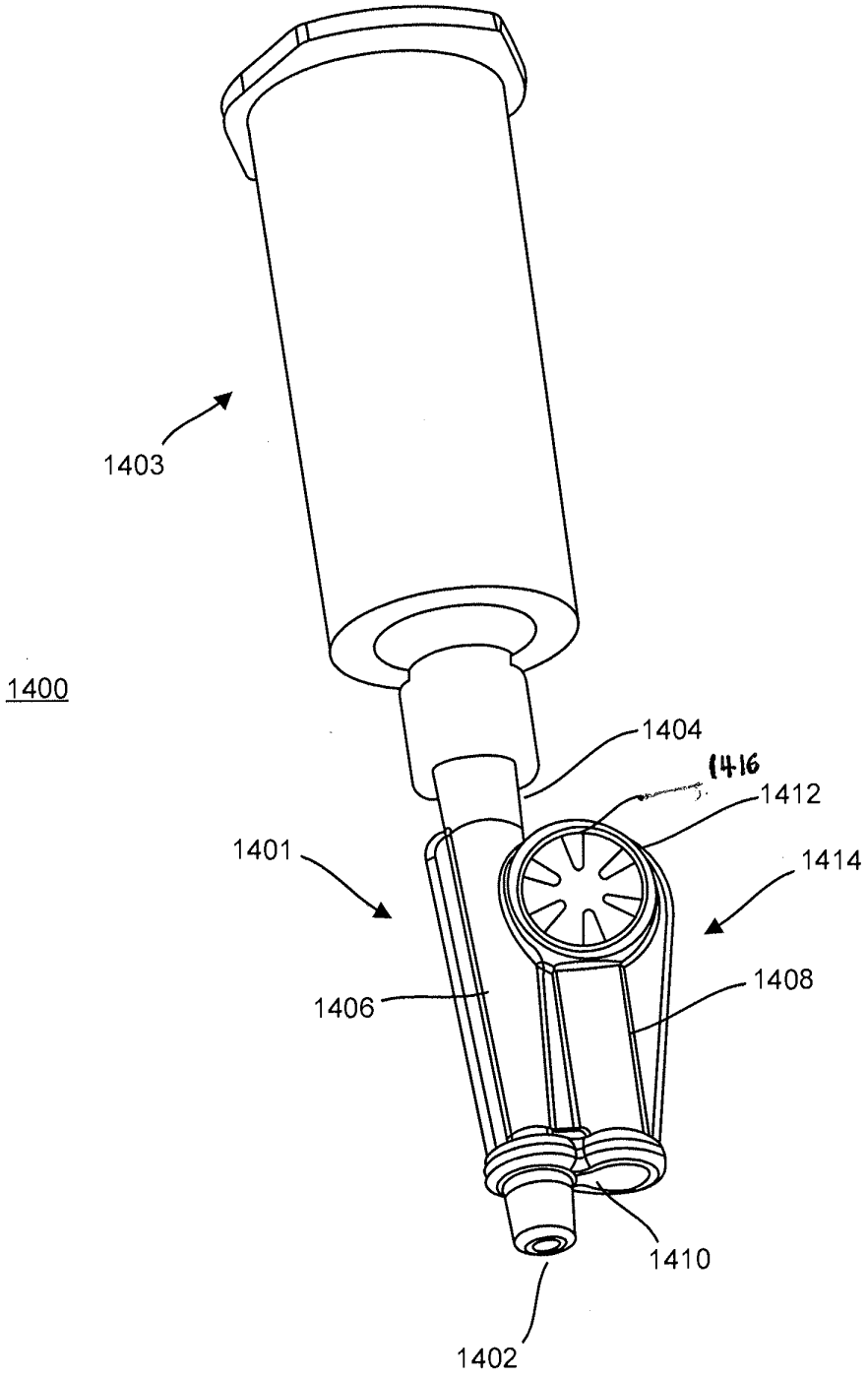


FIG. 14A

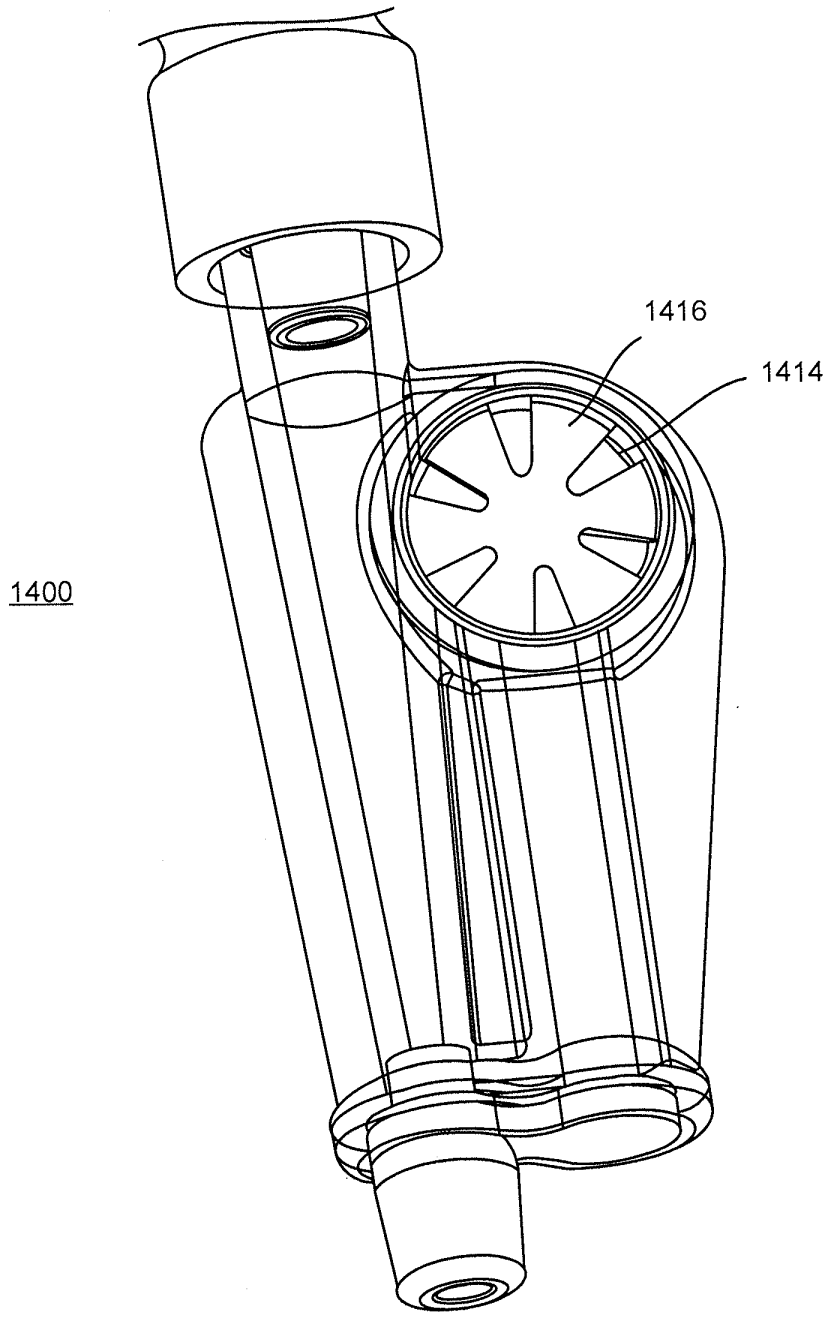


FIG. 14B

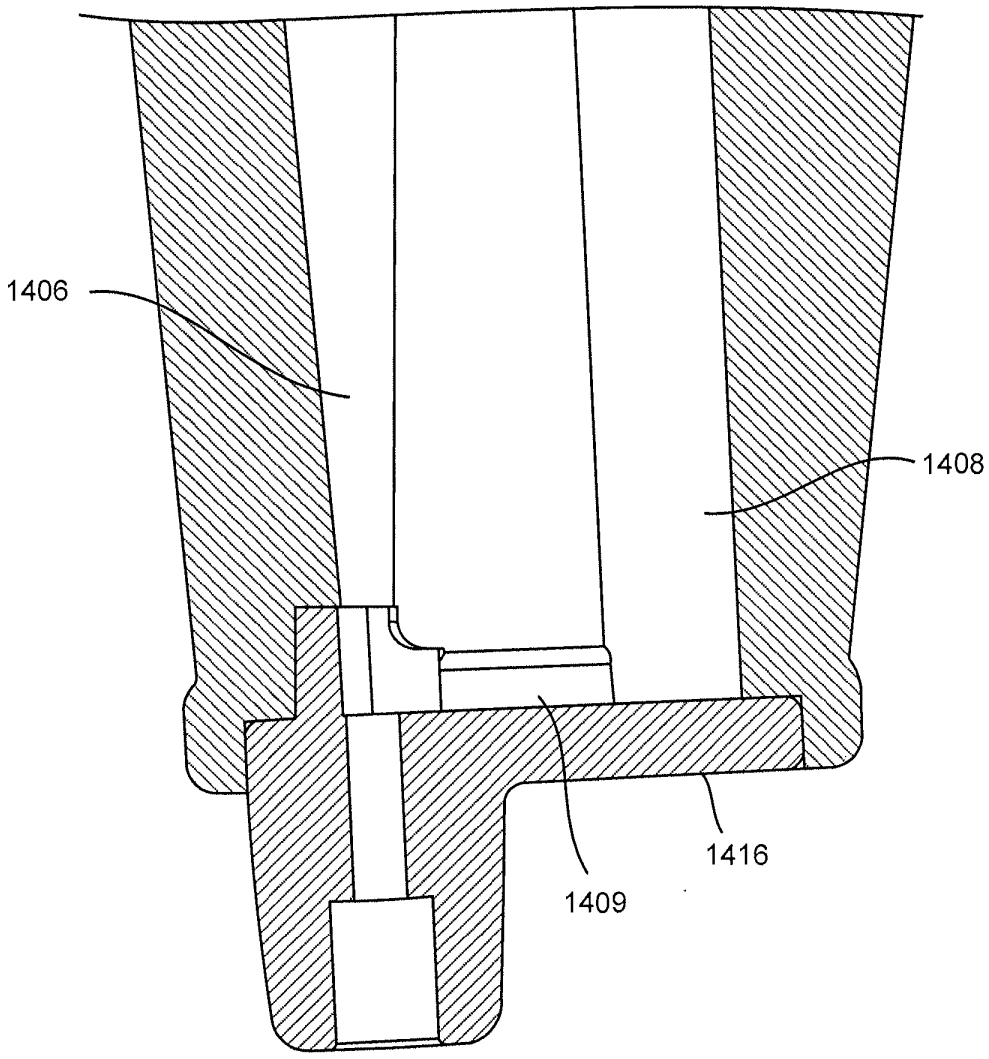


FIG. 14C

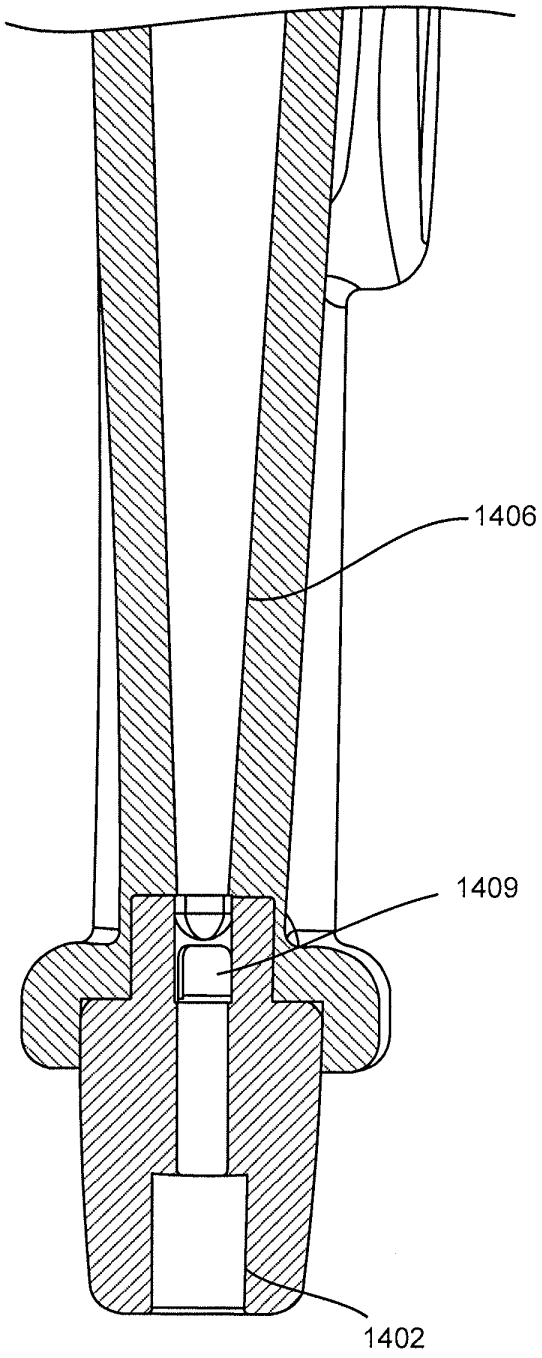


FIG. 14D

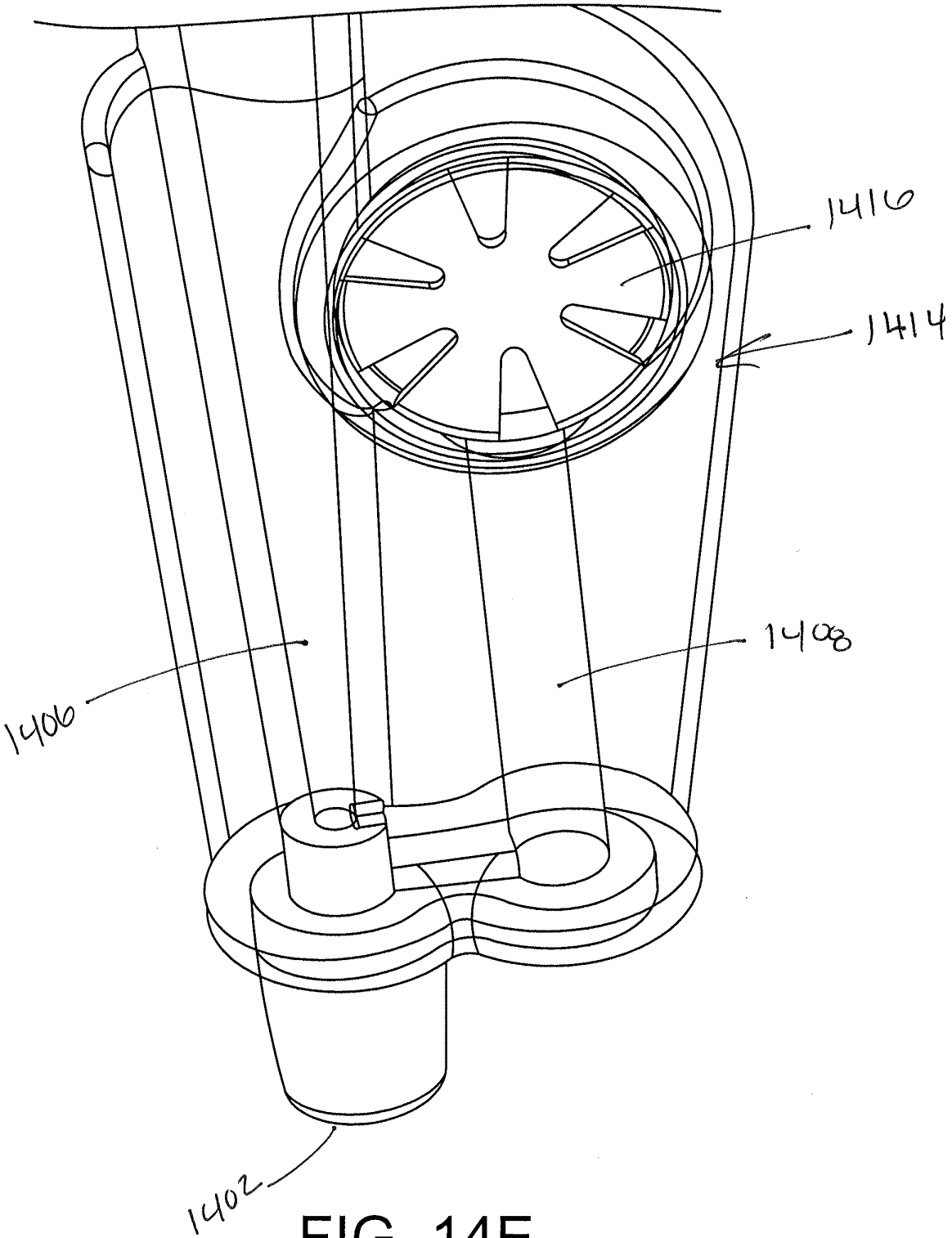


FIG. 14E

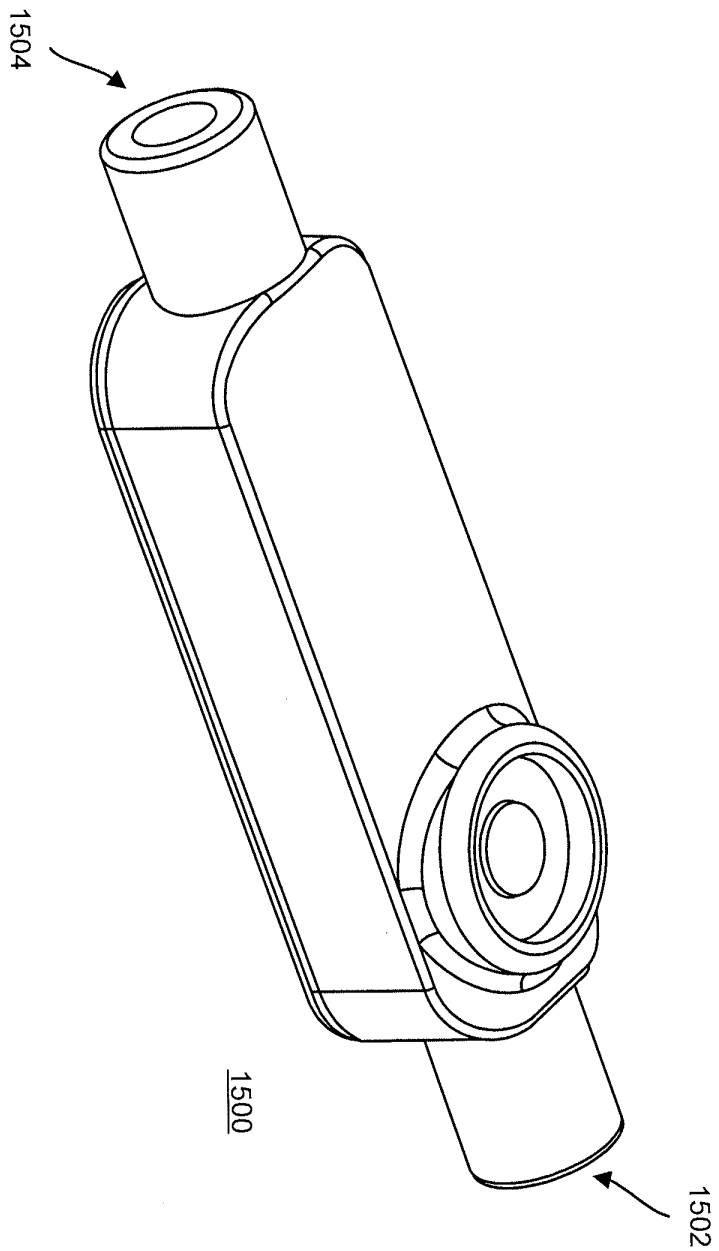


FIG. 15A

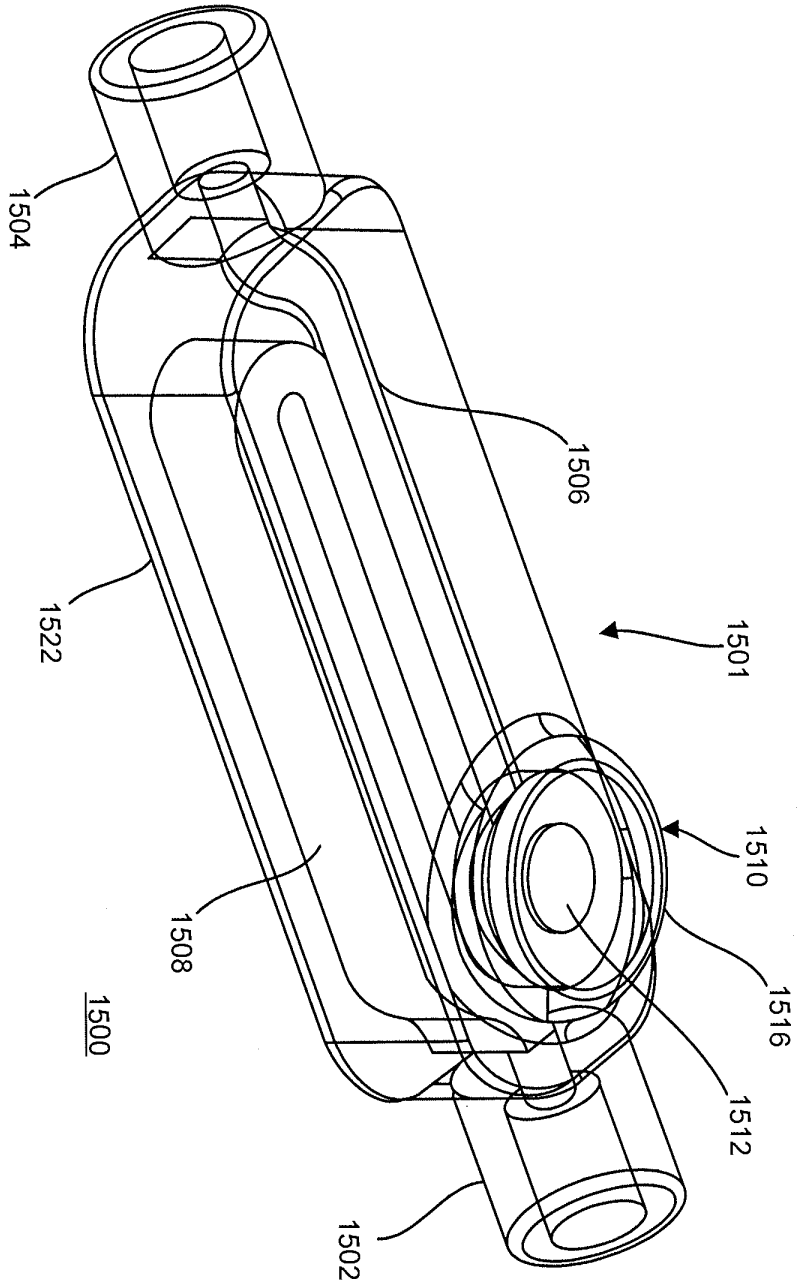


FIG. 15B

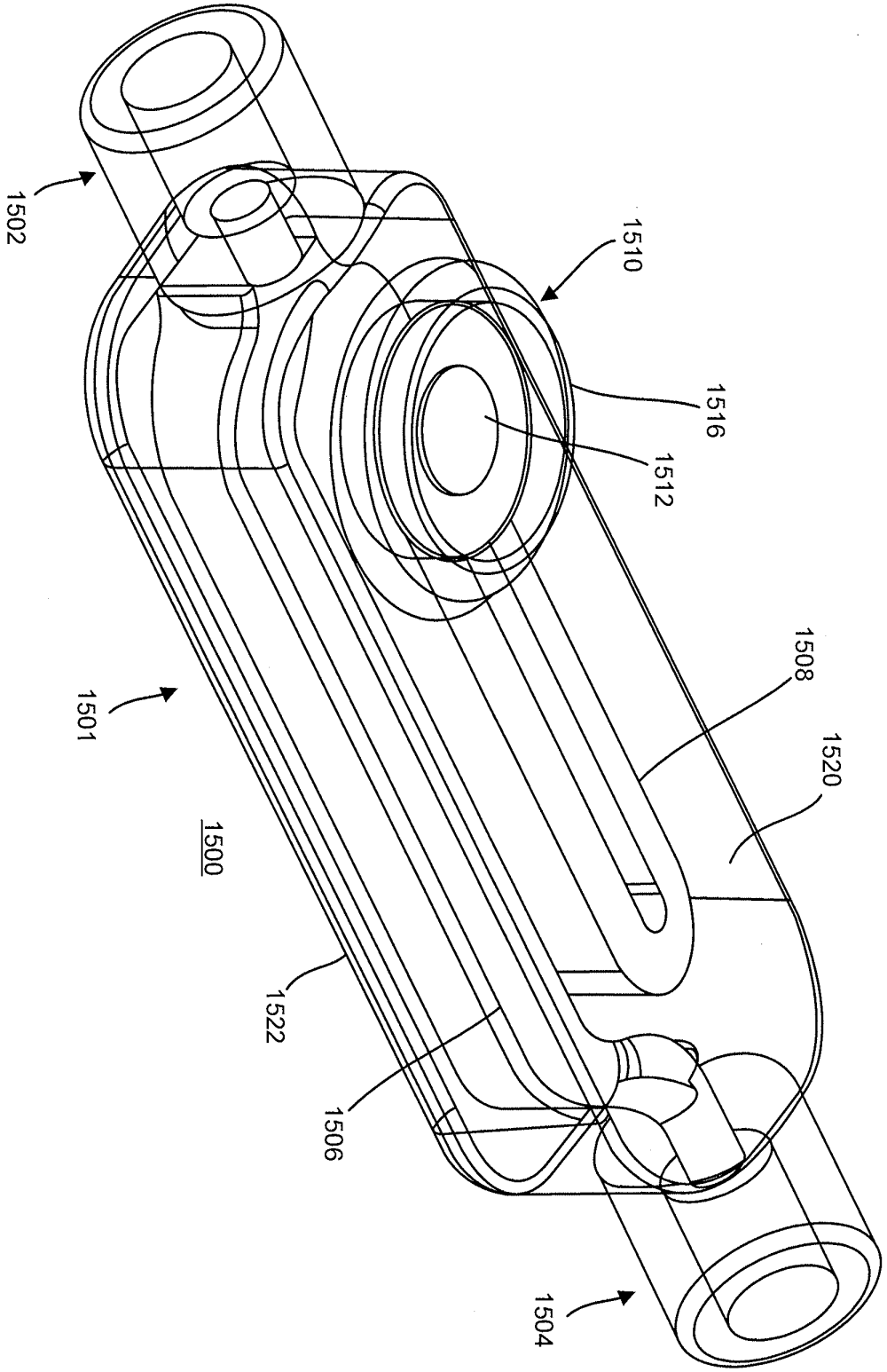


FIG. 15C

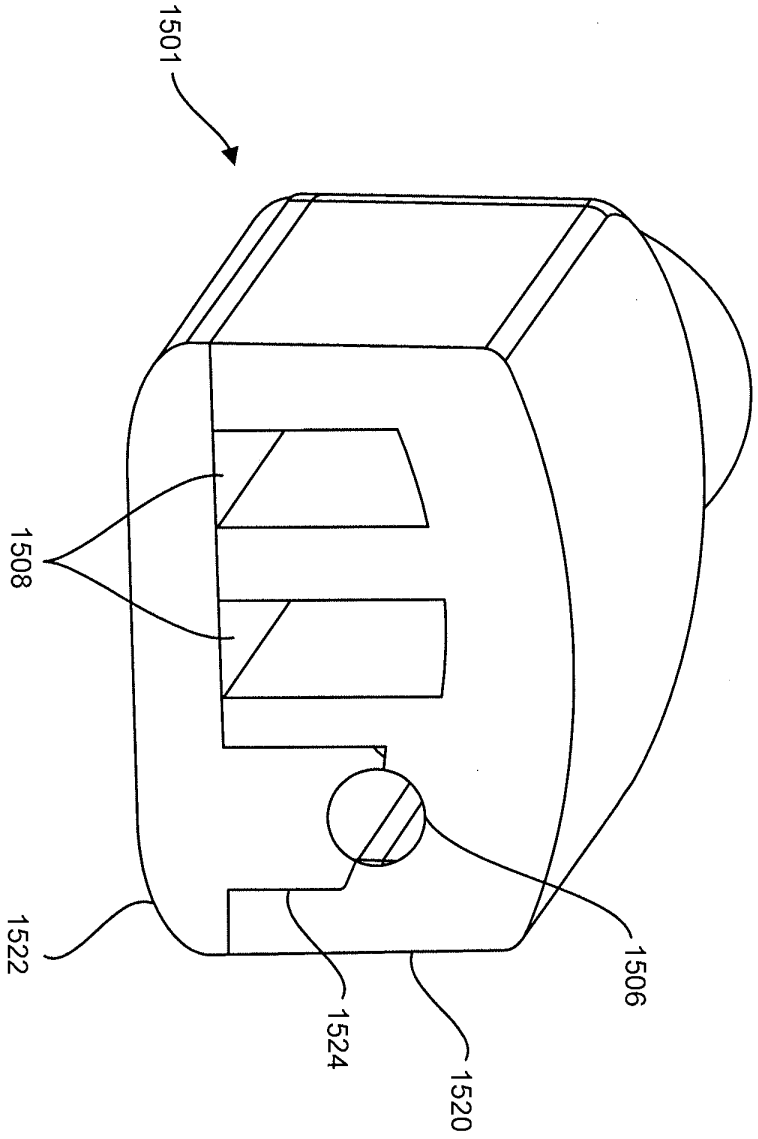


FIG. 15D

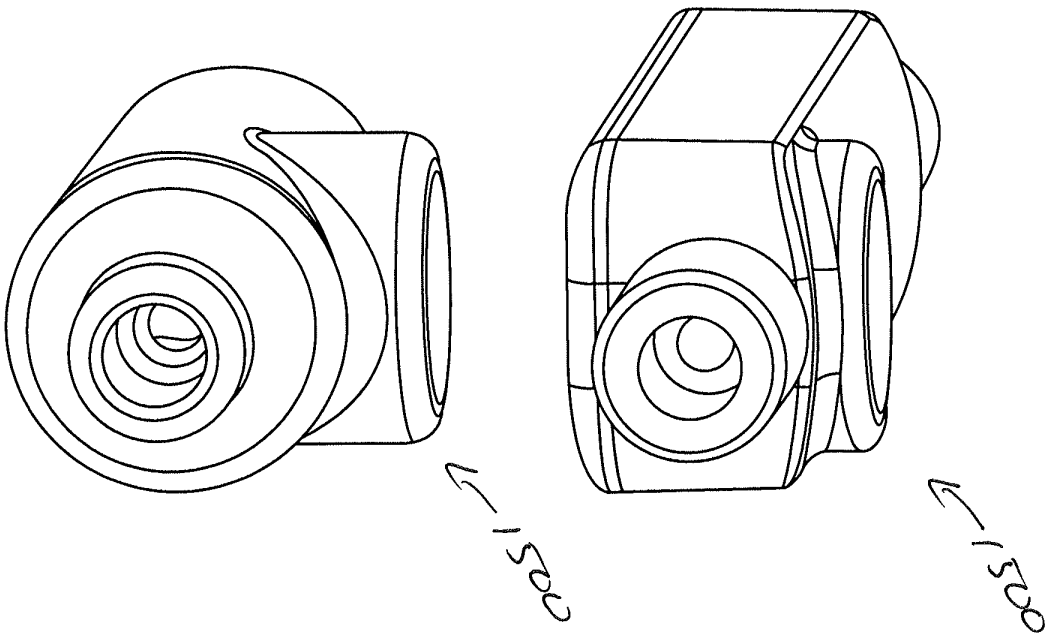


FIG. 15E

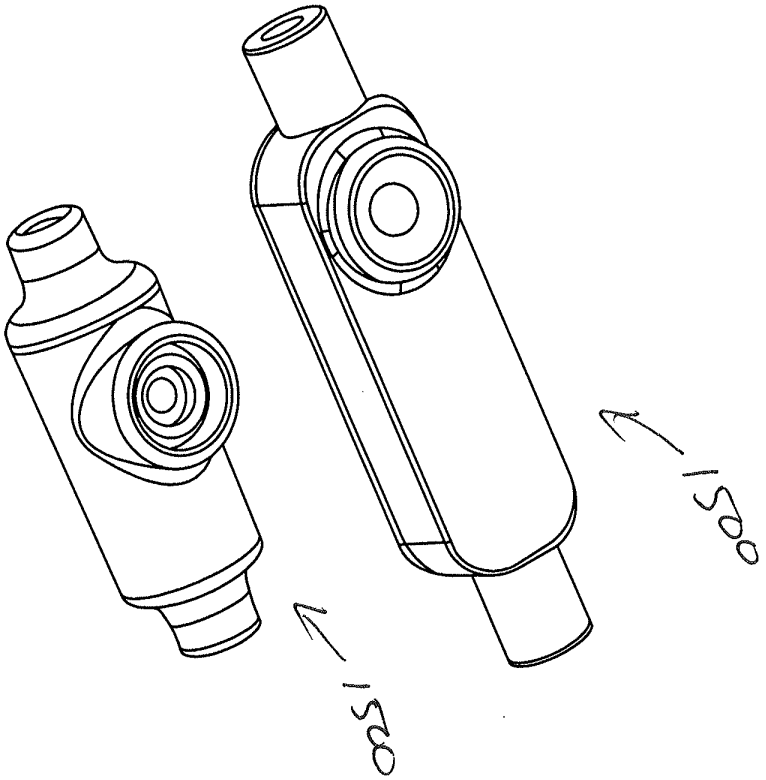


FIG. 15F

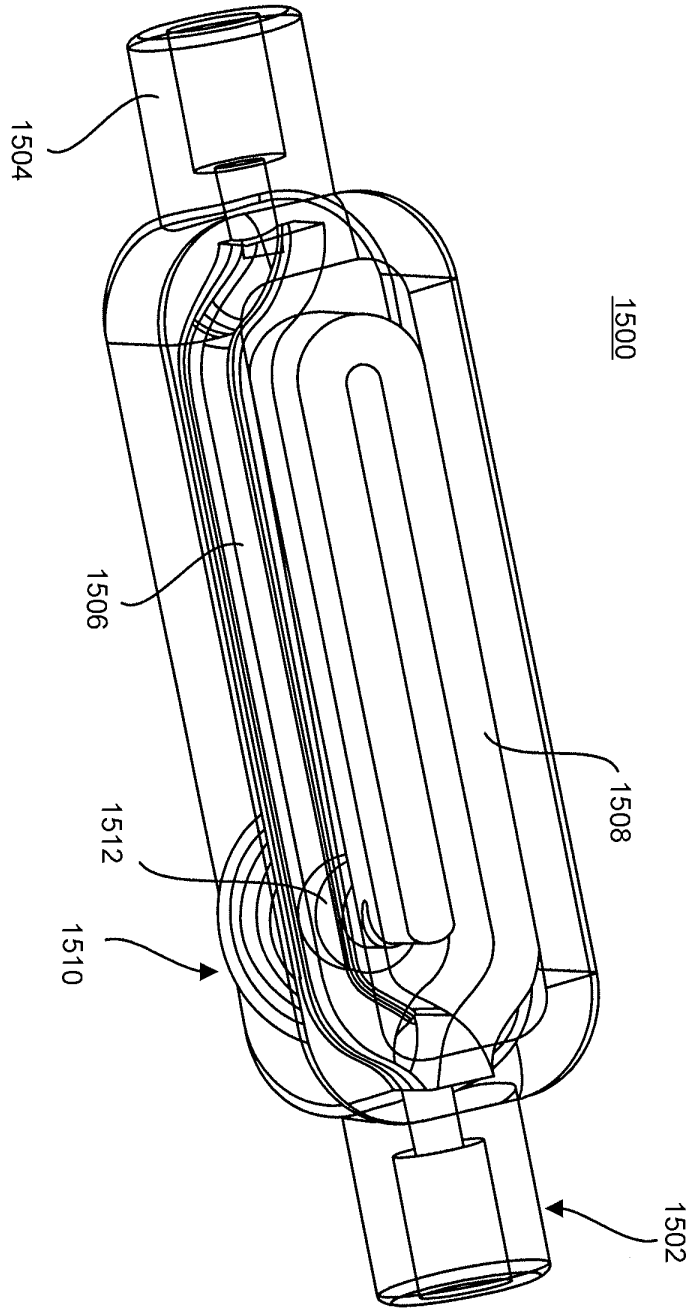


FIG. 15G

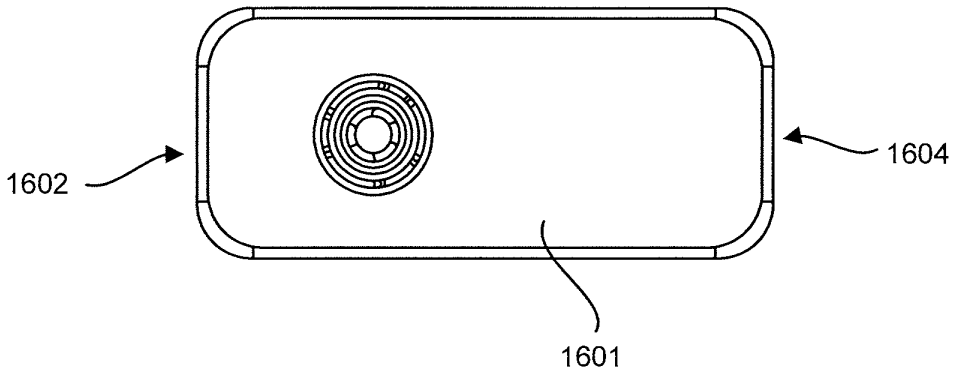


FIG. 16A

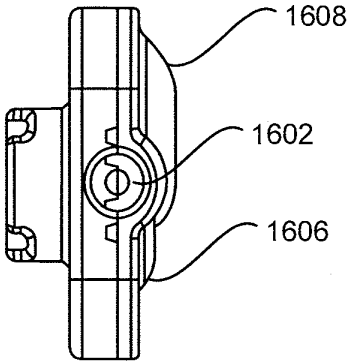


FIG. 16C

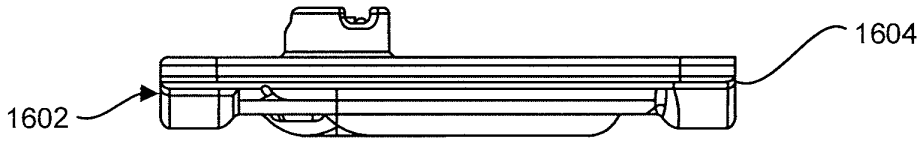


FIG. 16B

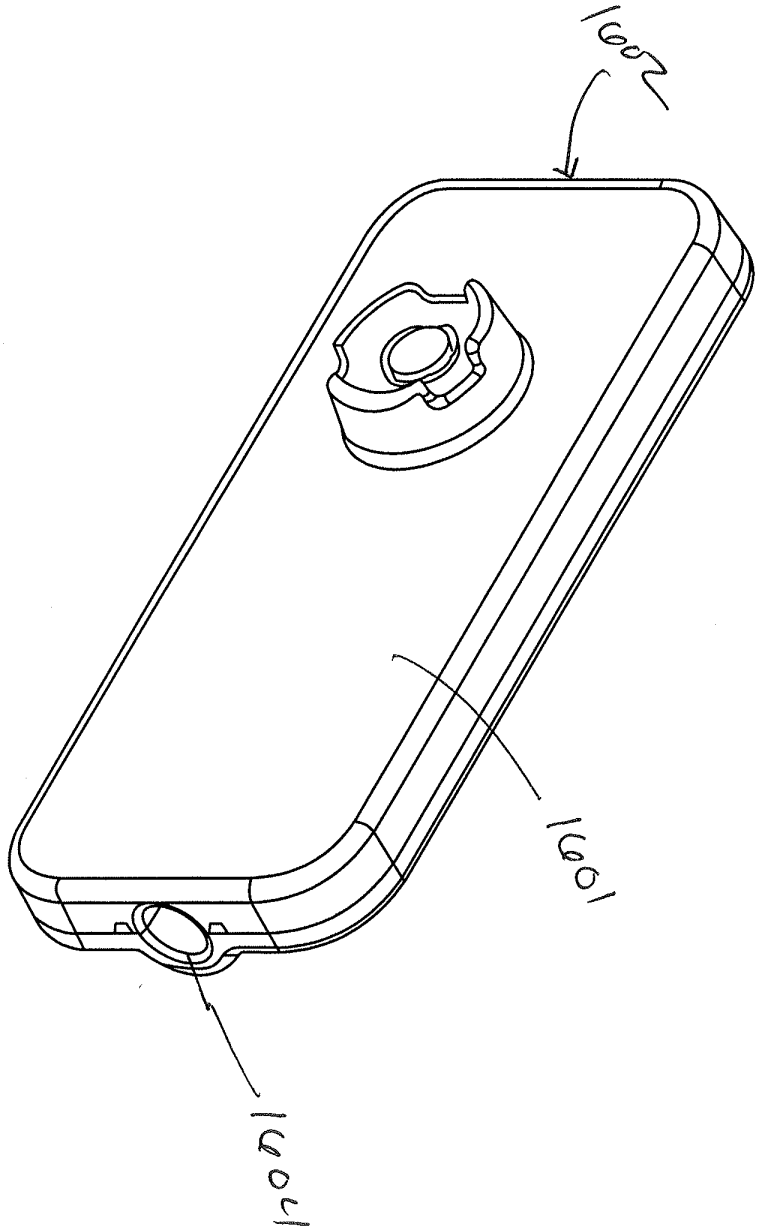


FIG. 16D

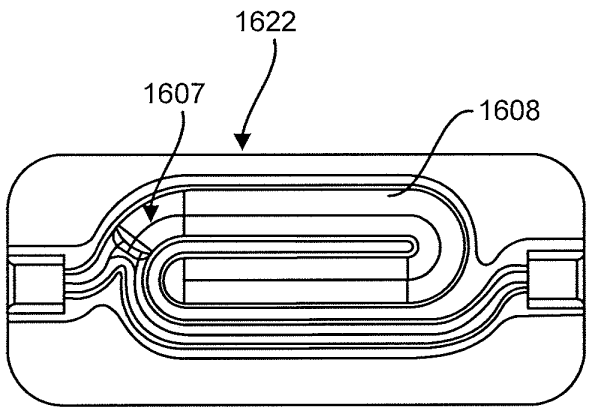


FIG. 17A

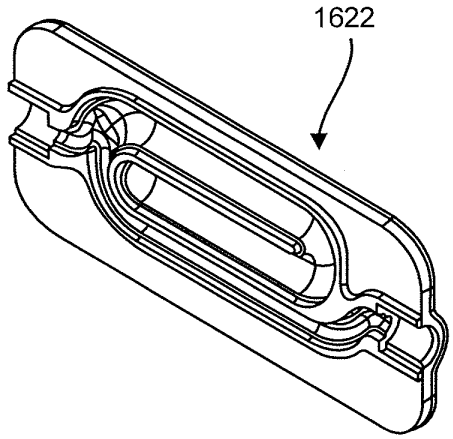


FIG. 17B

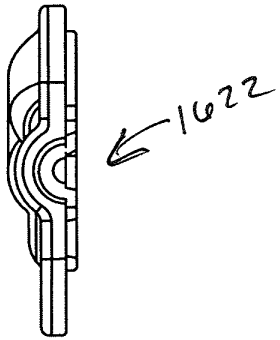


FIG. 17C

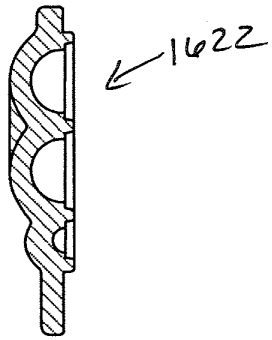


FIG. 17D

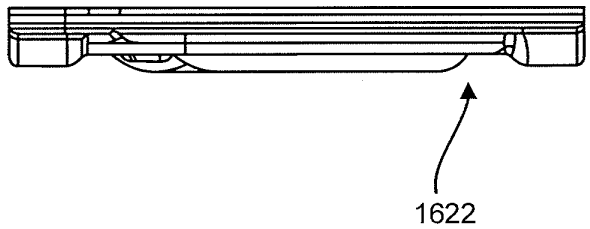


FIG. 17E

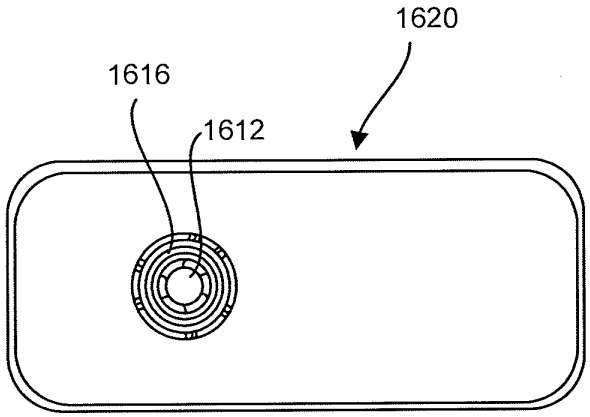


FIG. 18A

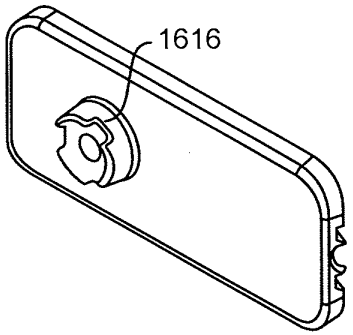


FIG. 18B

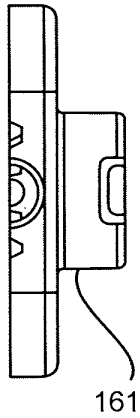


FIG. 18C

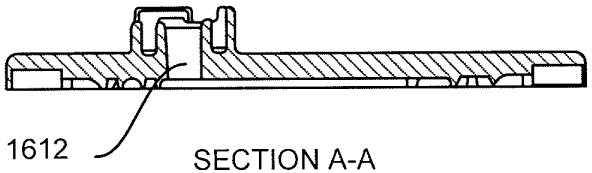


FIG. 18D

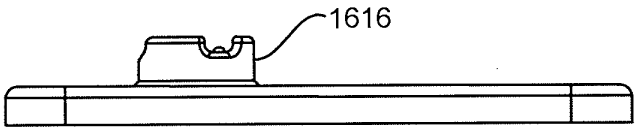


FIG. 18E

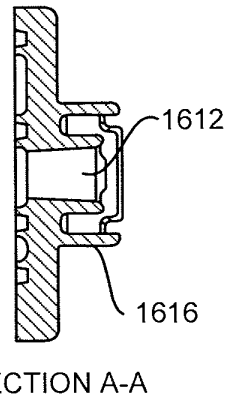


FIG. 18F

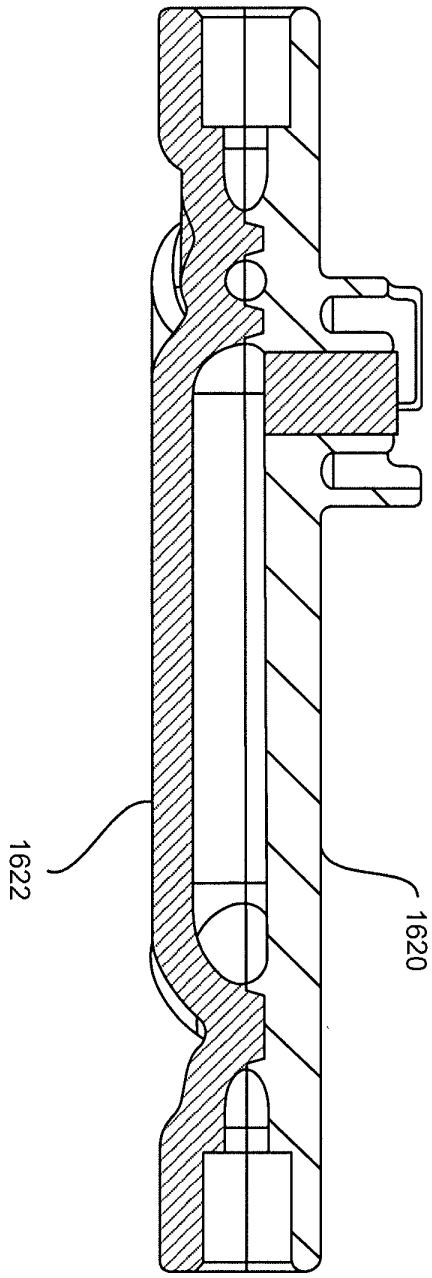


FIG. 19A

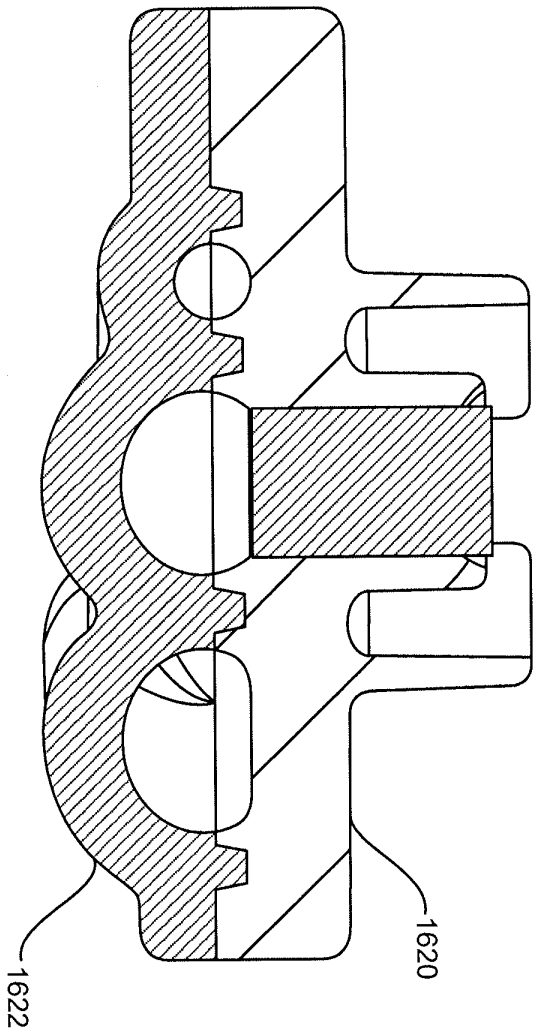


FIG. 19B

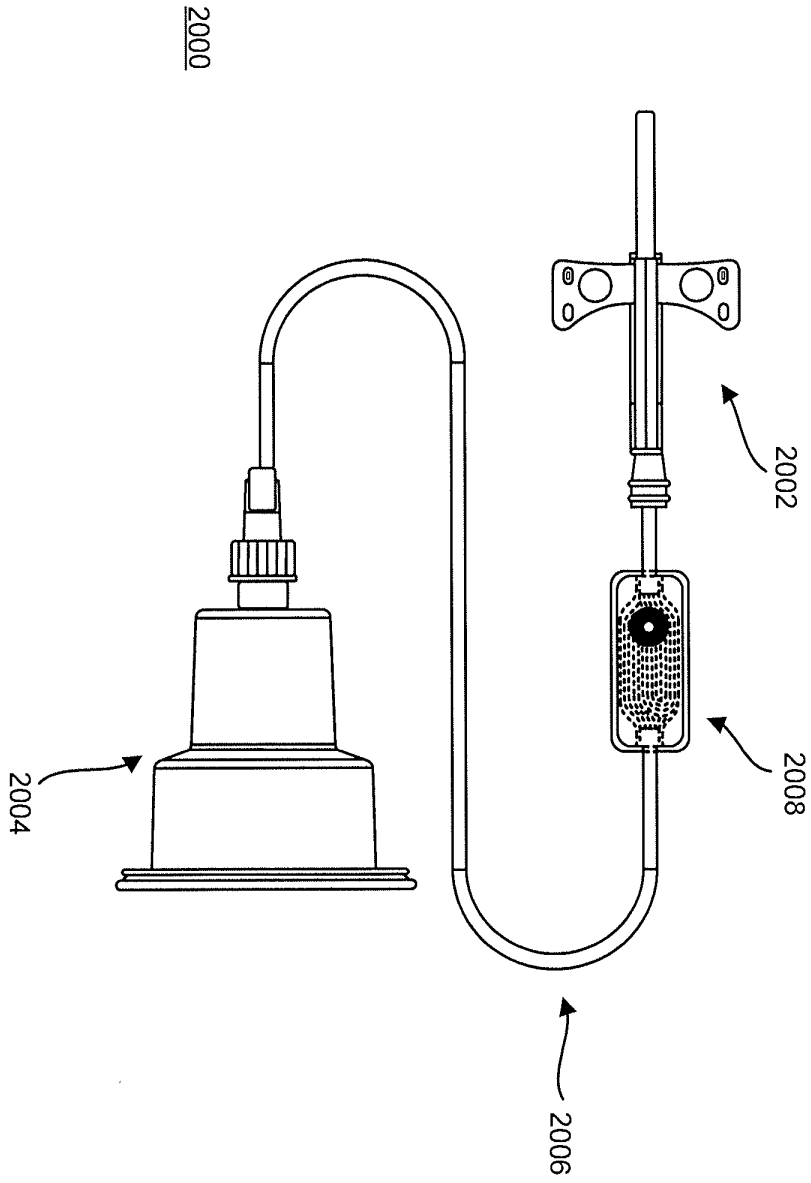


FIG. 20

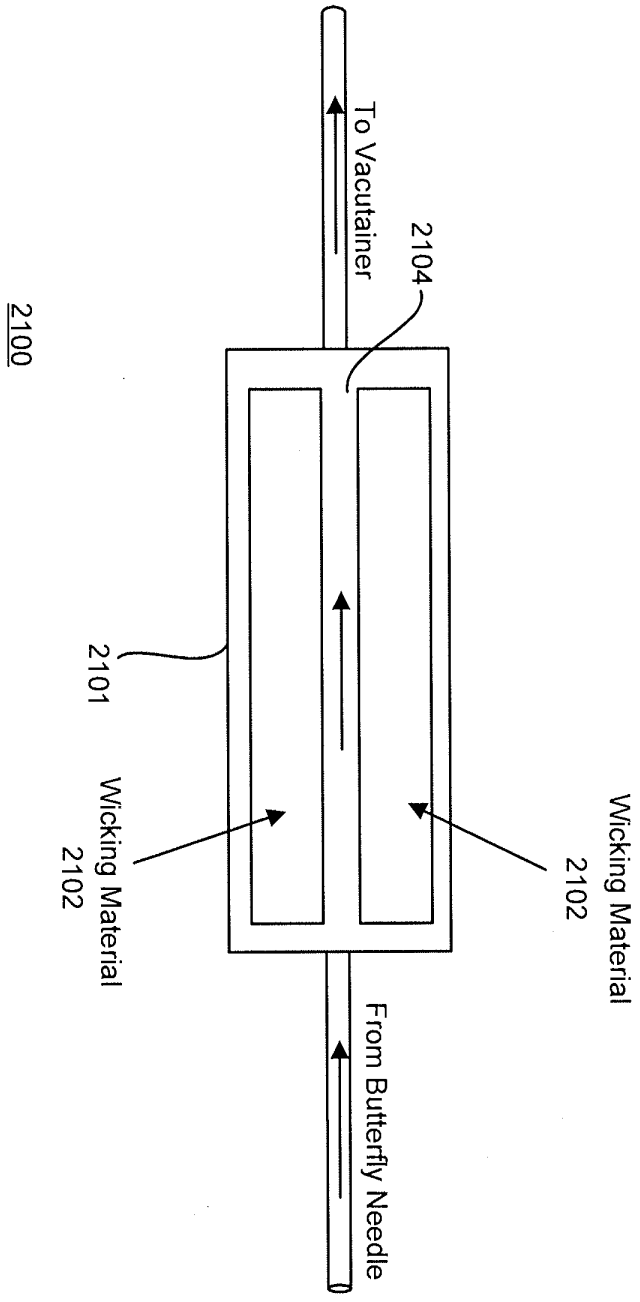

2100
To Vacutainer
2104
2101
Wicking Material
2102
Wicking Material
2102
From Butterfly Needle

FIG. 21

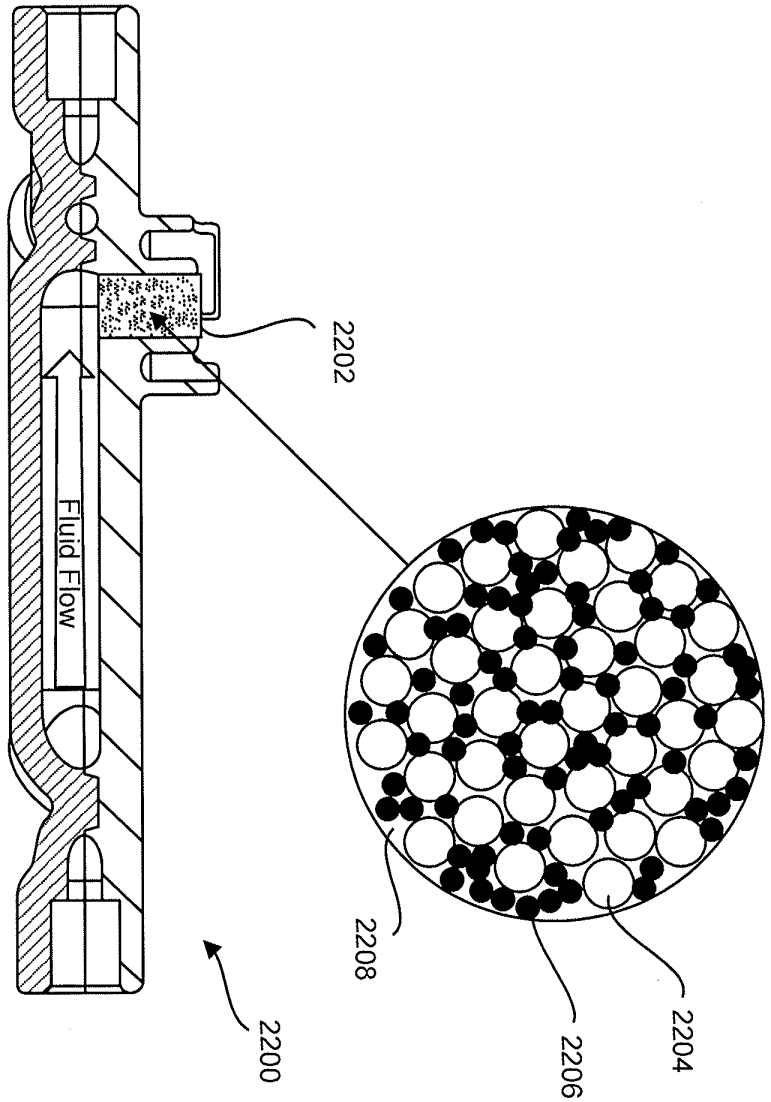


FIG. 22A

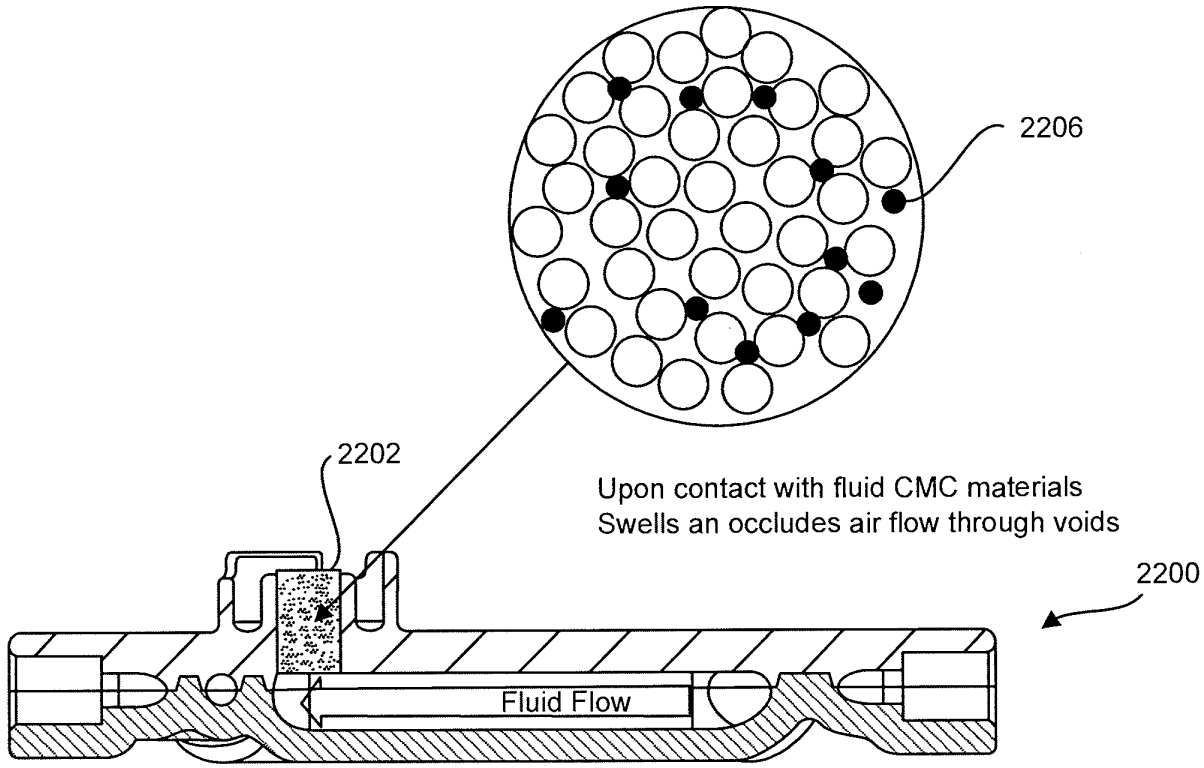

2206
2202
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2200
Fluid Flow

FIG. 22B

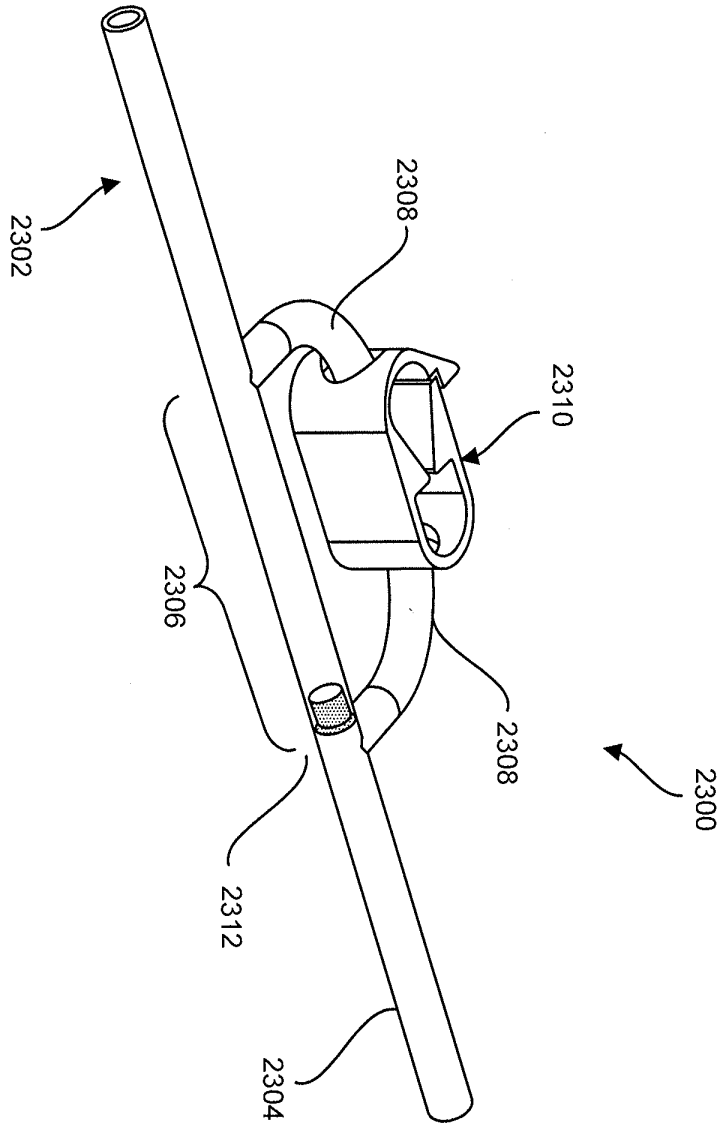


FIG. 23A

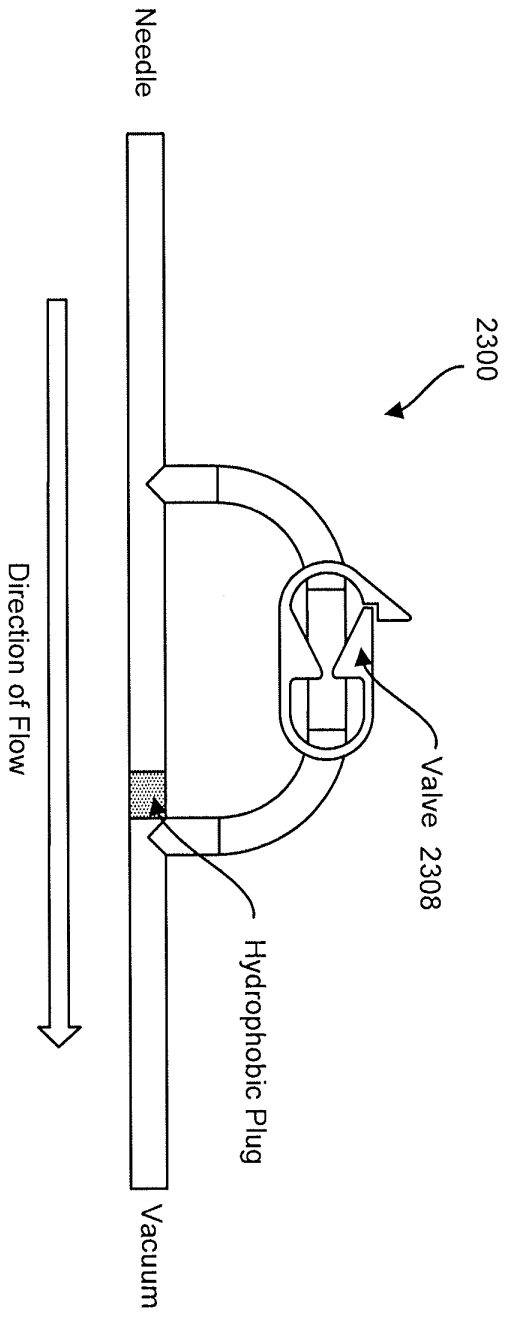

2300
Needle
Valve 2308
Hydrophobic Plug
Vacuum
Direction of Flow

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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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:

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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.**

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/538,990	11/30/2021		830	KURIN2CON4	20	3

CONFIRMATION NO. 3420

158174
Kurin, Inc.
P.O. Box 371710
San Diego, CA 92137

FILING RECEIPT

OC000000130389484

Date Mailed: 12/10/2021

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Bobby E. ROGERS, Park City, UT;
Gino KANG, Irvine, CA;
John DETLOFF, San Diego, CA;

Applicant(s)

Kurin, Inc., San Diego, CA;

Assignment For Published Patent Application

Kurin, Inc., San Diego, CA

Power of Attorney: The patent practitioners associated with Customer Number 158174

Domestic Priority data as claimed by applicant

This application is a CON of 16/208,559 12/04/2018 PAT 11185266
which is a CON of 15/994,559 05/31/2018 PAT 10143412
which is a CON of 15/140,448 04/27/2016 PAT 10010282
which claims benefit of 62/318,194 04/04/2016
and claims benefit of 62/238,636 10/07/2015
and claims benefit of 62/196,797 07/24/2015

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/09/2021

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/538,990**

Projected Publication Date: 03/17/2022

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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NOT GRANTED

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 17/538,990

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 50 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*	x 240 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	830		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

To: kurin@virtualipsupport.com,jsnolan1@hotmail.com,eofficeaction@appcoll.com
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 158174

Dec 10, 2021 04:51:49 AM

Dear PAIR Customer:

Kurin, Inc.
P.O. Box 371710
San Diego, CA 92137
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
17538990	APP.FILE.REC	12/10/2021	KURIN2CON4

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/538,990	11/30/2021	Bobby E. ROGERS	KURIN2CON4

CONFIRMATION NO. 3420

158174
Kurin, Inc.
P.O. Box 371710
San Diego, CA 92137

PUBLICATION NOTICE

OC000000132523874

Title:BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

Publication No.US-2022-0079483-A1
Publication Date:03/17/2022

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

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Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

To: kurin@virtualipsupport.com,jsnolan1@hotmail.com,eofficeaction@appcoll.com
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 158174

Mar 18, 2022 05:14:44 AM

Dear PAIR Customer:

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P.O. Box 371710
San Diego, CA 92137
UNITED STATES

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Application	Document	Mailroom Date	Attorney Docket No.
17538990	NTC.PUB	03/17/2022	KURIN2CON4

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UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
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NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	17/538,990
Filing Date	November 30, 2021
First Named Inventor	Bobby E. Rogers
Title	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	069366-0572201_KURIN2C03US

SIGNATURE of Applicant or Patent Practitioner

Signature	/Ben Hudson/	Date (Optional)	
Name	Benjamin F. Hudson	Registration Number	71,474
Title (if Applicant is a juristic entity)	agent of record		
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, 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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Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 27500

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Kurin, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	
Name	Bobby E. Rogers		
Title	CEO		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☐ Total of forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, 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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Electronic Acknowledgement Receipt

EFS ID:	46962283
Application Number:	17538990
International Application Number:	
Confirmation Number:	3420
Title of Invention:	BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD
First Named Inventor/Applicant Name:	Bobby E. ROGERS
Customer Number:	158174
Filer:	Benjamin F. Hudson/Bob Olinski
Filer Authorized By:	Benjamin F. Hudson
Attorney Docket Number:	KURIN2CON4
Receipt Date:	04-NOV-2022
Filing Date:	30-NOV-2021
Time Stamp:	17:01:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	069366-0572201_KURIN2C03US-POA.pdf	434273 2eda4b4d088c497b404a21fa36a905ed77149cf3	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	434273

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a 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.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/538,990	11/30/2021	Bobby E. ROGERS	069366-0572201_KURIN2C03U

CONFIRMATION NO. 3420

27500
PILLSBURY WINTHROP SHAW PITTMAN LLP (CV)
ATTENTION: DOCKETING DEPARTMENT
P.O BOX 10500
McLean, VA 22102

POA ACCEPTANCE LETTER

OC000000136800960

Date Mailed: 11/21/2022

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/04/2022.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/538,990	11/30/2021	Bobby E. ROGERS	KURIN2CON4

CONFIRMATION NO. 3420

158174
Kurin, Inc.
P.O. Box 371710
San Diego, CA 92137

POWER OF ATTORNEY NOTICE

OC000000136800957

Date Mailed: 11/21/2022

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Application	Document	Mailroom Date	Attorney Docket No.
17538990	N570	11/21/2022	069366-0572201_KUR2C03US
	N570	11/21/2022	069366-0572201_KUR2C03US

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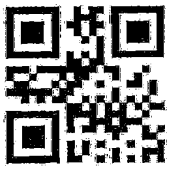
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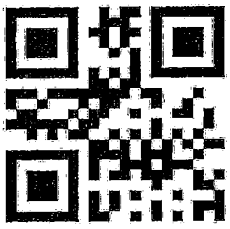
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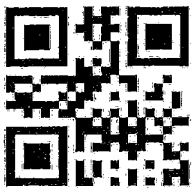
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	17538990
Filing Date	2021-11-30
First Named Inventor	Bobby E. ROGERS
Art Unit	OPAP
Examiner Name	CENTRAL, DOCKET
Attorney Docket Number	069366-0572201_KUR2C03US

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	5432084		1995-07-11	BRUBAKER DANIEL B	
	3	5972294		1999-10-26	SMITH JOHN L	
	4	6187347		2001-02-13	PATTERSON JAMES A	
	5	6599474		2003-07-29	EVTODIENKO VLADIMIR	
	6	8197420		2012-06-12	PATTON RICHARD G	
	7	8535241		2013-09-17	BULLINGTON GREGORY	
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	Attorney Docket Number	069366-0572201_KUR2C03US

	9	9155495		2015-10-13	BULLINGTON GREGORY J	
	10	4412548		1983-11-01	HOCH LOUIS	
	11	5222502		1993-06-29	KUROSE KATSUTOSHI	
	12	5520193		1996-05-28	SUZUKI ISSEI	
	13	9022951		2015-05-05	BULLINGTON GREGORY	
	14	6569117		2003-05-27	ZIV DAVID	
	15	3741197		1973-06-26	SANZ M	
	16	8603009		2013-12-10	TAN ALVIN CHEE LEONG	
	17	4207870		1980-06-17	ELDRIDGE WILLIAM N	
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	19	4444203		1984-04-24	ENGELMAN ALLAN	

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	20	6398743		2002-06-04	HALSETH THOR R	
	21	9022950		2015-05-05	BULLINGTON GREGORY	
	22	4436098		1984-03-13	KAUFMAN JOSEPH	
	23	9138572		2015-09-22	ZEYTOONIAN PAUL	
	24	8568371		2013-10-29	SIOPES WILLIAM	
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	46	8070725		2011-12-06	CHRISTENSEN KELLY D	
	47	4349035		1982-09-14	THOMAS JOSEPH J	
	48	4813433		1989-03-21	DOWNEY JOHN M	
	49	5401262		1995-03-28	KARWOSKI THEODORE	
	50	3859998		1975-01-14	THOMAS JOSEPH JOHN	
	51	4373535		1983-02-15	MARTELL MICHAEL D	
	52	4690154		1987-09-01	WOODFORD TIMOTHY	

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	54	5865803		1999-02-02	MAJOR MIKLOS	
	55	5873841		1999-02-23	BRANNON JAMES K	
	56	6013037		2000-01-11	BRANNON JAMES K	
	57	6913580		2005-07-05	STONE BENJAMIN CURTIS	
	58	11213232		2022-01-04	IVOSEVIC MILAN	
	59	6626884		2003-09-30	DILLON JAGMOHANBIR SINGH	
	60	4904240		1990-02-27	HOOVER ROCKLIN L	
	61	4673386		1987-06-16	GORDON MARK G	
	62	7461671		2008-12-09	EHWALD RUDOLF	
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	64	3382865		1968-05-14	WORRALL JR ASHTON L	
	65	3848579		1974-11-19	VILLA REAL A	
	66	6106509		2000-08-22	LOUBSER PAUL G	
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	70	5135489		1992-08-04	JEPSON STEVEN C	
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	80	8377040		2013-02-19	BURKHOLZ JONATHAN KARL	
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	82	6638252		2003-10-28	MOULTON WILLIAM G	
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	Examiner Name	CENTRAL, DOCKET
	Attorney Docket Number	069366-0572201_KUR2C03US

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	4	20040116830		2004-06-17	TRUDEAU WILLIAM M	
	5	20090299253		2009-12-03	HURSEY FRANCIS X	
	6	20130158506		2013-06-20	HARRIS ADRIENNE ROSE	
	7	20150246352		2015-09-03	BULLINGTON GREGORY J	
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	11	20180140240		2018-05-24	BULLINGTON GREGORY J	
	12	20140112841		2014-04-24	SCHOEN CHRISTIAN	
	13	20180271425		2018-09-27	ROGERS BOBBY E	

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	14	20080319346		2008-12-25	CRAWFORD JAMIESON	
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	16	20070088279		2007-04-19	SHUE MING-JENG	
	17	20080145933		2008-06-19	PATTON RICHARD G	
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	19	20100010372		2010-01-14	BROWN LEROY R	
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	26	20160174888		2016-06-23	BERTHIER ERWIN	
	27	20050240161		2005-10-27	CRAWFORD JAMIESON W M	
	28	20040147855		2004-07-29	MARSDEN STEWART	
	29	20040073171		2004-04-15	ROGERS BOBBY E	
	30	20050004524		2005-01-06	NEWBY C MARK	
	31	20030105414		2003-06-05	LEONG ALVIN TAN CHEE	
	32	20020004647		2002-01-10	LEONG ALVIN TAN CHEE	
	33	20140155781		2014-06-05	BULLINGTON GREGORY J	
	34	20030208151		2003-11-06	KRAUS MENACHEM	
	35	20090227953		2009-09-10	TAN CHEE LEONG	

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	39	20050007524		2005-01-13	LUO FANG-CHEN	
	40	20140039348		2014-02-06	BULLINGTON GREGORY J	
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	42	20140155782		2014-06-05	BULLINGTON GREGORY J	
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	44	20160017488		2016-01-21	KOBAYASHI MASAYUKI	
	45	20180177445		2018-06-28	ROGERS BOBBY E	
	46	20180353117		2018-12-13	BULLINGTON GREGORY J	

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	48	20050245885		2005-11-03	BROWN LEROY	
	49	20110306899		2011-12-15	BROWN LEROY R	
	50	20130116599		2013-05-09	BULLINGTON GREGORY J	
	51	20050273019		2005-12-08	CONWAY HUGH	
	52	20150351678		2015-12-10	BULLINGTON GREGORY	
	53	20220160271		2022-05-26	IVOSEVIC MILAN	
	54	20050161112		2005-07-28	EHWALD RUDOLF	
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	56	20220304600		2022-09-29	HAMMER JEREMY	

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	2	2009131273A	JP		2009-06-18	CSL BEHRING GMBH		☒
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	Examiner Name	CENTRAL, DOCKET
	Attorney Docket Number	069366-0572201_KUR2C03US

	11	2993646	CA		2017-02-02	KURIN INC		☒
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	1	International Search Report and Written Opinion dated Nov. 5, 2015, for PCT application No. PCT/US2015/035870. 6 pages.	
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The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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Signature	/Benjamin F. Hudson/	Date (YYYY-MM-DD)	2023-05-16
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A61M 5/158
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A61B 5/14 300H
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[Number of claims] 45
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(22) [Application date] June 2, 2005 (2005.6.2)

(31) [Priority claim number] 60/576,217

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(33) [Country claiming priority] United States (US)

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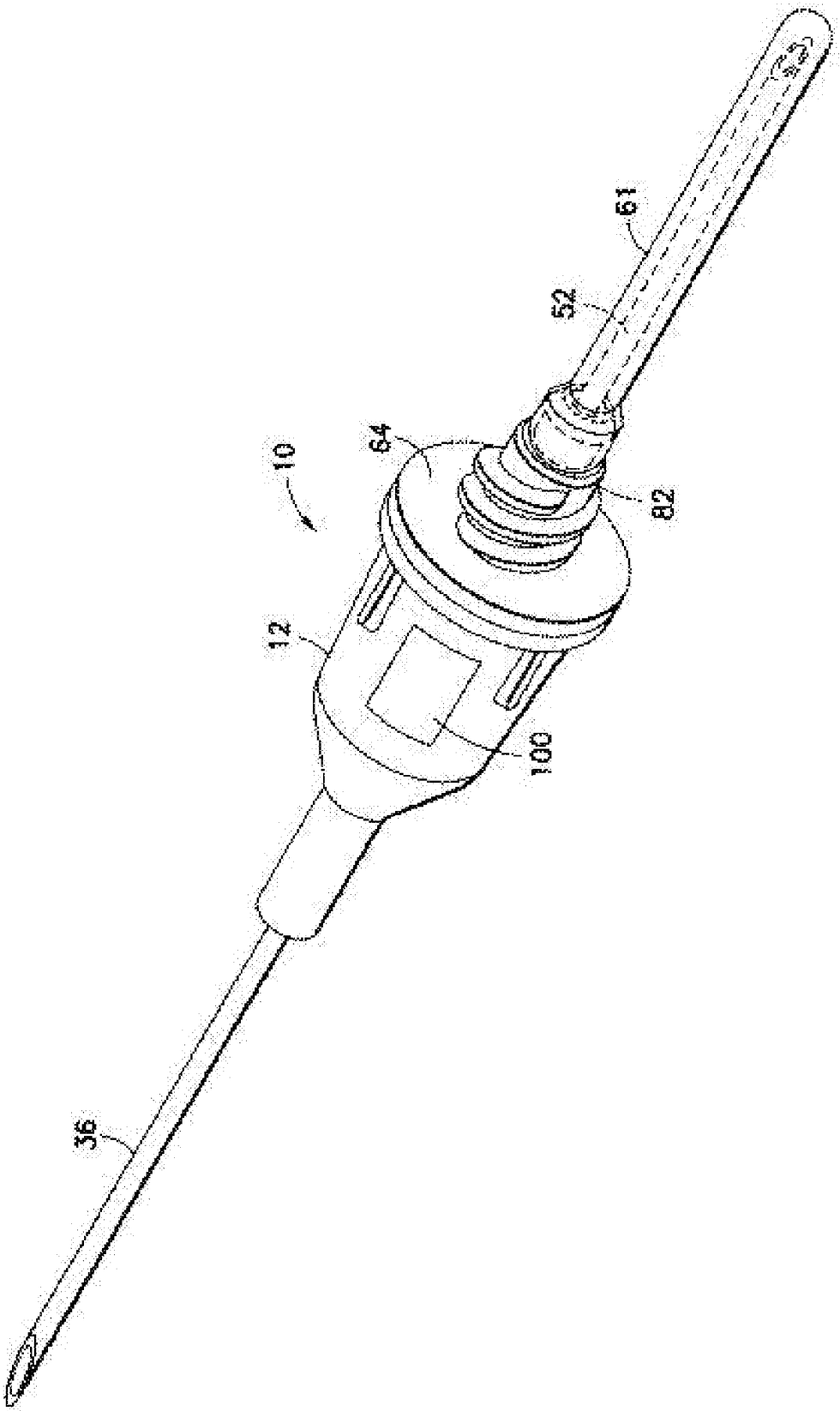
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wrap up close —

(57) [Summary] (Modified)
[Problem] To easily confirm that puncturing has been performed reliably when collecting bloo d, and to prevent outflow of fluid such as blood.
A self-venting blood collection needle assembly for extracting at least one fluid sample into a vacuum container for clinical testing, the blood collection needle assembly allowing a flow of b lood to allow a user to successfully perform a venipuncture. To provide a transparent or semi-transparent flashback chamber in which cracking can be visually confirmed. The self-venting mechanism is designed to allow the release of air and prevent the escape of fluids, such as bl ood, during use. Thus, air under venous pressure can be expelled from the blood collection ne edle assembly by the time the blood reaches the venting mechanism.
[Selection drawing] Fig. 1


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The scope of the claims

open —

1. A hub having an inlet end, an
outlet end and a chamber formed therebetween; an
inlet cannula, a distal end external to said hub; an inlet cannula extending through the cann ula and having a lumen attached to the hub in communication with the chamber; an outlet ca nnula having a proximal end outside the hub
; an exit cannula extending through and attached to the hub so as to communicate with the chamber; and multiple specimens mounted over
portions of the exit cannula outside the hub. a multiple sample sleeve, wherein the lumen of the inlet cannula, the chamber, the lumen of the outlet cannula, and an inner surface of the m ultiple sample sleeve form a fluid passage; the fluid passage and the external atmosphere
; a venting mechanism in communication with the needle assembly for permitting the outflo w of air from the needle assembly through the venting mechanism to an external atmosphere and substantially inhibiting the outflow of liquid from the needle assembly through the venting mechanism to the external atmosphere; and a venting mechanism,
wherein said inlet and outlet cannulas are separate or a single cannula having an opening co mmunicating with said chamber.
2.
The needle assembly as recited in claim 1, wherein said venting mechanism extends through said hub.
3.
The needle assembly as recited in claim 2, wherein said venting mechanism comprises a ven ting medium.
[Claim 4]
3. The needle assembly of claim 2, wherein said venting mechanism includes at least one op ening through said hub, said opening including a vent plug.
5. The
needle assembly as recited in claim 4, wherein said venting mechanism further comprises a check valve.
6.
The vent mechanism includes at least one opening through the hub and a vent ring surround ing the inlet cannula, the vent ring being positioned through the hub in the chamber proximat e to the opening. 2. The needle assembly of claim 1, wherein the needle assembly comprises:
7.
The needle assembly of claim 1, wherein said venting mechanism is disposed in said passag

e beyond the proximal end of said exit cannula.

8.

The needle assembly as recited in claim 7, wherein said venting mechanism comprises a ven ting medium.

9.

The needle assembly of claim 1, wherein said hub further comprises a non-patient locking pr ojection, said vent mechanism extending through said non-patient locking projection. .

10.

The needle assembly as recited in claim 9, wherein said venting mechanism comprises a ven ting medium.

11.

The needle assembly of claim 9, wherein said venting mechanism comprises a passageway t hrough said non-patient stop projection and a vent plug disposed in said passageway.

[Claim 12]

10. The needle assembly of claim 9, wherein said venting mechanism comprises a notch ext ending through said non-patient locking projection and a venting disc.

13. The method of claim

9, wherein said venting mechanism comprises at least one opening extending through said n on-patient side locking projection and a vent plug arranged in said opening. needle assembly.

14.

The needle assembly of claim 1, wherein said hub further comprises a non-patient locking pr ojection, at least a portion of said non-patient locking projection comprising said venting mec hanism. .

15. The

needle assembly as recited in claim 14, wherein said venting mechanism comprises a ventin g medium.

16.

At least part of said non-patient side locking projection is made of a porous hydrophobic mat erial, or at least part of said non-patient side locking projection is made of a porous material h aving a hydrophobic surface. 15. The needle assembly of claim 14, wherein the needle assem bly is made of material.

17.

A needle assembly as in claim 14, wherein said venting mechanism comprises a porous mat erial impregnated with a hydrophilic material.

18.

The hub further comprises a non-patient side locking projection to which the multiple sample sleeves are securely attached, and wherein the venting mechanism is disposed between the n on-patient side locking projection and the multiple sample sleeves. 2. The needle assembly of claim 1, wherein the needle assembly is .

19. The
needle assembly as recited in claim 18, wherein said venting mechanism comprises a ventin g sleeve.

[Claim 20]

20. The needle assembly of claim 19, wherein said vent sleeve comprises a porous hydropho bic material or said vent sleeve comprises a porous material with a hydrophobic surface.

21.
The needle assembly of claim 18, wherein said venting mechanism comprises a ventable ven t cord.

22.
The needle assembly of claim 18, wherein said venting mechanism comprises a textile surfac e.

23.
The needle assembly of claim 1, wherein said multiple sample sleeve includes said venting m echanism.

24. The
needle assembly as recited in claim 23, wherein said venting mechanism comprises a ventin g medium.

25. Said
multiple sample sleeve is formed of a porous hydrophobic material or said multiple sample sl eeve comprises a porous material having a hydrophobic surface. A needle assembly as describ ed in .

26.
The needle assembly of claim 1, wherein at least a portion of said hub is formed by a ventin g medium such that said hub constitutes said venting mechanism.

27.
At least a portion of said hub is made of a porous material such that said hub constitutes sai d ventilation mechanism.

2. The needle assembly of claim 1, wherein the needle assembly is formed by:

28.
The needle assembly of claim 1, wherein said hub further comprises a non-patient thread as sembly and a hub insert assembled together to form a reservoir.

29.
The venting mechanism includes a first passage through the non-patient thread assembly to the reservoir, a second passage from the reservoir to the outside atmosphere, and a vent loca ted in the reservoir. 29. The needle assembly of Claim 28, comprising:

30.
Further comprising a non-patient thread assembly, at least a portion of said non-patient thre ad assembly being defined by a vent medium such that said non-patient thread assembly con

stitutes said vent assembly. 2. The needle assembly of claim 1, wherein the needle assembly comprises:

31.

Further comprising a non-patient thread assembly, at least a portion of the non-patient thre ad assembly formed of a porous material such that the non-patient thread assembly constitut es the vent assembly. 2. The needle assembly of claim 1, wherein the needle assembly is .

32.

The needle assembly of claim 1, wherein said venting mechanism comprises a venting mediu m.

33.

The needle assembly of claim 1, further comprising a shield selectively covering said first ca nnula.

34.

a hub having an inlet end, an outlet end and a chamber formed therebetween;

a cannula having a distal end mounted to the hub so as to be external to the hub, a proxima l end and a lumen extending therebetween; and a proximal end of the cannula external to the hub

. Multiple sample sleeves mounted over a portion, wherein the lumen, the inner surface of th e multiple sample sleeve and the chamber form a fluid passageway, and the fluid passageway communicates with an external atmosphere

. a venting mechanism that allows air to escape from the needle assembly through the venti ng mechanism to the external atmosphere and substantially prevents fluid from exiting the ne edle assembly through the venting mechanism to the external atmosphere. A needle assembl y,

comprising: a venting mechanism.

35.

The needle assembly as recited in claim 34, wherein said venting mechanism is disposed in s aid passageway beyond said proximal end of said exit cannula.

36.

The needle assembly of claim 35, wherein said venting mechanism comprises a venting medi um.

37.

The needle assembly of claim 34, wherein the hub further comprises a non-patient locking p rojection, and wherein the vent mechanism extends through the non-patient locking projectio n. .

38. The

needle assembly as recited in claim 37, wherein said venting mechanism comprises a ventin g medium.

39. The needle assembly of claim 37,

wherein said venting mechanism comprises a passageway through said non-patient stop pro jection and a vent plug disposed in said passageway.

[Claim 40]

The vent mechanism includes a notch extending through the non-patient side locking project ion and a vent disc.

38. The needle assembly of claim 37, characterized by:

41. The needle of claim 37,

wherein said venting mechanism comprises at least one opening extending through said non -patient stop projection and a vent plug disposed in said opening. assembly.

42.

The needle assembly of claim 34, further comprising a non-patient locking projection, at leas t a portion of said non-patient locking projection comprising said venting mechanism.

43. The

needle assembly as recited in claim 42, wherein said venting mechanism comprises a ventin g medium.

44.

At least part of said non-patient side locking projection is formed of a porous hydrophobic m aterial, or at least part of said non-patient side locking projection is made of porous material having a hydrophobic surface. 43. The needle assembly according to Claim 42, comprising a material.

45. A

needle assembly as in claim 32, wherein said venting mechanism comprises a porous materi al impregnated with a hydrophilic material.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to a device for performing a vascular pun cture on a patient to obtain a blood sample. More particularly, the present invention is useful f or collecting multiple blood samples when collecting blood samples from a patient into a vacu um blood collection tube, where the self-venting feature allows the phlebotomist to know if th e vessel has been punctured. of the needle assembly. BACKGROUND OF THE INVENTION Vas cular puncture is the primary method used to obtain blood samples for clinical examination . P erforming a vascular puncture requires the phlebotomist to perform multiple steps simultaneo usly. This step includes evaluating the patient's overall physical and psychological condition to appropriately select the vascular puncture site and technique. The phlebotomist also needs to

select the proper instrumentation, perform techniques to control bleeding, and properly collec t and identify fluid samples for clinical examination. All of these concurrent factors must be id entified by the phlebotomist, as these factors adversely affect vessel dilatation and the length of the vascular puncture procedure. [0003] Various vascular puncture devices have been dev eloped to address the aforementioned problems. These devices include a needle assembly hav ing a hub defining a chamber therein with a single pointed cannula secured to the hub. The va scular end of the cannula is configured to be inserted into a patient's blood vessel and the non -patient end of the cannula has a sealable sleeve and pierces a pierceable stopper disposed wi thin the reduced pressure vessel. is configured as DISCLOSURE OF THE INVENTION [Problem to be Solved by the Invention]

When the vessel end of the cannula is inserted into the vessel, blood flows through the cann ula into the sealable sleeve and into the hub's chamber, which is transparent or translucent fo r visualization ("flashback"). When air is evacuated from the hub chamber, the blood therein is pressurized each time the sealable sleeve is pushed toward the hub chamber by the action of the vacuum reservoir. Due to the time lag between vessel insertion and flashback, the phleb otomist did not obtain a satisfactory vessel puncture because the transparent chamber did not immediately indicate that a vessel puncture had occurred

.

You may mistakenly believe that you were not. The phlebotomist then uses the vacuum cham ber and/or

Unnecessarily repeated vascular punctures requiring replacement of the needle assembly itsel f. Repetition of such procedures prolongs the physical and emotional discomfort experienced b y the patient.

[0006]

If no flashback occurs, the air in the injection cannula and flashback chamber is compressed there, so that the air in the needle hub is pressurized to venous pressure. This pressurized air needs to be expelled somewhere, so when the needle is withdrawn from the patient after the blood draw is complete, this pressurized air pushes the blood towards the tip of the needle. p ush out to

[0007]

Accordingly, to provide a rapid, accurate and cost-effective solution to conventional blood sa mpling methods in which phlebotomists consistently rely on flashback to achieve satisfactory venous punctures. is desired. In addition, a blood collection needle assembly is provided that allows blood to flow directly into the flashback chamber through a relatively short needle and to expel pressurized air from the interior of the needle assembly, thereby providing a vein. It would be particularly desirable to have a direct indication of successful puncture of the assem bly and no leakage of blood from the assembly. As used herein, ventilation media refers to ele ments that actually allow air to pass, such as plugs, coatings, surface treatments, and the lik e. Means

for Solving the Problems

SUMMARY OF THE INVENTION The present invention is a self-venting blood collection needle assembly for extracting at least one fluid sample into a vacuum vessel for clinical testing, the blood collection needle assembly providing visual confirmation of a successful venipuncture by the user. Provide a transparent or translucent flashback chamber for viewing by This self-venti ng mechanism allows the release of air during use, but prevents the escape of liquids such as blood. Venting mechanism, as used herein, refers to one or more devices or elements that all ow air to escape but prevent the passage of liquids. Thus, air under venous pressure can be e xpelled from the blood collection needle assembly by the time it reaches the venting mechanis m. The venting mechanism then blocks or prevents the flow of blood around or through it, all owing blood to be collected into a vacuum collection tube or other suitable blood collection co ntainer. The present invention provides good instant visualization within the flashback chambe r without adversely affecting the blood collection process. There are a variety of suitable vent mechanisms, vent media or vent locations, as described below.

[0009]

A self-venting blood collection needle assembly is provided for drawing at least one fluid sam ple from a patient and subsequently expelling it into at least one vacuum vessel. The self vent ed blood collection needle assembly of the present invention includes a hub having a fluid inle t defined by a cylindrical outer wall. The wall defines a flashback chamber for retaining the blo od sample within the hub and at least a portion of the wall being transparent or translucent so that the jet is visible from the outside. The hub further has a fluid outlet end communicating with the fluid inlet end. A first inlet cannula in fluid communication with the blood inlet end ex tends outwardly therefrom. The first cannula has an inner proximal end located at the proxim al end of the chamber and an opposite outer distal end adapted to puncture a patient's vein. Similarly, a second non-patient exit cannula is disposed in fluid communication with the fluid e xit end and extends outwardly therefrom. The second non-patient cannula has an inner distal end positioned proximal to the first inner end and further includes an outer proximal end oppo site the second inner end. The second non-patient outer proximal end is configured to pass th

rough a pierceable stopper of a vacuum vessel. The second patient cannula further includes a sealable multiple sample sleeve. However, a single cannula containing a notch could be used i nstead of two cannulas. Another alternative cannula configuration is to use a single cannula wi thout a notch to pass through the proximal end of the non-patient cannula, around multiple s ample sleeves and through a vent before flashback occurs. there is The outer portion of the h ub near the proximal end is formed with a single external thread, or other mounting structur e, for receiving blood.

A collection needle assembly can be attached to a collection tube holder or other medical devi ce. Alternatively, the holder can be pre-attached to the needle assembly.

[0010]

In one embodiment, the venting mechanism is located in the flashback chamber of the hub. The use of the double cannula type construction or the notched single cannula is suitable for t his configuration. The vent mechanism thereby communicates the fluid passageway with the o utside atmosphere via the hub.

In another embodiment, a venting mechanism is placed over the proximal end of the non-pati ent cannula which

allows air to pass through the proximal end of the non-patient cannula from which blood is a spirated and then through the vent. means to pass. A single cannula without a notch is suitabl e in this case, but any cannula construction can be used. Specifically, air flows through the sp ace between the outside of the needle and the multiple sample sleeve and exits the fluid pass ageway out the proximal end of the non-patient cannula. The air is then directed to the non-p atient locking lug, non-patient hub threads, non-patient hub body, multiple specimen sleeves, or other location beyond the proximal end of the non-patient cannula. or through vents in any combination of these locations. A collection tube attached to the proximal end of the non-pati ent cannula draws blood only from the fluid passageway and not from the vented space. This embodiment thus allows blood to flow through the entire collection passageway. This also pre vents contact of the blood sample with the vent, which could potentially lead to platelet activa tion or contamination or other undesirable consequences. This also prevents air from being dr awn back into the fluid passageway when a vacuum tube is installed. It should also be noted t hat this embodiment requires a smaller ejection chamber than the previous embodiment in w hich the vent is located in the hub.

[0012]

Another embodiment of the invention has a venting mechanism comprising an integral hub a t least partially formed of a porous material such as sintered plastic, ceramic or metal. This po rous material either before air enters the non-patient cannula or after air exits the proximal e nd and flows through the non-patient cannula into the space between the cannula and the mu ltiple sample sleeve. can be arranged so that the evacuation takes place at the same time. Th e porous material allows air to pass through but prevents blood from leaking. In typical embo diments, this porous material is hydrophobic. Porous materials further include materials that s

well when wet. Other venting methods are possible. The walls of the internal passageway may be coated with a sealant to prevent contamination of the blood sample with porous material. This embodiment allows blood to flow over the entire collection path. If desired, the hub can b e permanently joined to the tube holder to eliminate the need and inconvenience of a threade d connection. Bonding to this holder can be accomplished by solvent, welding, heat, pressure or other suitable means, or a combination thereof. A device integrated in this way can be man ufactured efficiently, and the holder can be discarded together with the needle, thereby increa sing the safety of medical procedures.

[0013]

In yet another embodiment, the vent mechanism vents air out through a side opening locate d in the hub, the opening being shaped to be mechanically retained in or against the opening. covered by a breathable material having This venting material is preferably hydrophobic and t he surface tension is also such that it prevents leakage. The vent media material of this embo diment preferably has a resilient nature and shape so that the energy of the spring holds the vent material against the device. For example, a C-shaped vent medium can be used where t wisting of the shape requires the vent medium to extend over the receiving structure on the h ub. When the vent media is placed on the support structure, it releases and uses its own elast icity to hold it in place without any bonding material such as epoxy that could be absorbed by the vent media and adversely affect it. be done. The venting mechanism of this embodiment may first compress the venting material, place the material in the opening, and then release t he venting material to expand within the opening. BEST

MODE FOR CARRYING OUT THE INVENTION

SUMMARY OF THE INVENTION The present invention is a self-venting blood collection needle assembly with a self-venting mechanism that prevents the escape of fluids such as blood and aids in the release of air, which draws blood or other fluids from a patient through one or mor e vacuum tubes. An assembly is provided that provides a visual indication of vascular insertio n ("flashback") as it is drawn into a blood collection tube. The aeration medium may be a se parate physical element, such as a plug or insert, or an integral part of the device, treated, su ch as by laser drilling, or made wholly or partially of a porous material, or impregnated, for ex ample

.

Note that it may be a film, layer, etc., formed by depositing the material on the device by, coa ting, spraying, or the like.

A blood collection needle assembly according to

one embodiment of the present invention is shown in FIG. The needle assembly 10 includes a hub 12 that carries a fluid entry needle (first cannula) 36 on one side and a fluid exit needle (second cannula) 52 on the opposite side. Fluid withdrawn from the first cannula passes throu gh the hub 12 and is immediately visible in the flashback chamber through the translucent wi

ndow 100, and with the aid of the venting mechanism, at the appropriate time that a proper v essel puncture has occurred. give proper instructions.

[0017]

Figures 2-28 illustrate various embodiments of the present invention including various config urations of venting mechanisms in blood collection needle assemblies. In particular, Figures 2, 3, 4A, 4B and 4C show embodiments in which the venting mechanism is located on the hub p ortion. Figures 5-12 show embodiments in which the venting mechanism is located beyond th e proximal end 60 of the non-patient cannula. Figures 13 and 14 show an embodiment in whic h a portion of the hub of the needle acts as the vent medium. FIG. 15 shows an embodiment i n which the venting mechanism is a unified hub 132 . Figures 16-26 show embodiments in wh ich the ventilation mechanism is a breathable cord. Figures 27A and 27B show an embodimen t in which the vent mechanism is a check valve. Figure 28 shows an embodiment with a single notched cannula. Note that in each of the two cannula embodiments below, a single notched c annula can be used as well.

FIGS.

2, 3, 4A, 4B and 4C illustrate a venting mechanism in which a venting ring 300 is placed aro und the proximal end 301 of first cannula 36. FIG. This vent ring forms an interference fit with the inner wall of flashback chamber 302 . Therefore, air can escape from the ventilation openi ngs 303 to the outside atmosphere through this ventilation ring. These openings can be locate d anywhere on the distal end of the hub. 2 and 3, these openings are located at the distal end of hub 304. FIG. 4A, 4B and 4C show another embodiment in which the vent openings are lon gitudinal vent windows 305 that abut the distal side of the vent ring 300. FIG.

[0019]

Some embodiments include a venting mechanism located beyond the proximal end 60 of the non-patient cannula. This venting mechanism uses a smaller flashback chamber 22a and redu ces the amount of air exhausted from the hub assembly 12 compared to the previous embodi ments such as FIGS. 2, 3, 4A, 4B, 4C. It is advantageous for The next embodiment uses a lar ger annular flange 68a to create a smaller flashback chamber 22a, although other designs are possible. Examples of these designs are a window of translucent/transparent material near th e surface of the hub and/or part of the flashback chamber for better visibility of the flash. Not e that a flashback chamber or window can be placed in the air/blood passageway, especially f or embodiments using a single cannula without a notch. In the embodiment of FIG. 5, air flo ws from the fluid passageway 306 to the proximal end 60 of the non-patient cannula and thro ugh the space 307 between the outside 308 of the needle and the inside of the multiple sampl e sleeve 61 to the non-patient cannula

.

It reaches the position of a vent hole 309 consisting of a locking projection 310 on the patient side and a vent plug 311 that allows air to escape but prevents blood or other fluids from esca ping to the outside atmosphere.

6, 7, 8A, 8B, 9A, 9B, 10A and 10B illustrate embodiments in which the venting mechanism is located beyond the proximal end 60 of the non-patient cannula . is shown. The embodiment o f Figures 6 and 7 shows a vent plug 312 that also functions as at least part of the non-patient side locking projection. As shown in these figures, in both embodiments, at least a portion of t he vent is close to the exterior through which air is exhausted. 8A and 8B show an embodime nt in which the notch 313 in the non-patient locking projection 314 is configured to allow air t o escape to the vent disc 315. FIG. 9A and 9B show another embodiment in which the notch 3 16 in the non-patient locking projection 314 contains a vent plug 317. FIG. 10A and 10B show a non-patient locking projection 318 configuration in which the ventilation sleeve 319 is modifi ed to allow air to escape. In each embodiment, the venting mechanism (and similar elements described herein) allows air to escape, but prevents blood or other fluids from escaping to the outside atmosphere.

FIG.

11 shows another embodiment of a venting mechanism located beyond the proximal end 60 of the non-patient cannula. According to this embodiment, air is vented through the material of the multiple sample sleeve 320 itself which prevents fluid from exiting the non-patient cann ula 52 . The multiple sample sleeve 320 maintains its normal function of being pierced by the sharpened proximal end 60 of the non-patient cannula 52 in response to the force created by the vacuum tube stopper. A multiple sample sleeve 320 can be made that also functions as a vent by forming the sleeve from a porous, hydrophobic material such as those previously desc ribed.

[0023]

12 shows that air passes through narrow passage 353 between the outside of non-patient ne edle 52 and non-patient locking projection 354 and then between base 64 and annular flange 68 to contain vent medium 357. Another embodiment is shown in which it enters the reservoi r 355 of the hub 356 and is discharged to the outside atmosphere via a passageway 358 at th e interface 80 between the hub 356 and the base 64 of the non-patient hub. A hub insert 359 forms a reservoir 355 .

FIGS.

13 and 14 illustrate a venting mechanism in which hub 321 or non-patient threaded assembl y 322 is made of a porous material and thus acts as a venting medium. FIG. 13 shows hub 32 1 as a venting medium for venting air through ramp 28 of hub 321 and out of annular groove 26 into the surrounding atmosphere. FIG. 14 shows a non-patient threaded assembly 322 as a venting medium. This embodiment allows air to pass through the wall of the flashback cham ber 22a and then out through the non-patient side locking projection 324 .

FIG .

15 is made of a porous material venting medium that allows air to escape through the wall o f the annular groove 26 and the flashback chamber 22a and through the fluid passageway 30

6 and out the proximal end 60 of the non-patient cannula. The venting mechanism is shown t o be an integral one-piece hub 325 with the air further passing through the space 307 betwee n the outside of the needle 308 and the inside of the multiple specimen sleeve 61 and then th rough the non-patient locking projections 326 . through and into the surrounding atmosphere. Due to the integral nature of the hub 325, this holder is not threaded and can be pre-attached to the hub 325 by bonding. However, threads may be provided if desired, as shown. Solvents, welding, heat, pressure, other conventional means or combinations thereof are used to bond t he tube holder to the integral non-patient hub 325 .

FIG.

16 illustrates the venting mechanism of a breathable ventable cord 326 located between the inside of the sealing surface of multiple sample sleeve 61 and the non-patient locking projecti on 327 . Due to the cord being placed on the sealing surface, air is evacuated from the space 307 between the outside of the needle 308 and the outside of the multiple sample sleeve 61, but only through the nature of the material of the cord and/or the passageway formed by the cord. The very small dimensions of the prevent fluid leakage

. Venting using this mechanism is accomplished by positioning a venting medium (eg, placem ent, coating, treatment, etc.) between any one or more of the sealing surfaces along the fluid path 306 . Figures 17-26 show cross-sections of cords with suitable breathability. Other shape s and combinations of these shapes are also available. The cord is made by extruding, spinnin g or the like and is advantageously coated with a hydrophobic coating such as wax.

[0027]

In other embodiments, the venting mechanism uses a check valve located anywhere along t he fluid passageway. This valve allows air to pass through but closes when a vacuum is applie d, so when a vacuum collection tube is attached to the tip of the needle, this tube will draw bl ood from the fluid passageway, but not air. Figures 27A and 27B show an example of a check valve. The venting mechanism may be located at any point or points along fluid passageway 3 06 , but is preferably located at hub 328 . The valve 349 itself may be a thin flap such as a pl astic film 350 covering the vent, a seal such as a deformable rubber, or a plastic duckbill type valve, a deformable wrap over the vent, or any other means. or a combination thereof. This v alve 349 is located either proximally or distally to the vent. In the embodiment shown in FIG. 27B, a thin plastic film valve 349 is attached to hub 328 along one sealed edge of film 351 an d is pulled out of fluid passageway 306 by venous pressure during an initial venipuncture. Air i s pushed through the porous vent plug 352 and out under the free edge of the plastic film 34 9 . However, when a vacuum is applied to the fluid passageway 306 (via the blood collection t ube attachment), the thin plastic film 349 sucks tightly against the porous vent plug 352, seal ing the vent to keep air out. Prevents re-entry into the fluid passageway. Thus, this embodime nt serves the primary or backup function of preventing air from re-entering the system after e vacuation has taken place.

[0028]

FIG. 28 shows a blood collection needle assembly with a single cannula 360 and a vent plug 361 that serves as a non-patient locking projection. This cannula 360 is positioned in bore 34 such that bore 365 of cannula 360 is provided at the location of annular groove 26 and remai ns in fluid communication therewith. When cannula 360 is properly positioned, it frictionally e ngages hole 34 or is secured thereto, such as by adhesive. During venipuncture, air flows fro m fluid passageway 306, exits proximal end 362 of cannula, and flows into space 307 betwee n the outside of needle 363 and the inside of multiple sample sleeve 61 to vent plug 361. .
As will be appreciated by those skilled in the art, it

is possible to combine more than one vent mechanism in one device, and to attach the same vent mechanism to one location in one device. Additionally, any of a variety of venting media may be used in the venting mechanism of the present invention. Moreover, the venting mecha nisms described herein are applicable to various devices other than blood collection needle as semblies. Venting media, as used herein, include, for example : a generally hydrophobic sub strate or carrier coated, impregnated, or containing a hydrophilic material that swells on conta ct with water-soluble or water-containing substances
; A porous plug formed of a material whose swellable properties provide a sealing function to the vent when in contact with blood; Matte finish, micro-sized passages, laser drilled holes, to rtuous passages ; vent holes provided by a porous material or holes, gaps or passages large e nough to allow air to pass but small enough to prevent blood leakage, e.g. provided between sealing surfaces in the cord;

A porous plug that closes when in contact with blood, using biological phenomena such as coa gulation and/or cell agglutination to block the vent, or a super plug that seals the vent by swe lling on contact with aqueous fluids
. Absorbent material; or
Check valves: thin flaps such as plastic films covering vents, deformable seals such as rubber or duckbill type valves, or deformable wraps covering vents.
or combinations thereof. Preferably, the porous plug is coated with, impregnated with, or con taining a hydrophilic material such as carboxymethylcellulose (CMC) or polyacrylate, or a hydr ophobic material such as high density polyethylene (HDPE)
.
formed by Alternative hydrophobic materials include, but are not limited to, polytetrafluoroeth ylene (PTFE), ultra high molecular weight polyethylene (UHMPE), nylon 6, polypropylene (PP), polyvinylidene fluoride, or polyethersulfone. (PES). As will be described in further detail belo w, the venting media of the present invention are suitable for venting mechanisms and device s, including one or more micro-dimensioned matte-finished passages, laser-drilled holes, vent able Cords, superabsorbent check valves, or other means, or any combination thereof, may al

ternatively be used. Thus, although any particular venting medium, such as, for example, a pl ug, is referred to herein, it is intended to be non-limiting and to include other suitable membe rs of venting media.

[0032]

One embodiment of the venting media consists of micro-sized holes formed in the outer wal l. These holes are large enough to allow air to pass, but small enough to prevent blood leakag e. The vent can be any number, including one, but multiple holes are preferred for reliable fun ction. These holes are laser drilled, ie they are burned through the wall using one or more las er beams. The substrate can be any common material, but a thin plastic film is preferred. The venting mechanism can include a check valve as previously described. This venting mechanis m may be located at any convenient space along the fluid passageway within the syringe or p atient cannula, hub, or additional component, but to produce a flush along the entire length of the tube, , is preferably provided at the proximal end.

[0033]

Porous plugs that are sealed by biological phenomena when in contact with blood use porous materials such as sintered plastics, ceramics, or metals, or use breathable cords, or have sma ll pores between parts. or by placing a biological agent in the space. The vent may be of any c onventional shape. Venting may occur at any location(s) in the fluid passageway, but preferab ly at the proximal end, such as the hub, close to the collection device. The vent is made of an d includes a stimulant that interacts with blood to promote clotting and/or cell clumping such t hat clotted and/or congealed cells inhibit flow through the vent. , preferably adjacent to or co operating with. Examples of clotting stimulants are silica, crushed glass, or glass fibers. One e xample of a glue is a lectin. Examples of platelet activators are collagen or thrombin. Neutraliz ing agents for anticoagulants such as protomin sulfate may be included. The biological stimula nt can be applied as a powder, solution, suspension, slurry, or other form using any convenien t process. It may be dried or vacuum freeze dried. Various other changes and modifications can be made by those skilled in the art without departing from the scope or spirit of this inven tion, all of which are intended to be within the scope of the invention

.

is intended as

BRIEF DESCRIPTION OF THE DRAWINGS

[0035]

FIG. 1 is a perspective view of a blood collection needle assembly;

2 is a cross-sectional view of another embodiment of the blood collection needle assembly of t he present invention; FIG.

3 is a side sectional view similar to FIG. 2, but showing another embodiment of the invention; FIG.

4A is a side cross-sectional view similar to FIG. 2, but showing another embodiment of the pr esent invention; FIG.

4B is a side view of FIG. 4B; FIG.

4C is a front view of FIG. 4BA looking in the direction of RR; FIG.

5 is a cross-sectional view of one embodiment of a blood collection needle assembly; FIG.

FIG. 6 is a cross-sectional view similar to FIG. 5, but showing another embodiment of the inve ntion;

FIG. 7 is a cross-sectional view similar to FIG. 5, but showing another embodiment of the inve ntion;

8A is a cross-sectional view similar to FIG. 5, but showing another embodiment of the inventi on; FIG.

8B is a front view of FIG. 8A looking in the direction XX; FIG.

9A is a cross-sectional view similar to FIG. 5, but showing another embodiment of the inventi on; FIG.

9B is a front view of FIG. 9A looking in the direction YY; FIG.

10A is a cross-sectional view similar to FIG. 5, but showing another embodiment of the invent ion; FIG.

10B is an enlarged view of FIG. 10A viewed from area Z; FIG.

FIG. 11 is a cross-sectional view of one embodiment of a blood collection needle assembly;

FIG. 12 is a cross-sectional view of one embodiment of a blood collection needle assembly;

FIG. 13 is a cross-sectional view of one embodiment of a blood collection needle assembly;

FIG. 14 is a cross-sectional view of one embodiment of a blood collection needle assembly;

15 is a cross-sectional view of one embodiment of a blood collection needle assembly; FIG.

FIG. 16 is a cross-sectional view of one embodiment of a blood collection needle assembly;

FIG. 17 is a cross-sectional view of one embodiment of a ventable cord;

FIG. 18 is a cross-sectional view similar to FIG. 17 but showing another embodiment of the in vention;

Figure 19 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

Figure 20 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

Figure 21 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

Figure 22 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

Figure 23 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

FIG. 24 is a cross-sectional view similar to FIG. 17 but showing another embodiment of the in vention;

Figure 25 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

Figure 26 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

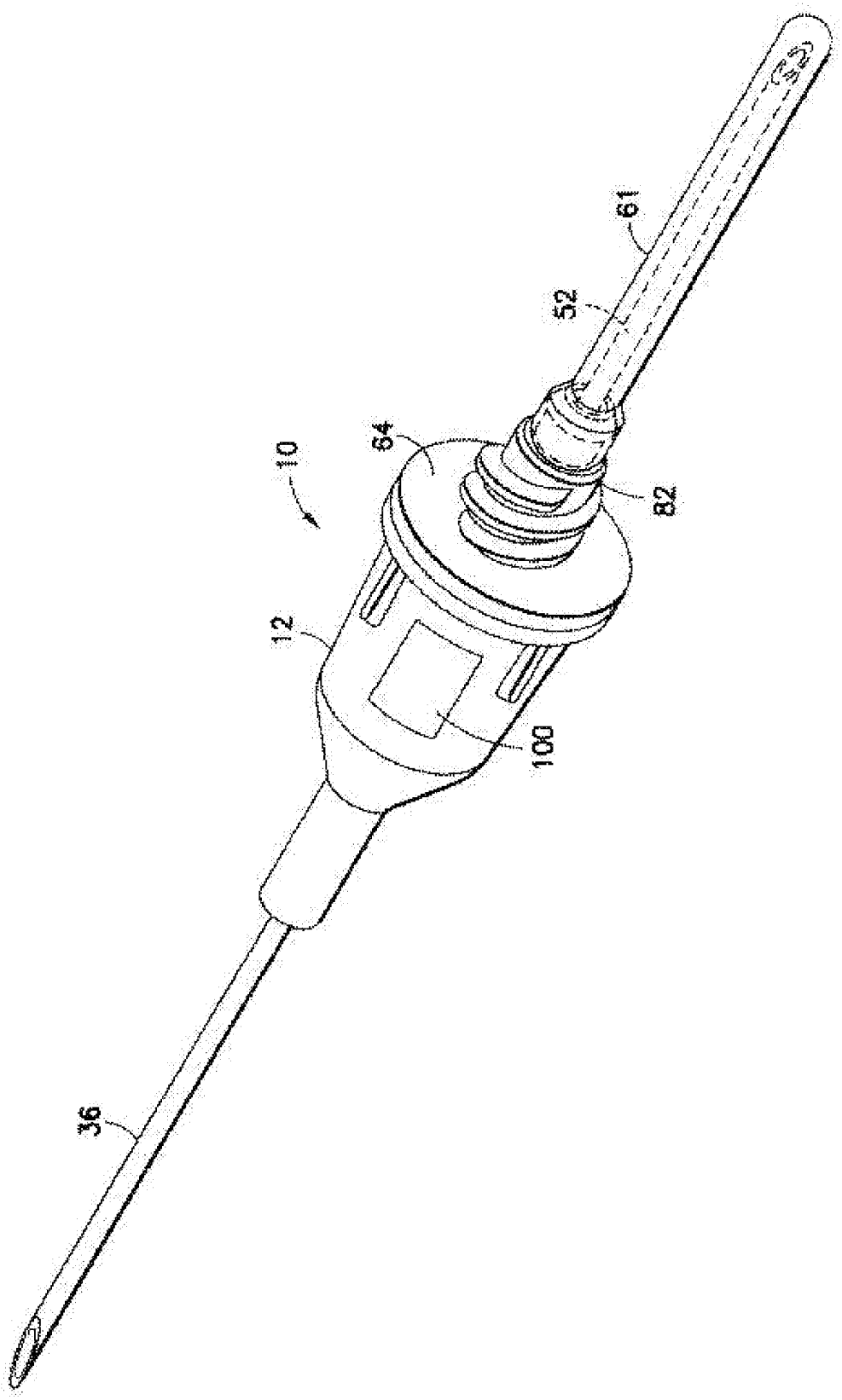
Figure 27A is a cross-sectional view of one embodiment of a blood collection needle assembly;

27B is an enlarged view of FIG. 27A viewed from region R; FIG.

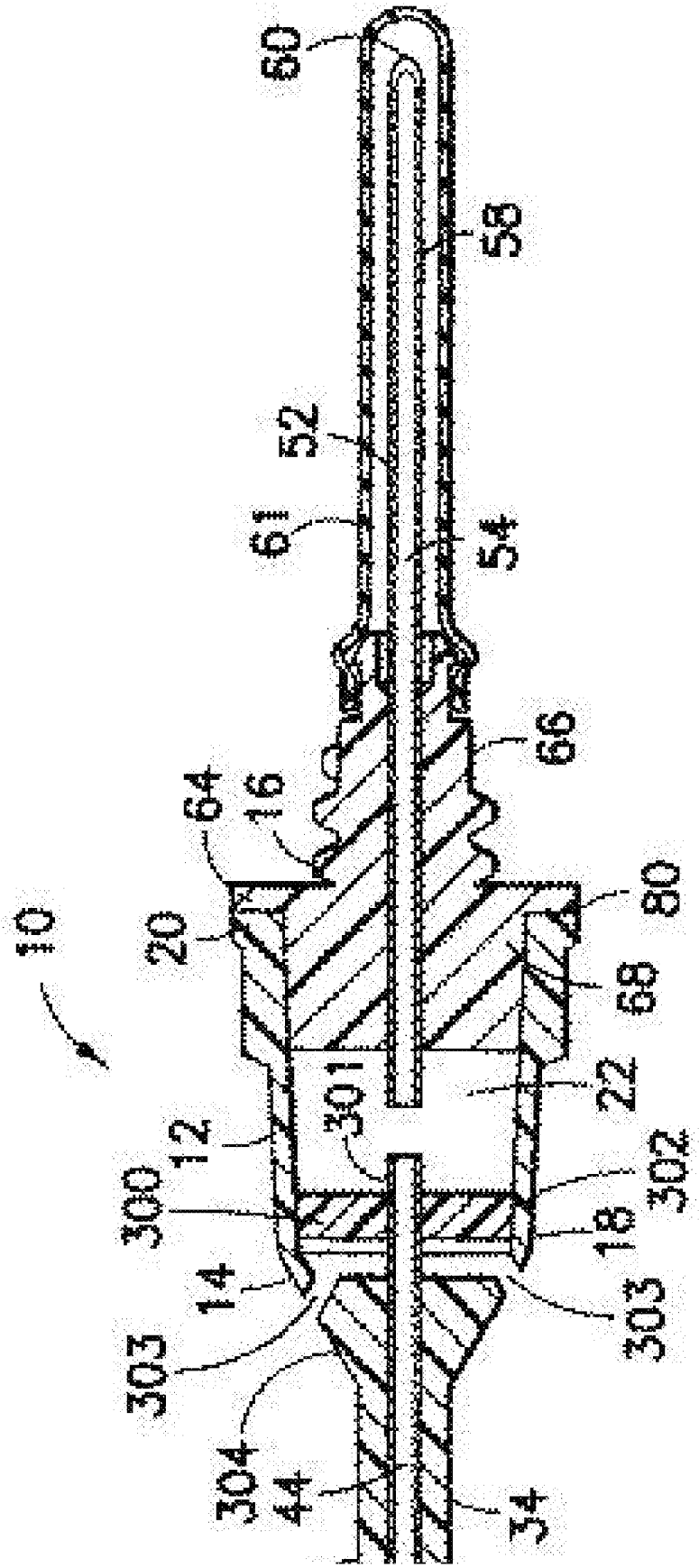
Figure 28 is a cross-sectional view of one embodiment of a blood collection needle assembly;

drawing	open ----

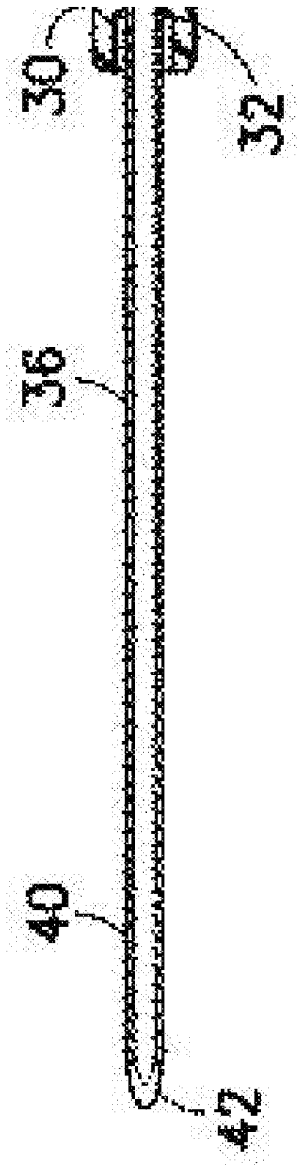
[Fig. 1]

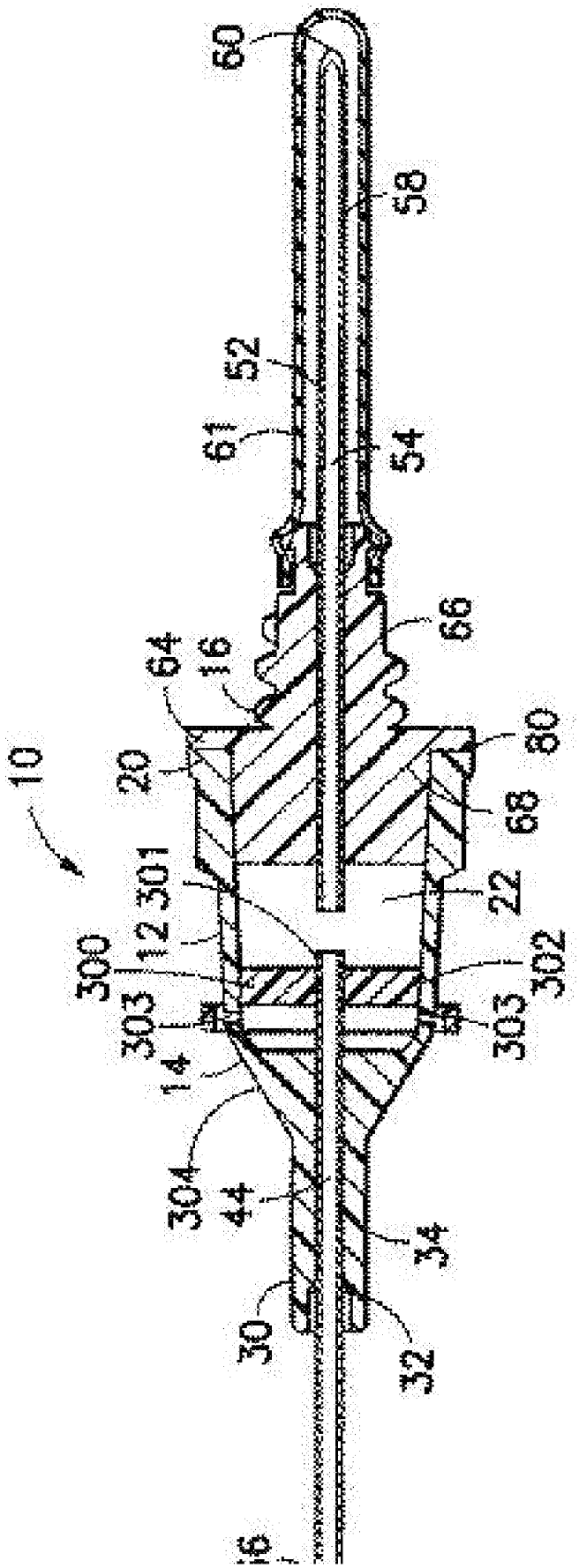


[Figure 2]

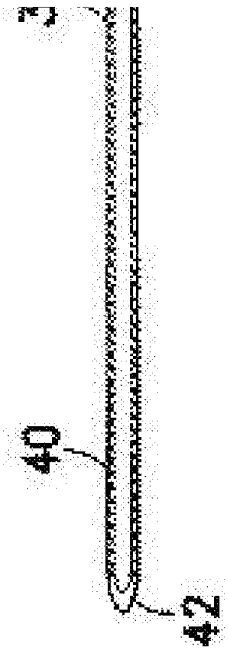

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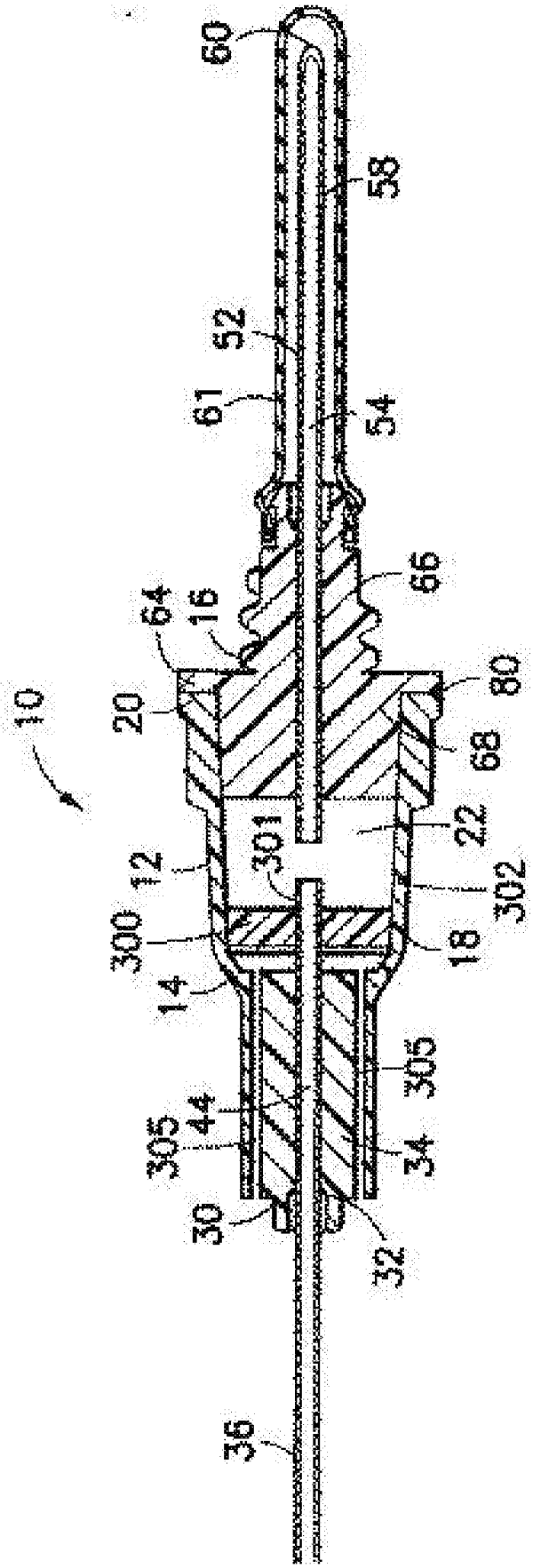
[Figure 3]



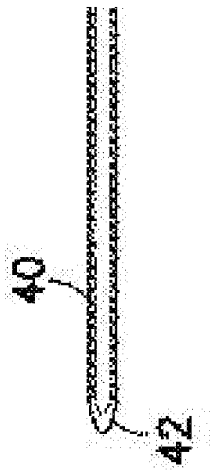

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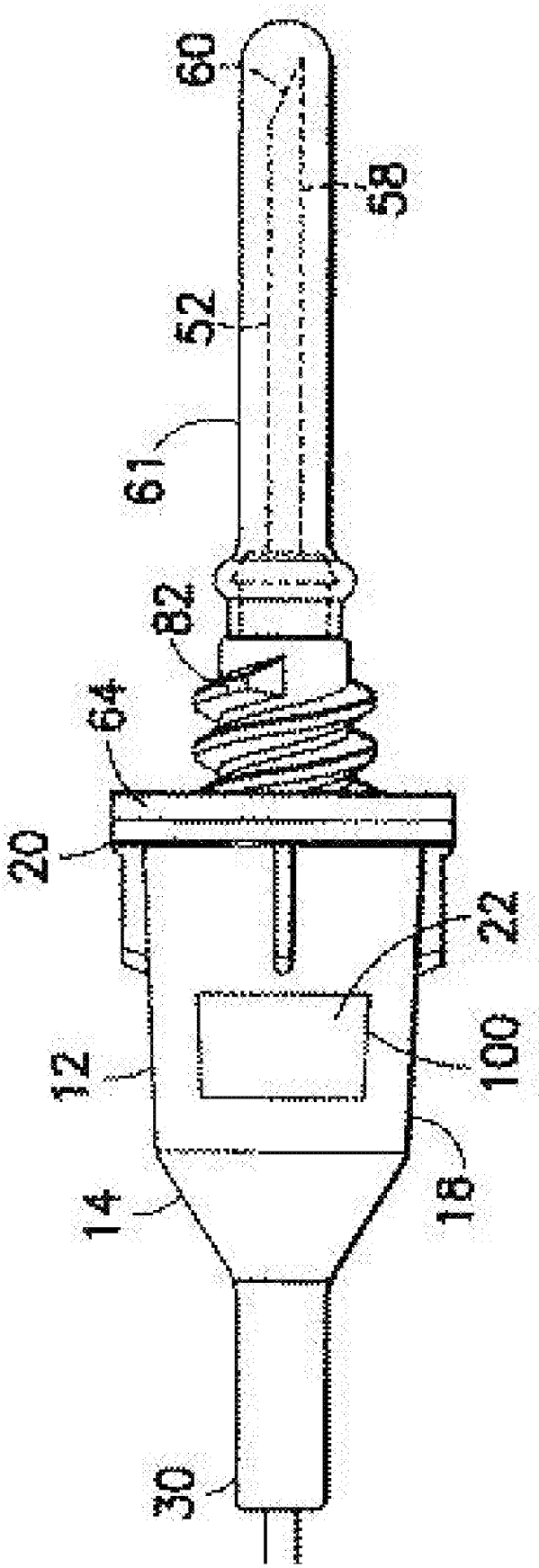
[Fig. 4A]



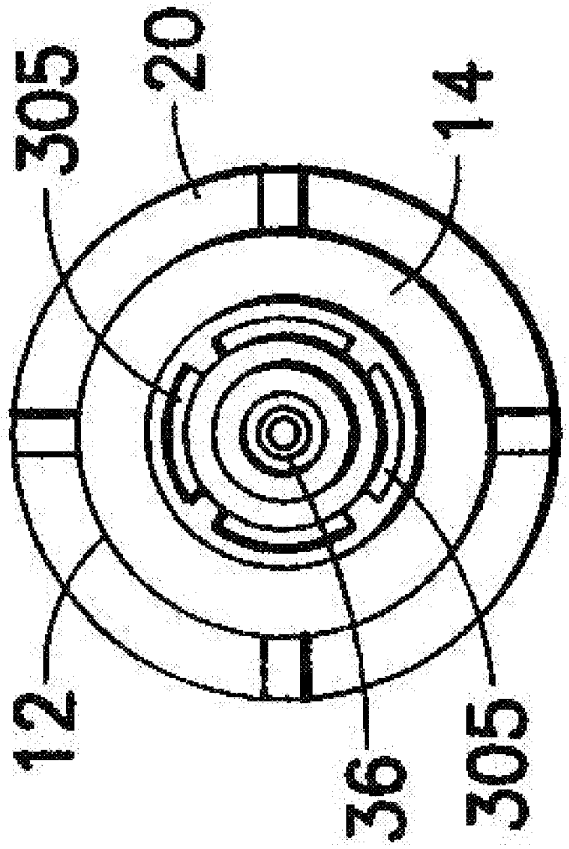

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[Fig. 4B]

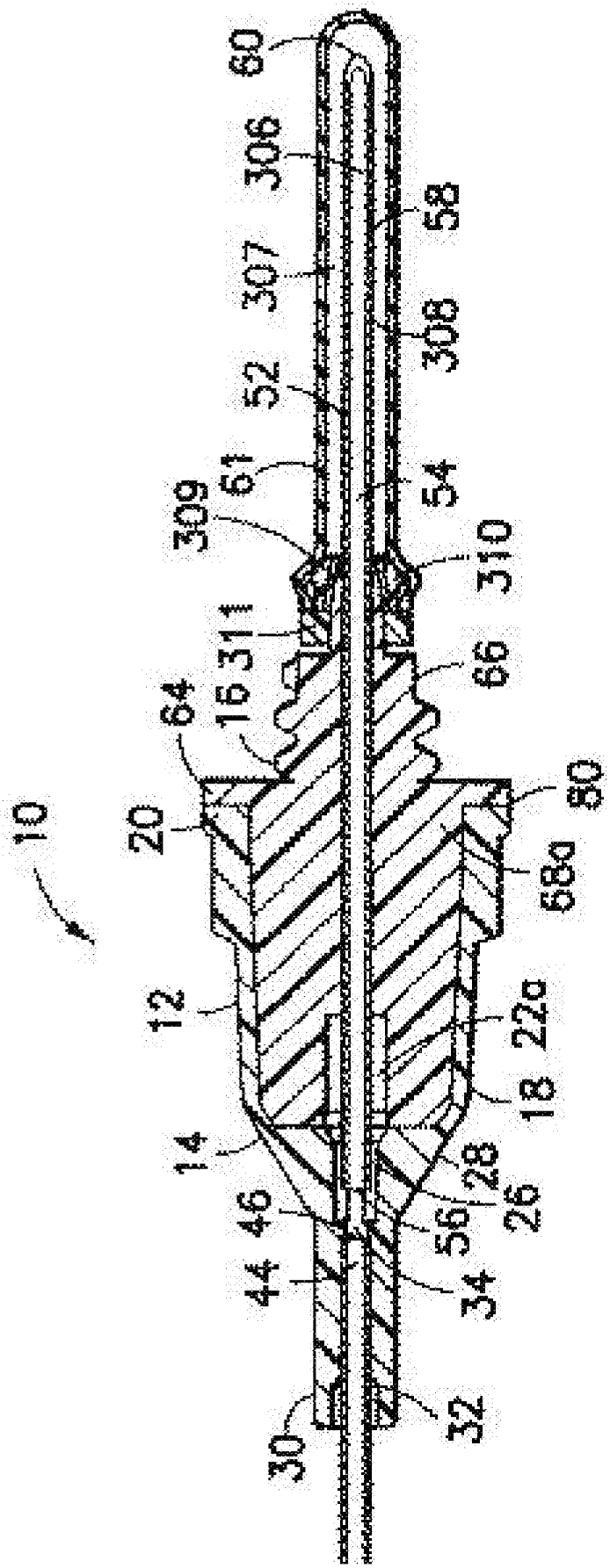



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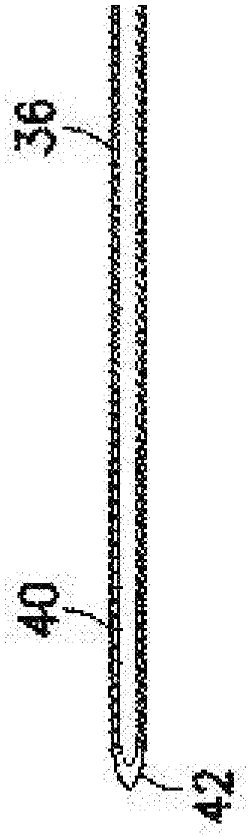
[Fig. 4C]

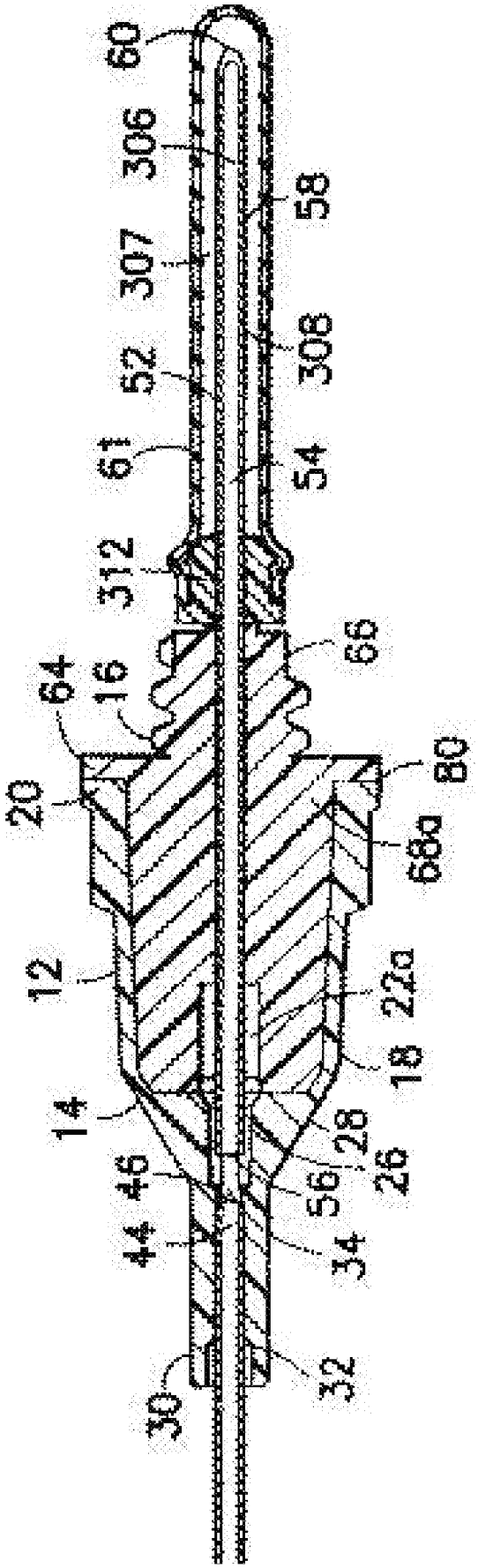


[Figure 5]

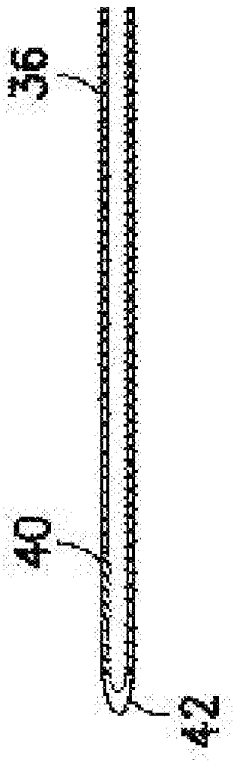

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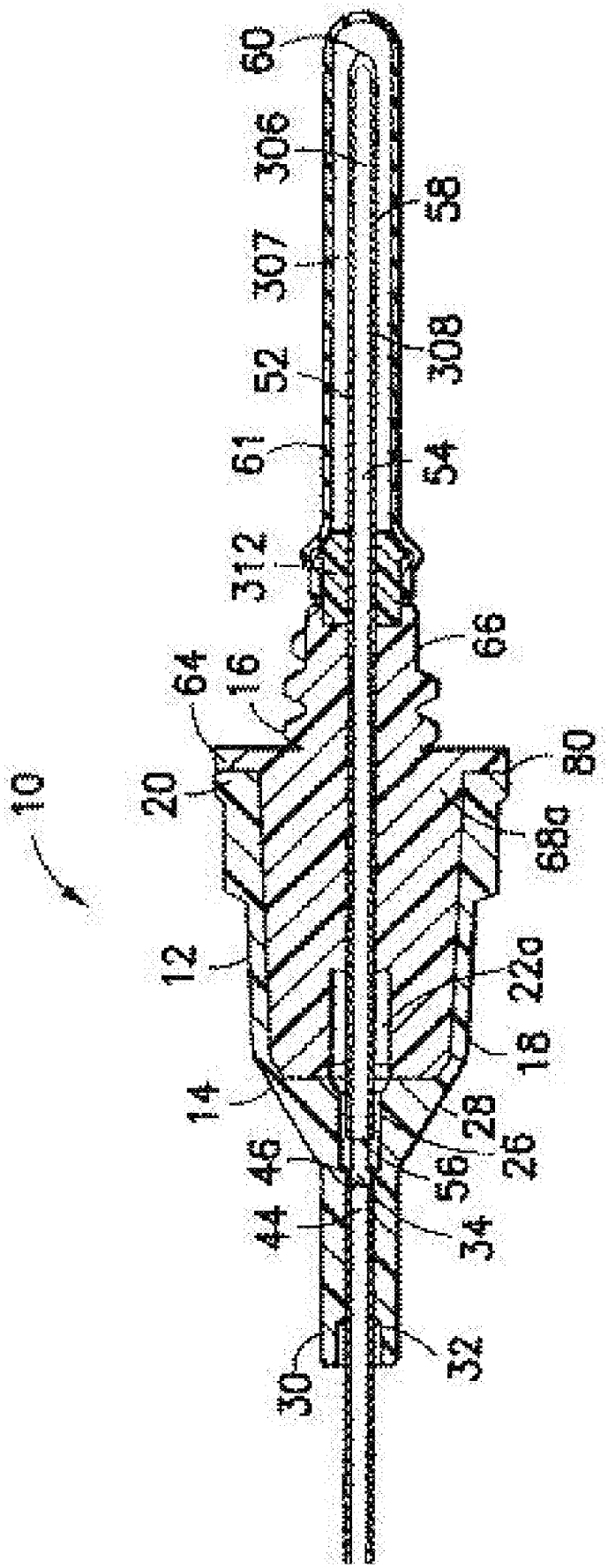
[Fig. 6]



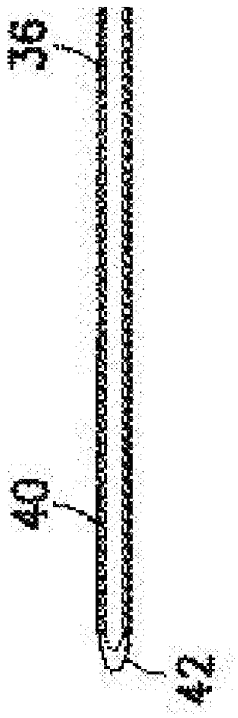

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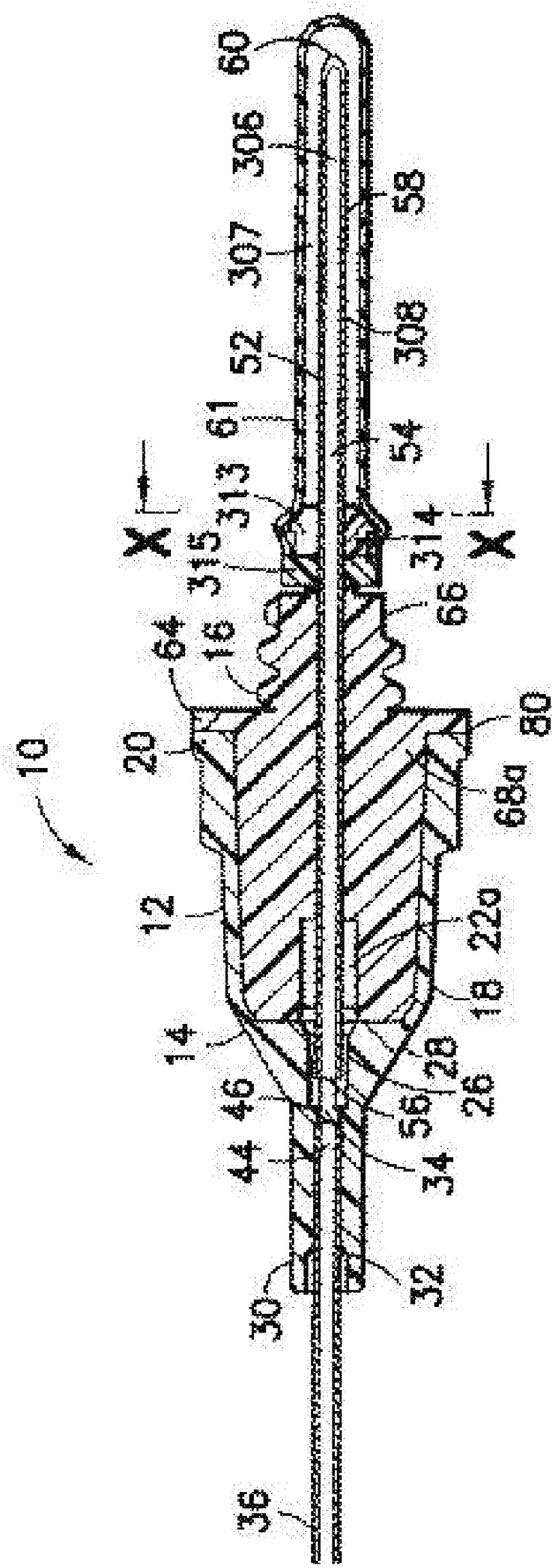
[Fig. 7]



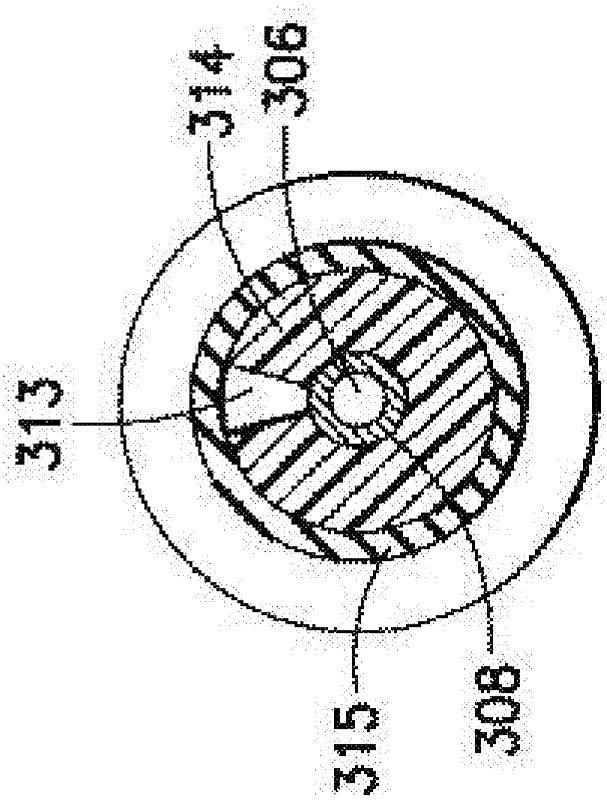

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[Fig. 8A]

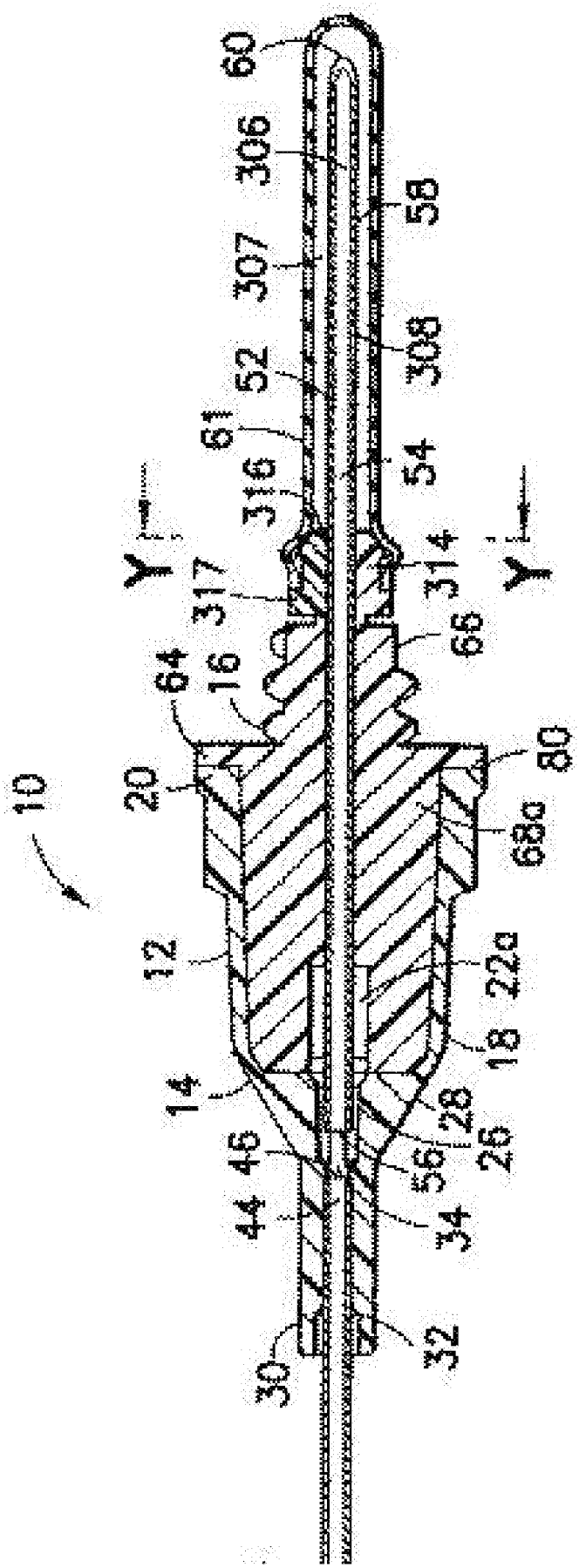



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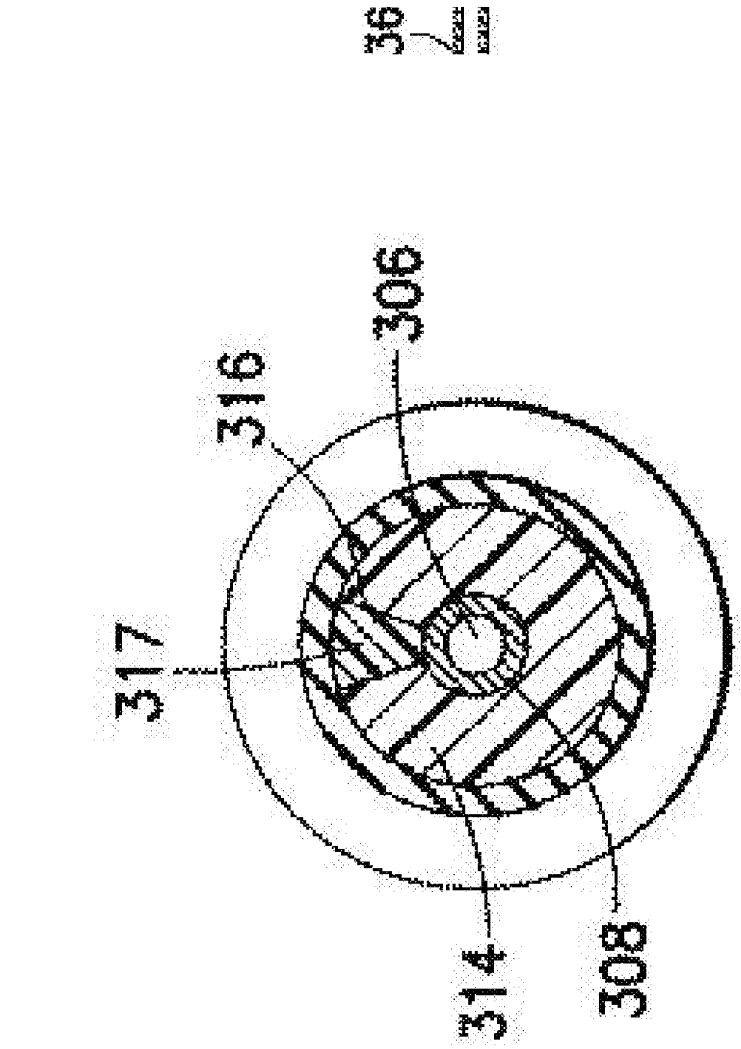
[Fig. 8B]



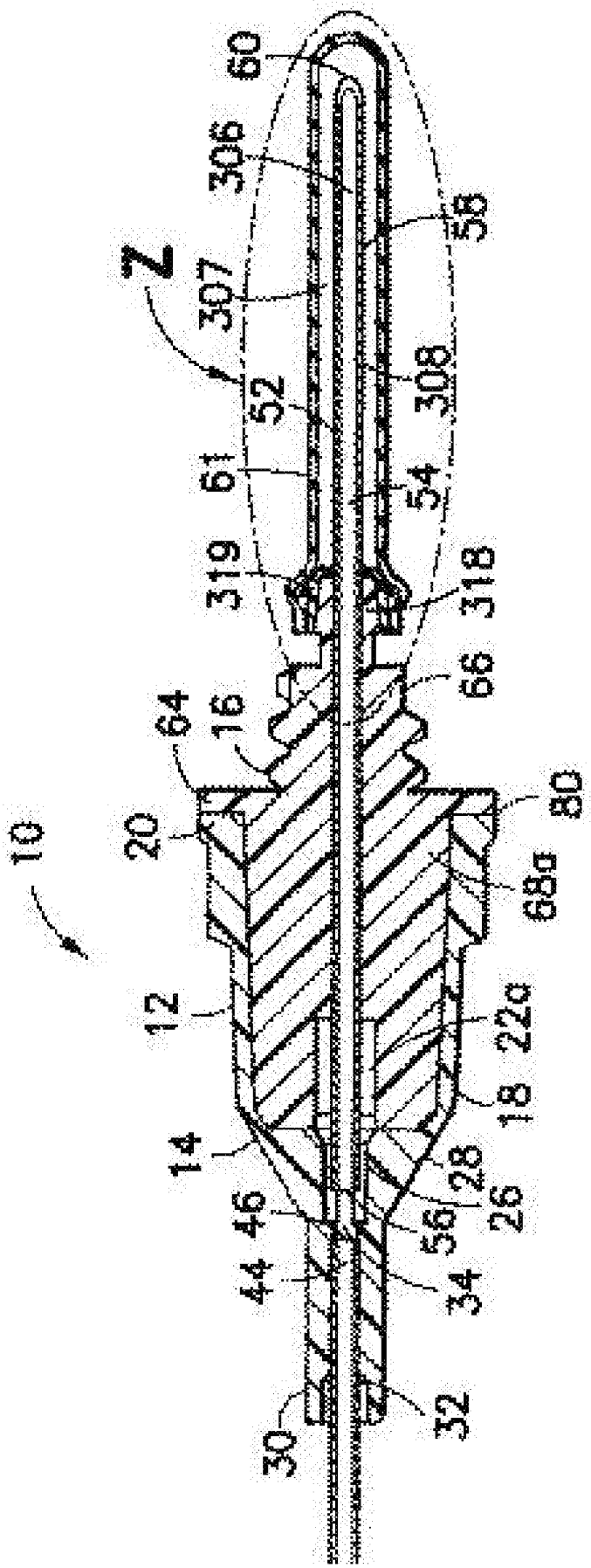
[Fig. 9A]


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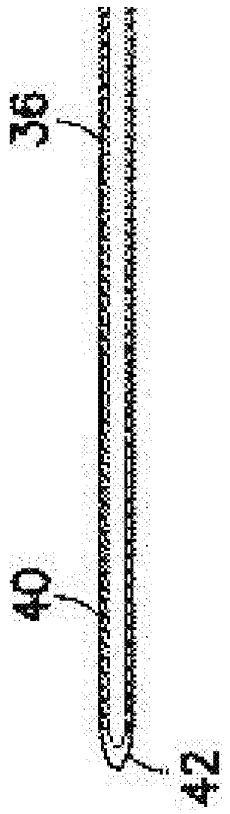
[Fig. 9B]

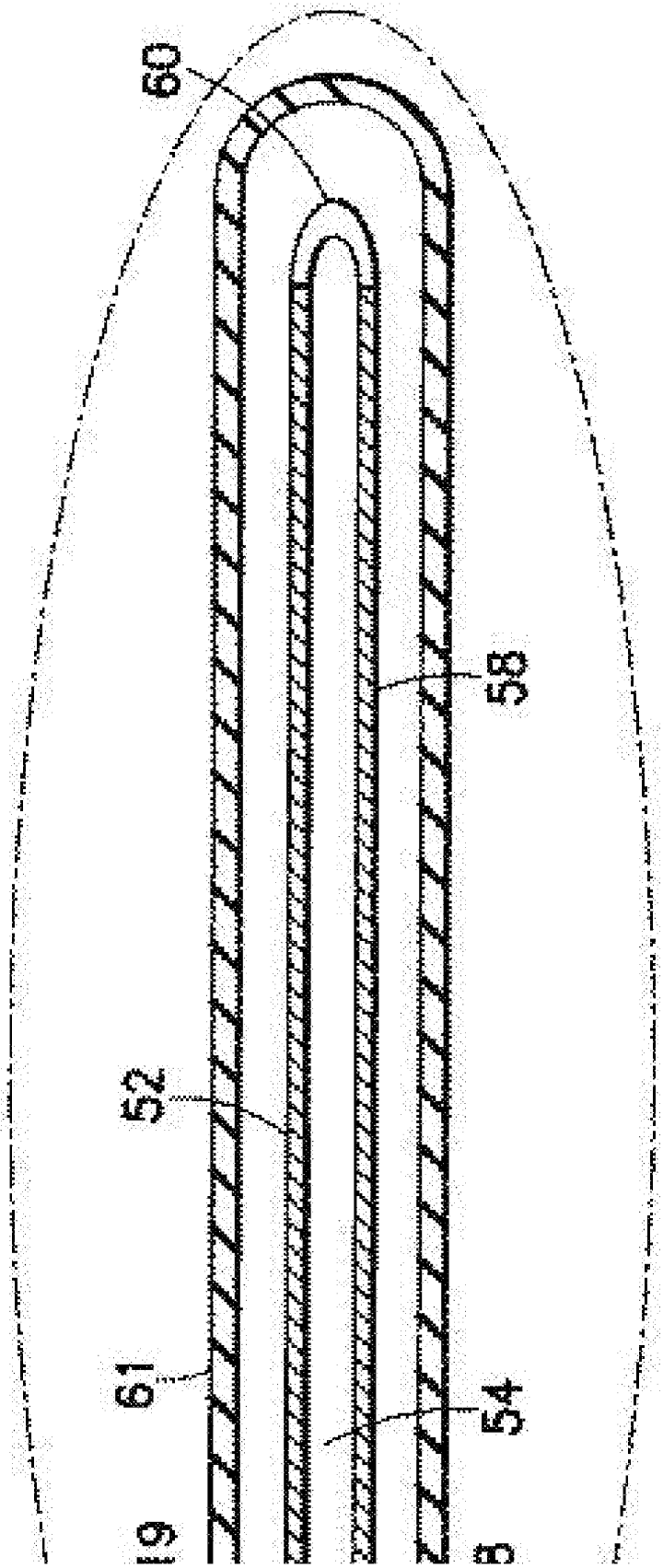


[Fig. 10A]

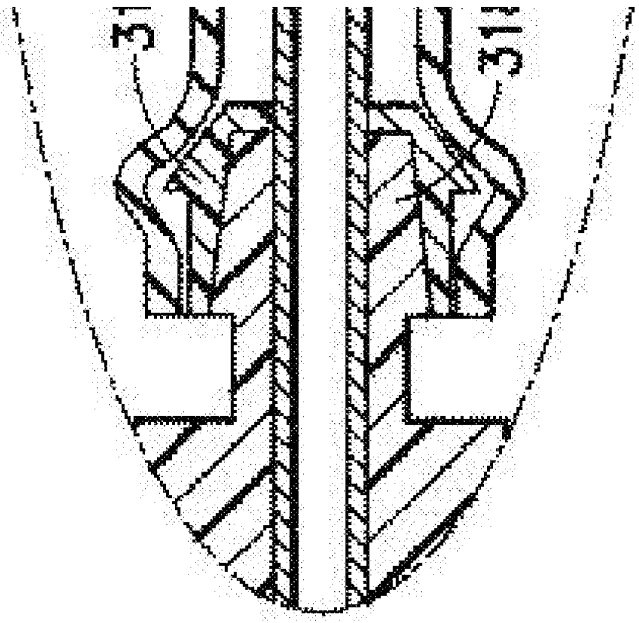

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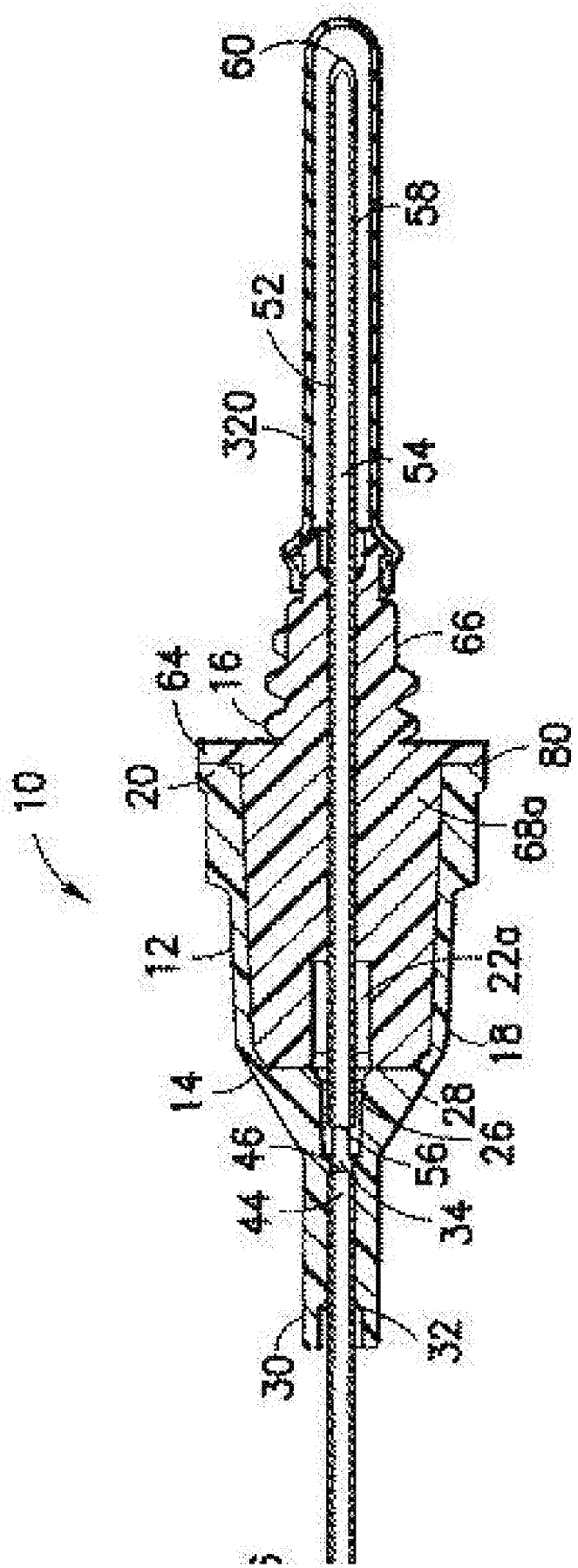
[Fig. 10B]



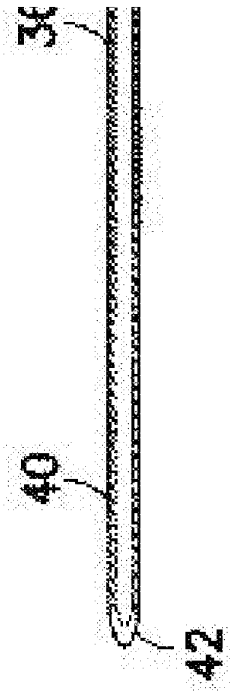

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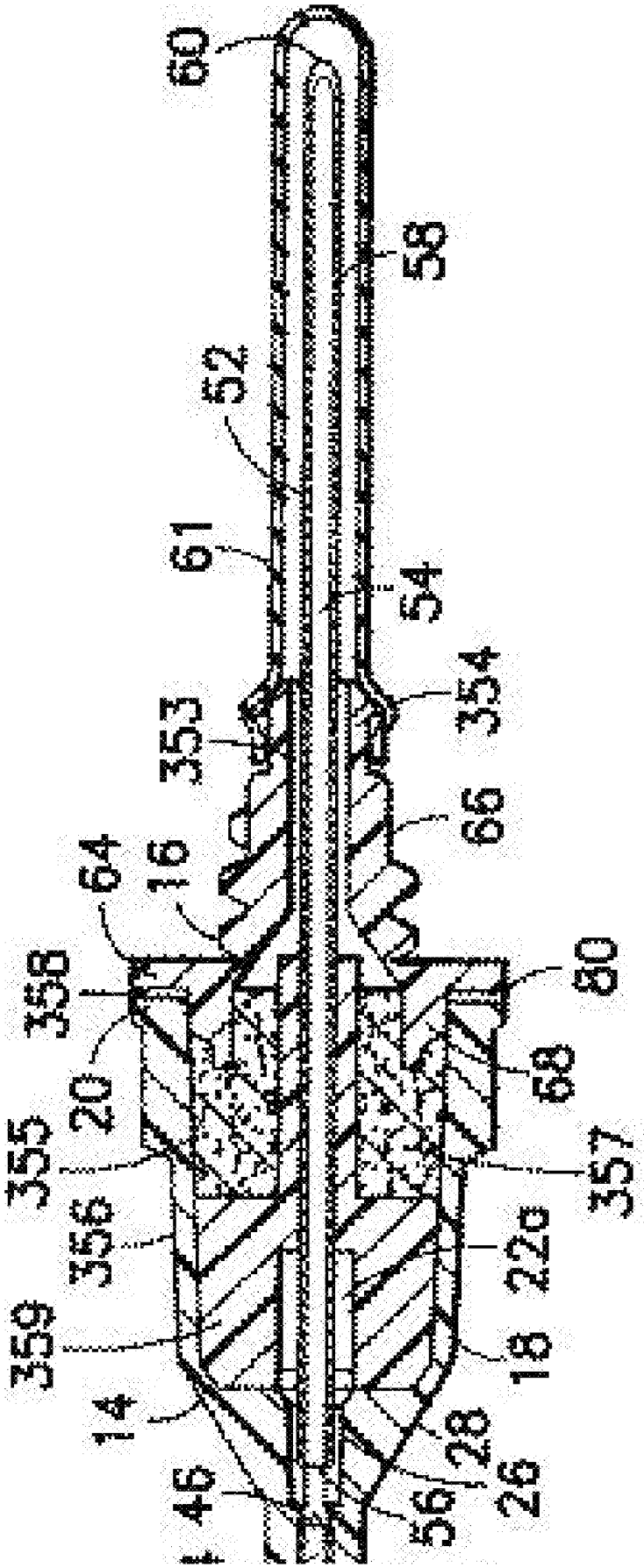
[Fig. 11]



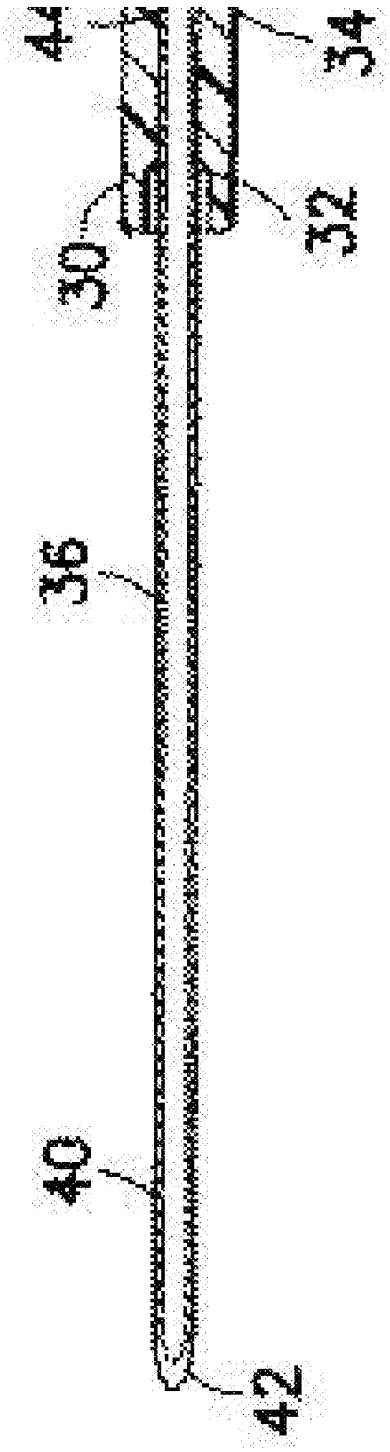

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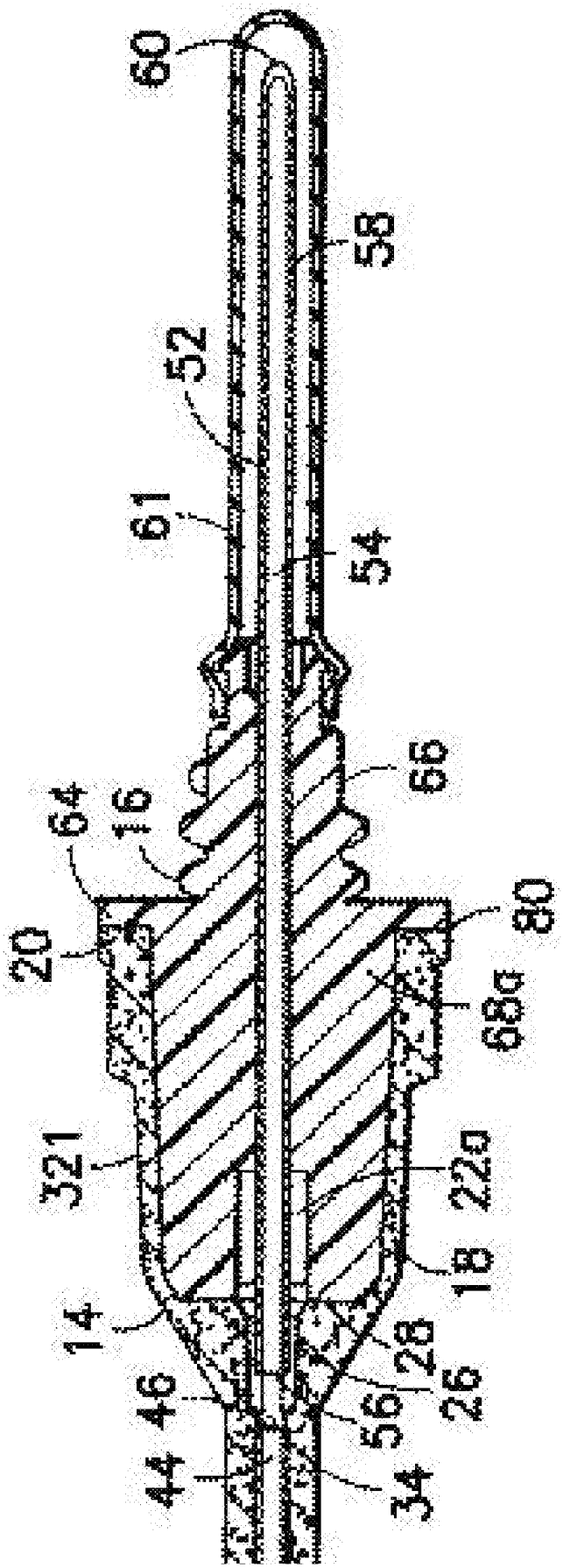
[Fig. 12]



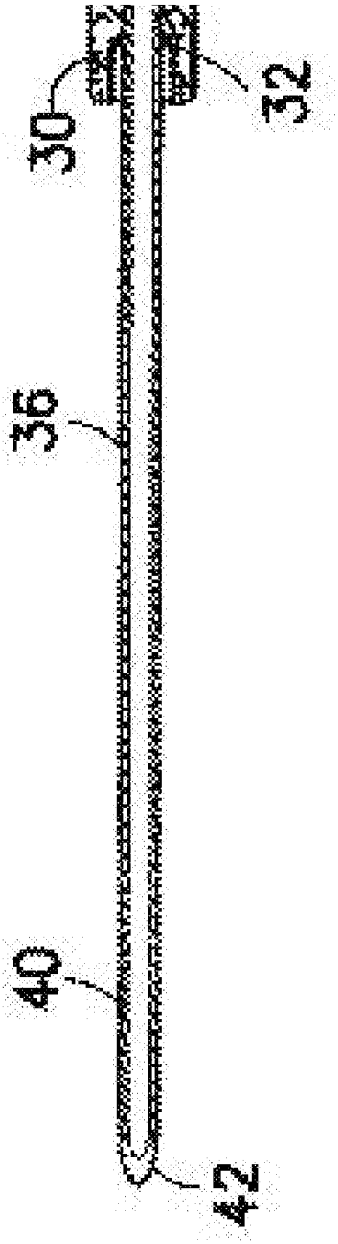

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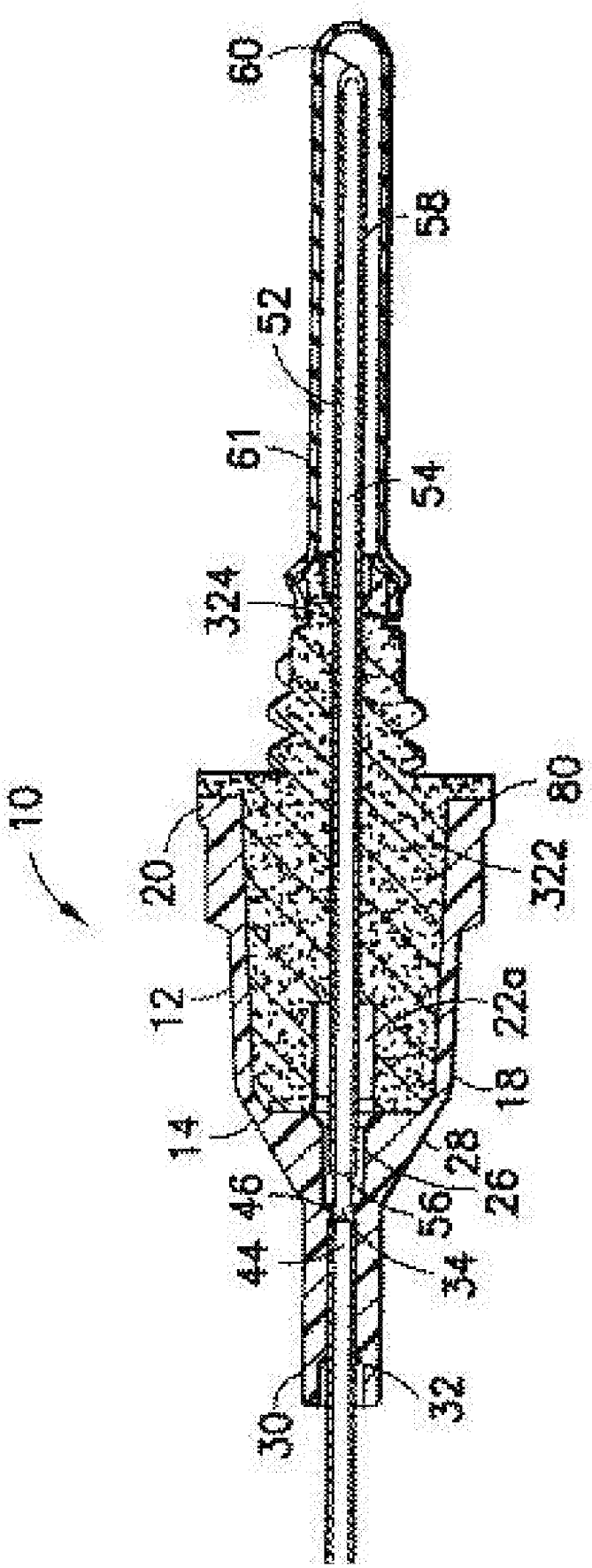
[Fig. 13]



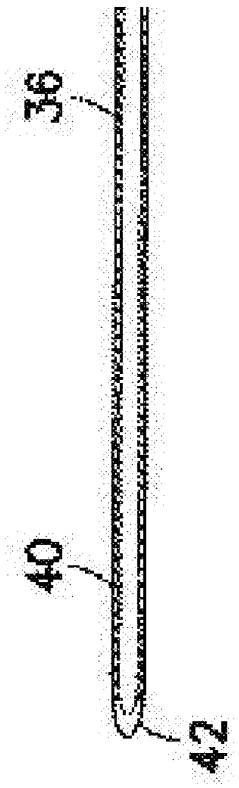

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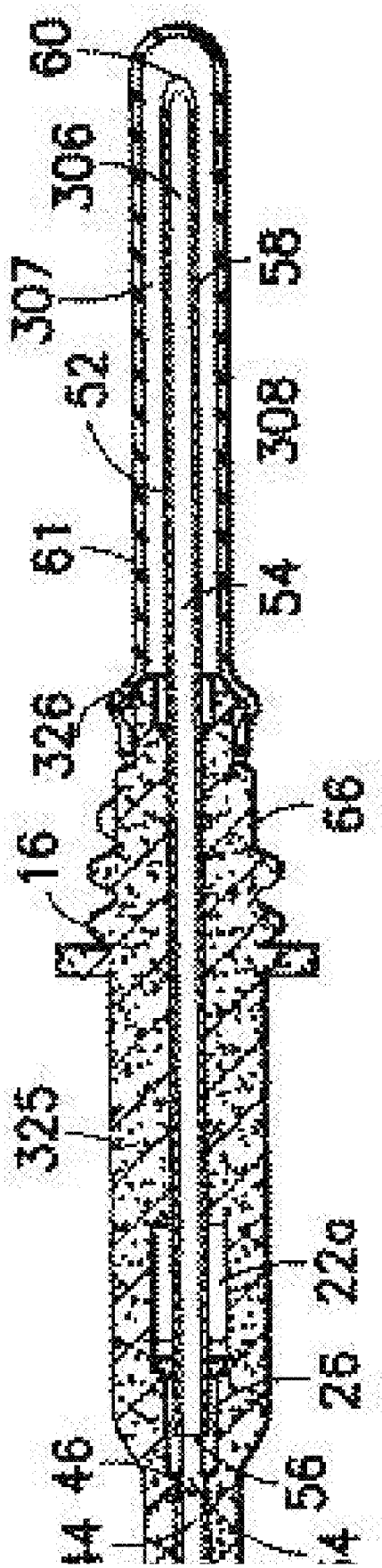
[Fig. 14]



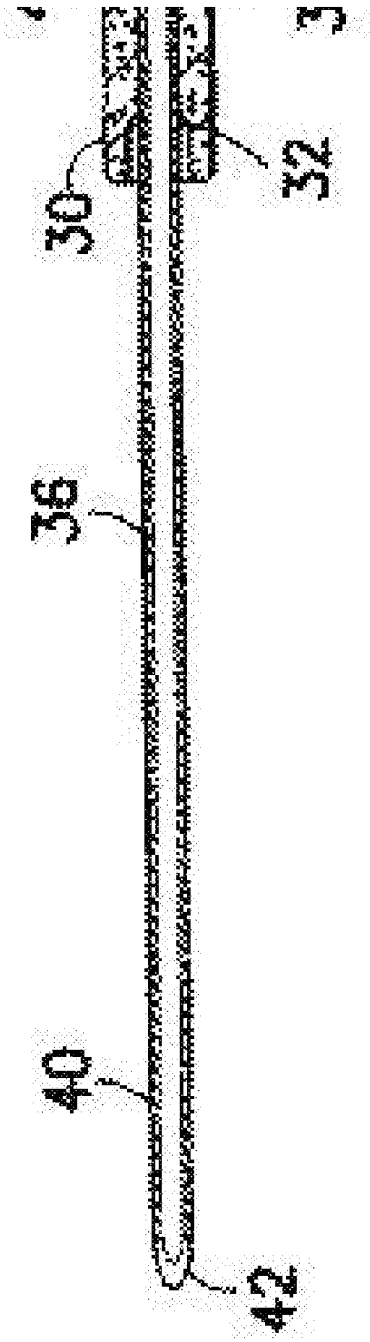

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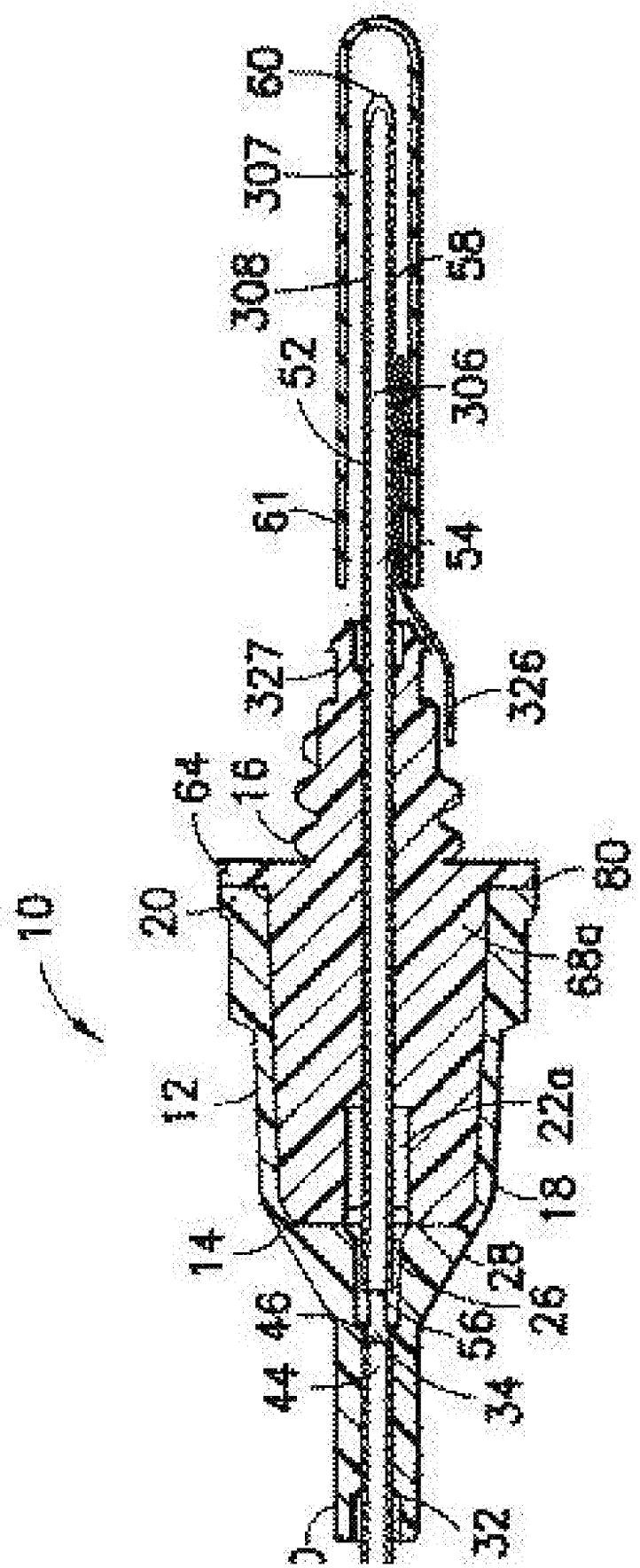
[Fig. 15]



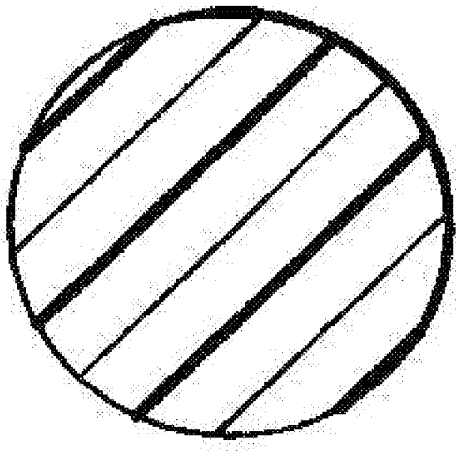

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[Fig. 16]



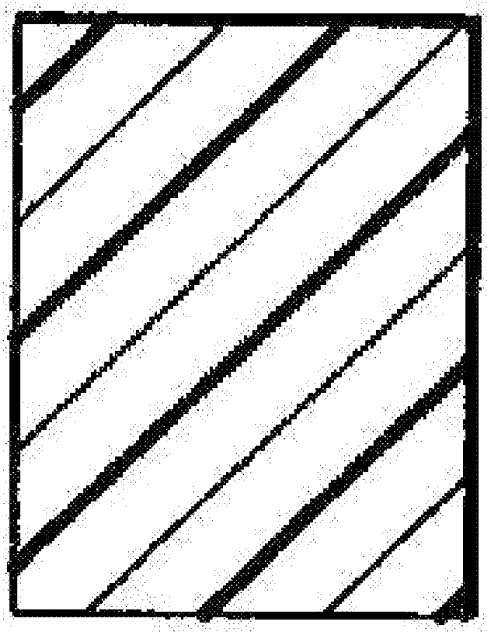

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[Fig. 17]

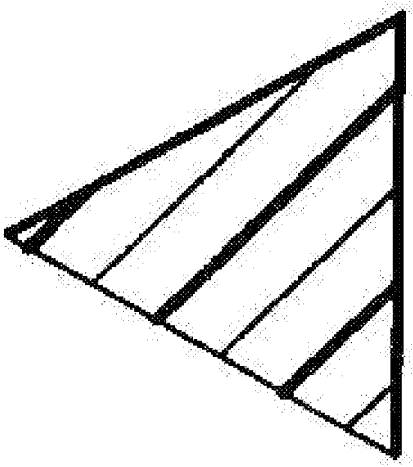


[Fig. 18]

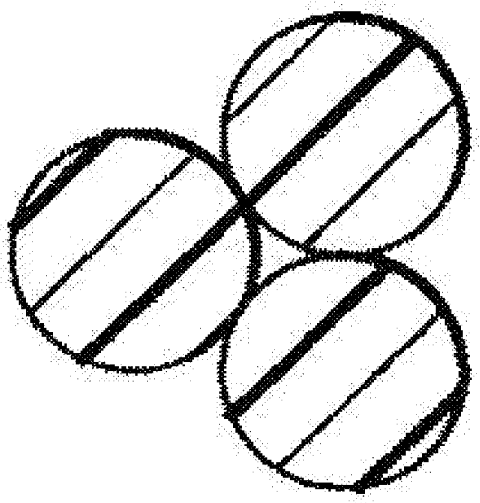




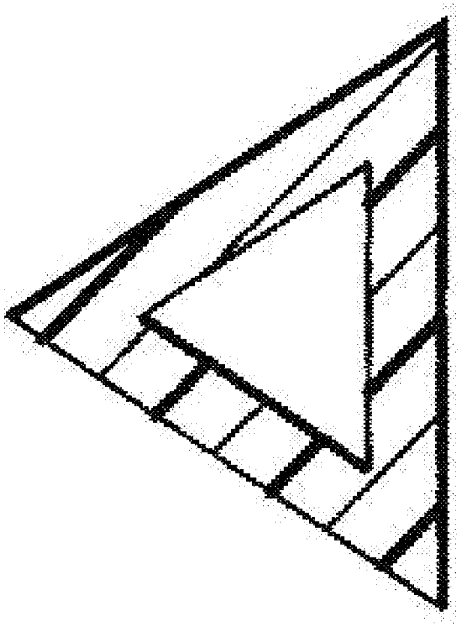
[Fig. 19]



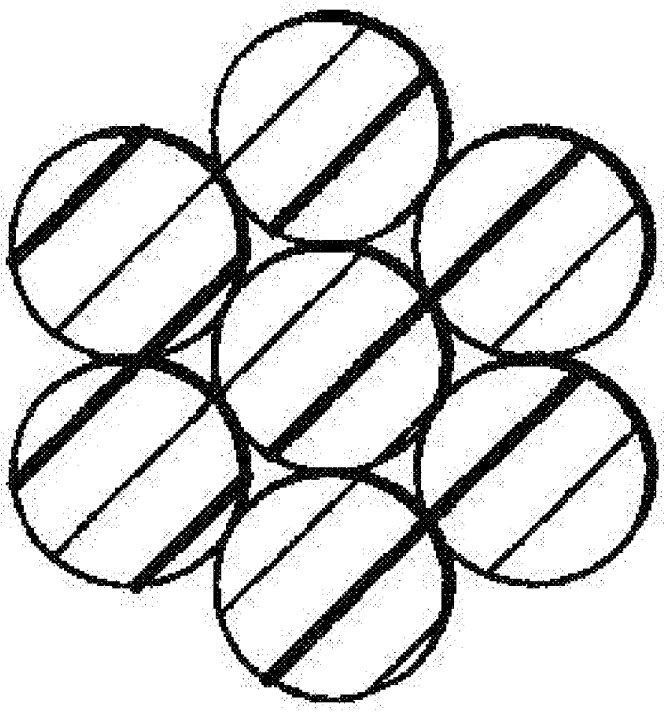
[Fig. 20]



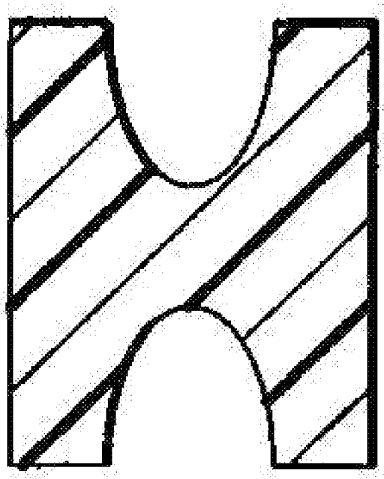
[Fig. 21]



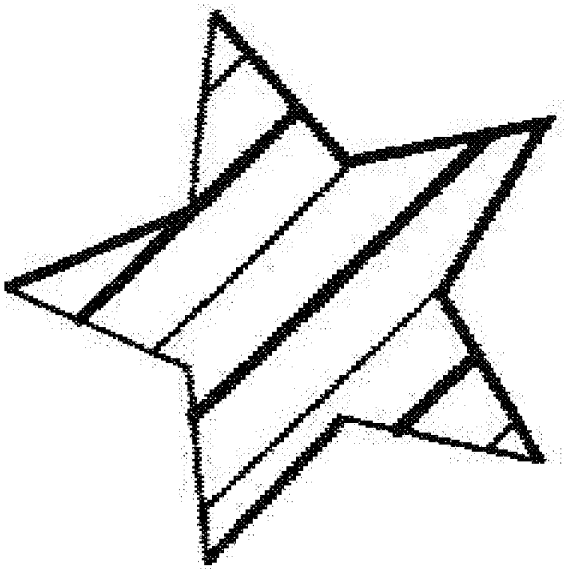
[Fig. 22]



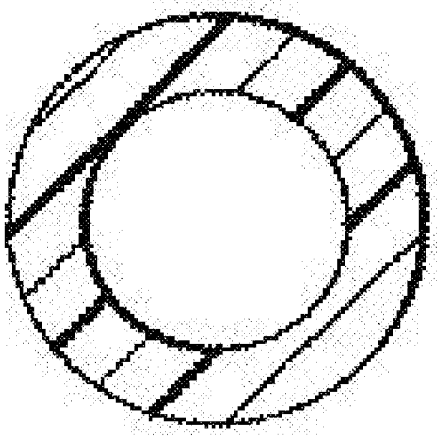
[Fig.23]



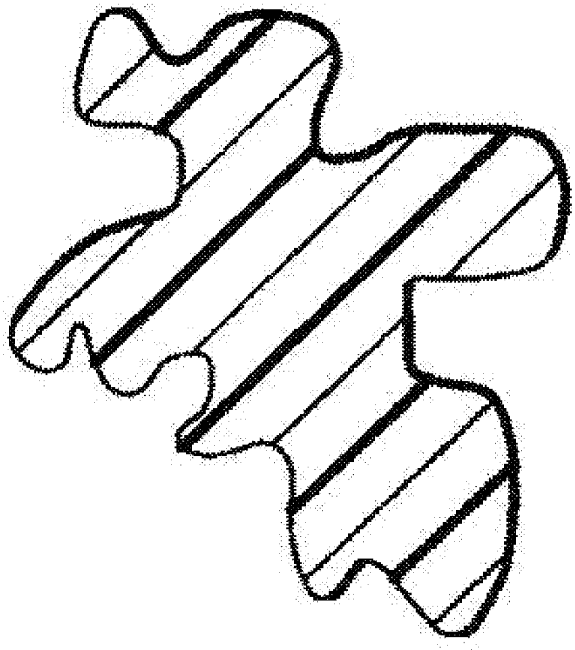
[Fig.24]



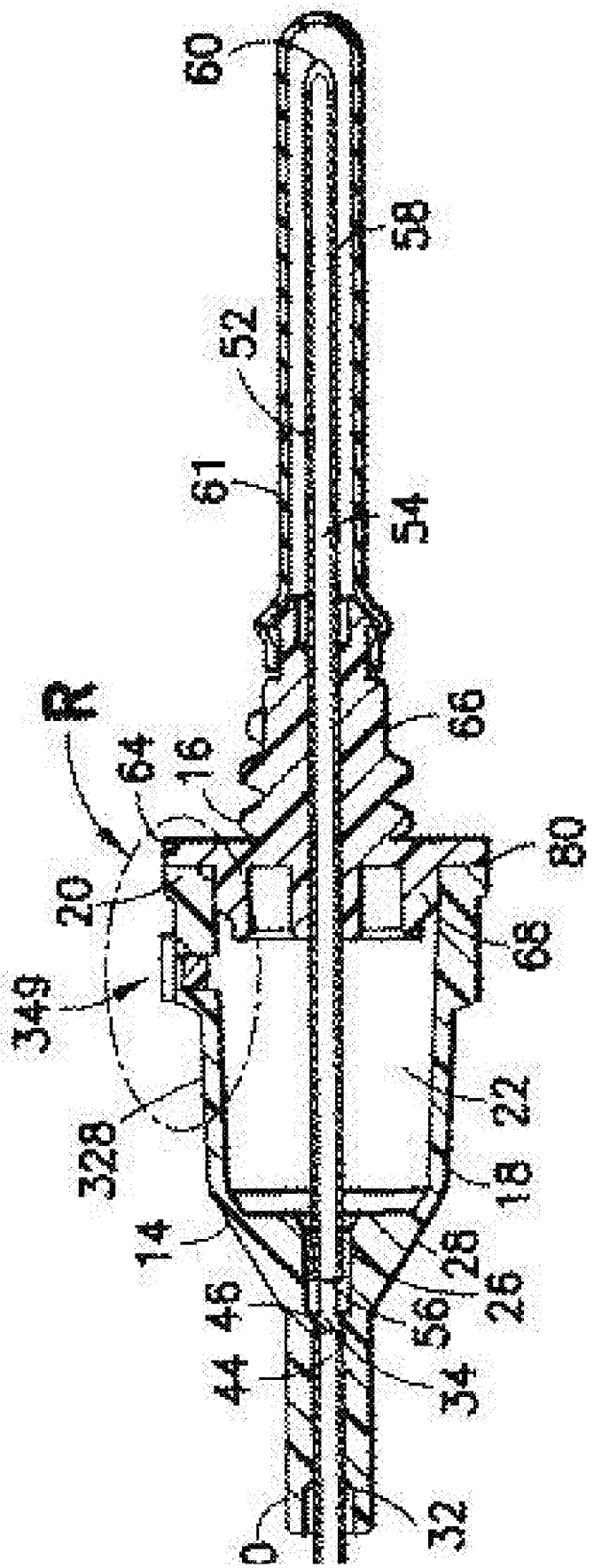
[Fig.25]



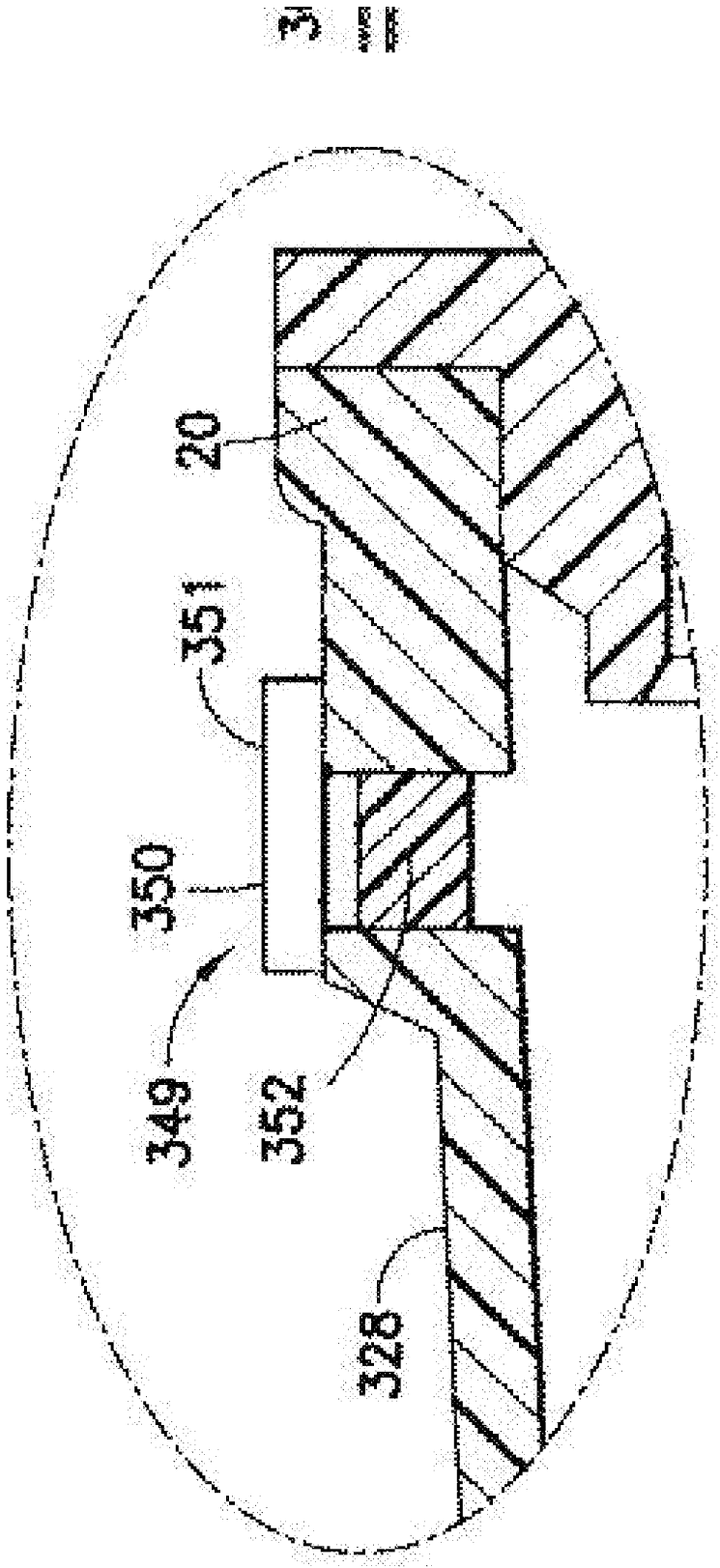
[Fig.26]



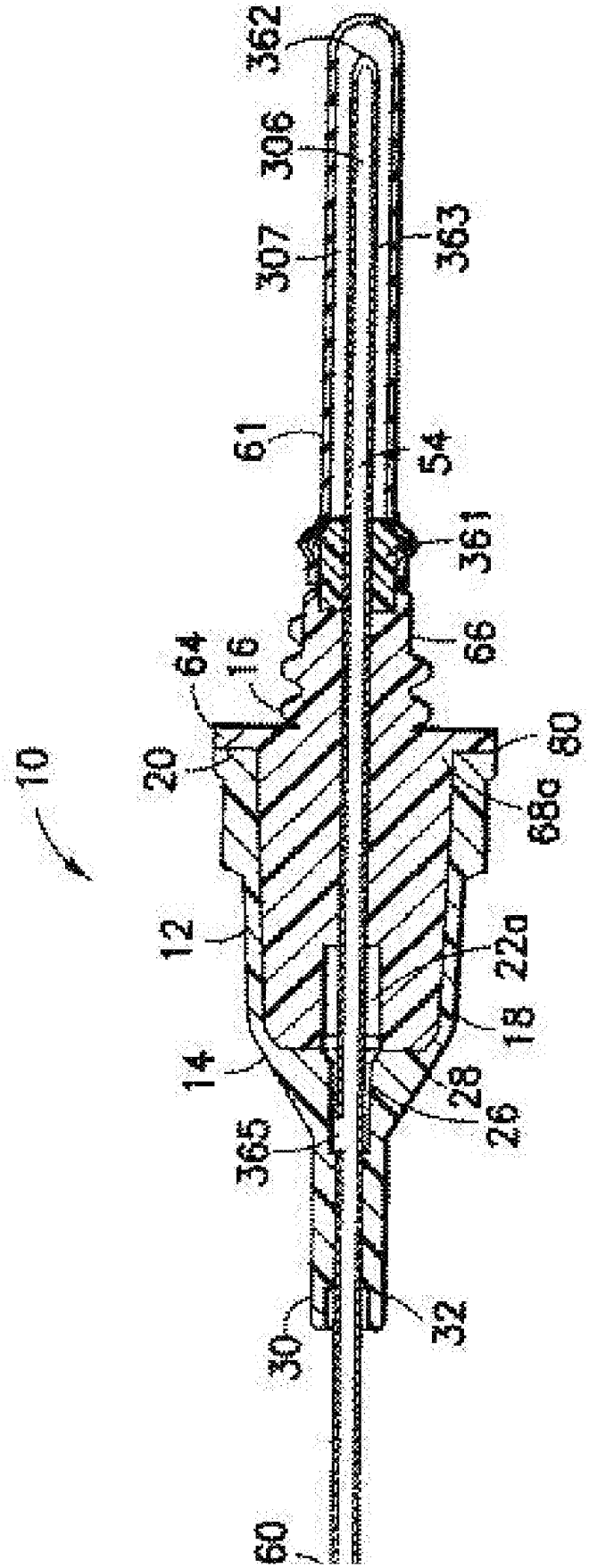
[Fig. 27A]


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[Fig. 27B]



[Fig.28]


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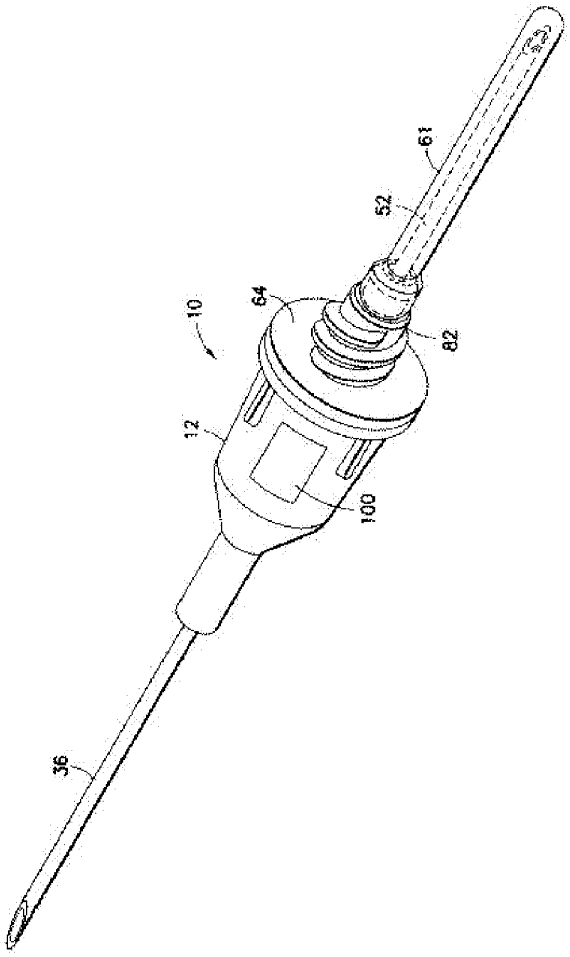
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Representative drawing

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Bibliographic data: JP2005349196 (A) — 2005-12-22

FLASHBACK BLOOD COLLECTION NEEDLE

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Abstract of JP2005349196 (A)

PROBLEM TO BE SOLVED: To easily confirm that puncture is surely performed at the time of blood collection and to prevent an outflow of fluid such as blood. ;SOLUTION: The application refers to a self-venting blood collection needle assembly for the extraction of at least one fluid sample into an evacuated container for laboratory testing. This blood collection needle assembly provides a clear or translucent flashback chamber for the blood to flow into, for visualization by a user to confirm successful vein puncture. The self-venting mechanism permits escape of air during use, and which, typically, also prevents an outflow of fluid, such as blood. Thus, air under venous pressure will be allowed to escape from the blood collection needle assembly until the blood reaches the venting mechanism. ;COPYRIGHT: (C)2006,JPO&NCIPI

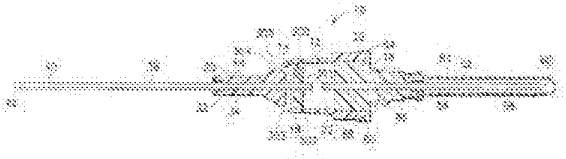


FIG.2

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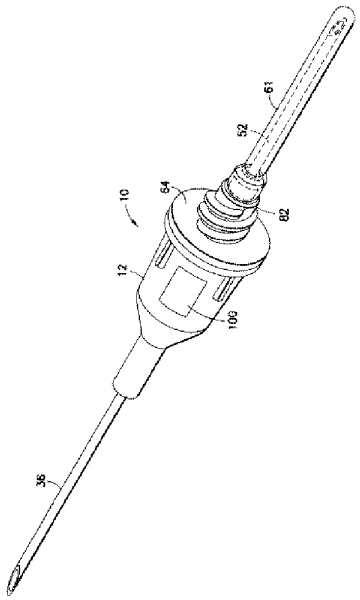
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(54)【発明の名称】フラッシュバック式血液採取針

(57)【要約】　（修正有）
【課題】血液採取時に穿刺が確実に行なわれていることを容易に確認でき、且つ血液などの流体の流出を防止する。
【解決手段】臨床検査のために減圧容器に少なくとも１つの流体試料を抽出する自己通気型血液採取針アセンブリであり、この血液採取針アセンブリは、血液を流入させて使用者が静脈穿刺がうまく行われたことを目視によって確認できる透明または半透明のフラッシュバックチャンバを提供する。この自己通気機構は使用の際に空気の放出を可能にし、且つ血液などの流体の流出を防止するように構成されている。こうして、静脈圧力下の空気は、血液が通気機構に到達するまでにこの血液採取針アセンブリから放出することができる。
【選択図】図１



【特許請求の範囲】
【請求項1】
入口端と、出口端と、これら両端の間に形成されたチャンバを有するハブと、
入口カニューレであって、前記ハブの外側にある末端と、この入口カニューレを貫通して延在し、前記チャンバと連通するように前記ハブに装着される内腔とを有する入口カニューレと、
出口カニューレであって、前記ハブの外側にある基端と、この出口カニューレを貫通して延在し、前記チャンバに連通するように前記ハブに装着される内腔とを有する出口カニューレと、
前記ハブの外側に位置する前記出口カニューレの部分を覆って装着されるマルチプル試料スリーブであって、前記入口カニューレの内腔と、前記チャンバと、前記出口カニューレの内腔と、このマルチプル試料スリーブの内面とが流体通路を形成するマルチプル試料スリーブと、
前記流体通路と外部雰囲気とを連通させる通気機構であって、針アセンブリからこの通気機構を介して外部雰囲気への空気の流出を可能にすると共に前記針アセンブリから前記通気機構を介して前記外部雰囲気への液体の流出を実質的に阻止する通気機構と、
を具え、前記入口および出口カニューレが別個のものであるか、または前記チャンバに連通する開口を持った１本のカニューレであることを特徴とする針アセンブリ。
【請求項2】
前記通気機構が前記ハブを介して延在していることを特徴とする請求項１に記載の針アセンブリ。
【請求項3】
前記通気機構が通気媒体を具えていることを特徴とする請求項２に記載の針アセンブリ。
【請求項4】
前記通気機構が前記ハブを貫通する少なくとも１つの開口を具え、該開口は通気栓を具えていることを特徴とする請求項２に記載の針アセンブリ。
【請求項5】
前記通気機構が逆止め弁をさらに具えていることを特徴とする請求項４に記載の針アセンブリ。
【請求項6】
前記通気機構が前記ハブを貫通する少なくとも１つの開口と、前記入口カニューレを取り囲む通気リングとを具え、該通気リングは前記チャンバ内の前記ハブを介して前記開口の近傍に位置していることを特徴とする請求項１に記載の針アセンブリ。
【請求項7】
前記通気機構が前記出口カニューレの基端を越えて前記通路に配されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項8】
前記通気機構が通気媒体を具えていることを特徴とする請求項７に記載の針アセンブリ。
【請求項9】
前記ハブが非患者側係止突起をさらに具え、前記通気機構がこの非患者側係止突起を介して延在していることを特徴とする請求項１に記載の針アセンブリ。
【請求項10】
前記通気機構が通気媒体を具えていることを特徴とする請求項９に記載の針アセンブリ。
【請求項11】
前記通気機構が前記非患者側係止突起を貫通する通路と、この通路に配された通気栓とを具えていることを特徴とする請求項９に記載の針アセンブリ。

【請求項12】
前記通気機構が前記非患者側係止突起を貫通する切欠きと、通気円板とを具えていることを特徴とする請求項９に記載の針アセンブリ。
【請求項13】
前記通気機構が、前記非患者側係止突起を貫通する少なくとも１つの開口と、この開口に配された通気栓とを具えていることを特徴とする請求項９に記載の針アセンブリ。
【請求項14】
前記ハブが非患者側係止突起をさらに具え、この非患者側係止突起の少なくとも一部が前記通気機構を具えていることを特徴とする請求項１に記載の針アセンブリ。
【請求項15】
前記通気機構が通気媒体を具えていることを特徴とする請求項１４に記載の針アセンブリ。
【請求項16】
前記非患者側係止突起の少なくとも一部が多孔質疎水性材料で形成されているか、または前記非患者側係止突起の少なくとも一部が疎水性の表面を持った多孔質材料で形成されていることを特徴とする請求項１４に記載の針アセンブリ。
【請求項17】
前記通気機構が親水性材料を含浸させた多孔質材料を具えていることを特徴とする請求項１４に記載の針アセンブリ。
【請求項18】
前記ハブは、前記マルチプル試料スリーブがしっかりと装着される非患者側係止突起をさらに具え、前記通気機構が前記非患者側係止突起と前記マルチプル試料スリーブとの間に配されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項19】
前記通気機構が通気スリーブを具えていることを特徴とする請求項１８に記載の針アセンブリ。
【請求項20】
前記通気スリーブが多孔質の疎水性材料を具えるか、または前記通気スリーブが疎水性表面を持った多孔質材料を具えていることを特徴とする請求項１９に記載の針アセンブリ。
【請求項21】
前記通気機構が通気可能な通気コードを具えていることを特徴とする請求項１８に記載の針アセンブリ。
【請求項22】
前記通気機構が織物面を具えていることを特徴とする請求項１８に記載の針アセンブリ。
【請求項23】
前記マルチプル試料スリーブが前記通気機構を具えていることを特徴とする請求項１に記載の針アセンブリ。
【請求項24】
前記通気機構が通気媒体を具えていることを特徴とする請求項２３に記載の針アセンブリ。
【請求項25】
前記マルチプル試料スリーブが多孔質の疎水性材料にて形成されるか、または前記マルチプル試料スリーブが疎水性表面を持った多孔質材料を具えていることを特徴とする請求項２３に記載の針アセンブリ。
【請求項26】
前記ハブが前記通気機構を構成するように、前記ハブの少なくとも一部が通気媒体によって形成されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項27】

前記ハブが前記通気機構を構成するように、前記ハブの少なくとも一部が多孔質材料によって形成されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項28】
前記ハブが非患者側ねじ山アセンブリとハブインサートとをさらに具え、これらを組み立ててリザーバを形成することを特徴とする請求項１に記載の針アセンブリ。
【請求項29】
前記通気機構が、前記非患者側ねじ山アセンブリを通って前記リザーバに達する第１通路と、前記リザーバから外部雰囲気に至る第２通路と、前記リザーバに配された通気栓とを具えていることを特徴とする請求項２８に記載の針アセンブリ。
【請求項30】
非患者側ねじ山アセンブリをさらに具え、この非患者側ねじ山アセンブリの少なくとも一部は、当該非患者側ねじ山アセンブリが前記通気アセンブリを構成するように、通気媒体によって形成されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項31】
非患者側ねじ山アセンブリをさらに具え、この非患者側ねじ山アセンブリの少なくとも一部は、当該非患者側ねじ山アセンブリが前記通気アセンブリを構成するように、多孔質材料によって形成されていることを特徴とする請求項１に記載の針アセンブリ。
【請求項32】
前記通気機構が通気媒体を具えていることを特徴とする請求項１に記載の針アセンブリ。
【請求項33】
前記第１カニューレを選択的に被覆するシールドをさらに具えていることを特徴とする請求項１に記載の針アセンブリ。
【請求項34】
入口端と、出口端と、これら両端の間に形成されたチャンバとを有するハブと、
このハブの外側にあるように前記ハブに装着される末端と、基端と、これら両端の間に延在する内腔とを有するカニューレと、
前記ハブの外側に位置する前記カニューレの基端の部分を覆って装着されるマルチプル試料スリーブであって、前記内腔と、このマルチプル試料スリーブの内面と、前記チャンバとで流体通路を形成するマルチプル試料スリーブと、
前記流体通路と外部雰囲気とを連通する通気機構であって、針アセンブリからこの通気機構を通って外部雰囲気への空気の流出を可能にすると共に針アセンブリから当該通気機構を介して外部雰囲気への液体の流出を実質的に阻止する通気機構と
を具えたことを特徴とする針アセンブリ。
【請求項35】
前記通気機構が前記出口カニューレの前記基端を越えて前記通路に配されていることを特徴とする請求項３４に記載の針アセンブリ。
【請求項36】
前記通気機構が通気媒体を具えていることを特徴とする請求項３５に記載の針アセンブリ。
【請求項37】
前記ハブが非患者側係止突起をさらに具え、前記通気機構がこの非患者側係止突起を通って延在していることを特徴とする請求項３４に記載の針アセンブリ。
【請求項38】
前記通気機構が通気媒体を具えていることを特徴とする請求項３７に記載の針アセンブリ。
【請求項39】
前記通気機構が前記非患者側係止突起を貫通する通路と、この通路に配された通気栓とを具えていることを特徴とする請求項３７に記載の針アセンブリ。
【請求項40】

前記通気機構が前記非患者側係止突起を貫通する切欠きと、通気円板とを具えていることを特徴とする請求項３７に記載の針アセンブリ。
【請求項41】
前記通気機構が前記非患者側係止突起を貫通する少なくとも１つの開口と、この開口に配された通気栓とを具えていることを特徴とする請求項３７に記載の針アセンブリ。
【請求項42】
非患者側係止突起をさらに具え、この非患者側係止突起の少なくとも一部が前記通気機構を具えていることを特徴とする請求項３４に記載の針アセンブリ。
【請求項43】
前記通気機構が通気媒体を具えていることを特徴とする請求項４２に記載の針アセンブリ。
【請求項44】
前記非患者側係止突起の少なくとも一部が多孔質の疎水性材料にて形成されるか、または前記非患者側係止突起の少なくとも一部が疎水性表面を持った多孔質材料を具えていることを特徴とする請求項４２に記載の針アセンブリ。
【請求項45】
前記通気機構が親水性材料を含浸した多孔質材料を具えていることを特徴とする請求項３２に記載の針アセンブリ。
【発明の詳細な説明】
【技術分野】
【0001】
本発明は、患者に血管穿刺を行って血液試料を採取する装置に関する。さらに詳しくは、本発明は、患者から血液試料を減圧血液採取管に採取する場合、自己通気特性によって瀉血士が血管への穿刺ができたか否かを知ることができるマルチプル血液試料を採取するための針アセンブリに関する。
【背景技術】
【0002】
血管穿刺は臨床検査用の血液試料を得るのに用いられる主たる方法である。血管穿刺を行う場合、瀉血士は複数のステップを同時に行う必要がある。このステップとしては、患者の全体的な身体的および心理的状態を評価して、血管穿刺箇所と技術を適正に選択することを含む。瀉血士は、適正な対応器具を選び、出血を制御する技術を実行し、そして臨床検査用の流体試料を適正に採取し且つ特定することも必要である。これらの要因は血管の膨張と血管穿刺処置の長さに悪影響を与えるので、瀉血士はこれらの同時に起こる要因のすべてを確認しなければならない。
【0003】
前述の問題に対応するため、種々の血管穿刺装置が開発されている。これらの装置は、内部にチャンバを画成したハブを有する針アセンブリを含んでおり、両端が尖った１本のカニューレがこのハブに固定されている。このカニューレの血管側の端は患者の血管に挿入されるように構成され、このカニューレの非患者側の端は密閉可能なスリーブを有し、減圧容器内に配された突き刺し可能なストッパを突き刺すように構成されている。
【発明の開示】
【発明が解決しようとする課題】
【0004】
カニューレの血管側の端を血管に挿入すると、血液はカニューレを通って密閉可能なスリーブと、可視化（「フラッシュバック」）のために透明または半透明であるハブのチャンバとに流入する。ハブのチャンバから空気が排出されると、その中の血液は減圧容器の作用によって密閉可能なスリーブがハブのチャンバの方に押される度に加圧される。
【0005】
血管挿入とフラッシュバックとの間の時間差に起因して、血管穿刺が行われたことが即時に透明チャンバに示されなかったことによって、瀉血士は満足すべき血管への穿刺が得られなかったと誤って信じるかもしれない。そして、瀉血士は、減圧容器および／または

針アセンブリ自体の交換を必要とする血管穿刺を不必要に繰り返しことになる。このような処置の繰り返しは患者の受ける身体的、情緒的不快感を長引かせる。

【0006】

フラッシュバックが生じなかった場合、注射カニューレおよびフラッシュバックチャンバの空気がそこで圧縮されるので、針のハブ内の空気は静脈圧力まで加圧される。この加圧された空気は、何れかに排出されることが必要であり、そこで、血液採取が終了した後に注射針が患者から引き抜かれる時、この加圧空気は血液を注射針の先端の方に押し出す。

【0007】

従って、瀉血士が一貫してフラッシュバックを頼りにしている従来の血液採取方法に対し、迅速、正確且つコスト効果の高い解決策を提供し、満足すべき静脈への穿刺を行うことが望まれている。さらに、血液を比較的短い針を介してフラッシュバックチャンバに直接流すことができ、そして針アセンブリの内部から加圧された空気を排出することができる血液採取針アセンブリを提供し、それによって静脈への穿刺が成功し、このアセンブリからの血液の漏洩が無いことを直接的に示すことが、特に望まれている。ここで用いられるように、通気媒体は空気を実際に通す要素、例えば栓，被覆，表面処理などを示している。

【課題を解決するための手段】

【0008】

本発明は、少なくとも１つの流体試料を臨床検査用に減圧容器に抽出する自己通気型の血液採取針アセンブリであり、この血液採取針アセンブリは、静脈穿刺がうまく行われたことを使用者が目視によって確認するための、透明または半透明のフラッシュバックチャンバを提供する。この自己通気型機構は、使用の際に空気の放出を可能にするが、血液などの液体の流出は阻止する。ここで使用されている通気機構とは、空気を排出させるが、液体の通過を阻止する１つ以上の装置または要素のことを称する。従って、静脈圧力下の空気を、通気機構に到達するまでに血液採取針アセンブリから排出することができる。そしてこの通気機構は、これを迂回または通って血液が流れることを遮断または防止し、血液が減圧採取管その他の適宜な血液採取容器に採取されることを可能にする。本発明は、血液採取プロセスに悪影響を与えることなく、フラッシュバックチャンバ内における良好な瞬時可視化を提供する。以下に述べるように、好適な種々の通気機構，通気媒体または通気位置が存在する。

【0009】

少なくとも１つの流体試料を患者から採取して少なくとも１つの減圧容器内に引き続いて排出するため、自己通気型血液採取針アセンブリが提供される。本発明の自己通気型血液採取針アセンブリは、円筒状外壁によって画成された流体入口を有するハブを具えている。この壁は、ハブ内に血液試料を保持するためのフラッシュバックチャンバと、外から噴出が目視できるように透明または半透明の壁の少なくとも一部とを画成している。このハブは、流体入口端に連通する流体出口端をさらに具えている。この血液入口端に流体連通する第１の入口側カニューレがそこから外向きに延在している。この第の１カニューレはチャンバの基端に位置する内側基端と、これと反対側で患者の静脈を穿刺するように構成された外側末端とを有する。同様に、流体出口端に流体連通する第２の非患者側出口カニューレが配され、そこから外向きに延在している。この第２の非患者側カニューレは、前記第１の内側端の基端側に位置決めされた内側末端を有し、前記第２の内側端の反対側の外側基端をさらに具えている。この第２の非患者側外側基端は、減圧容器の突き刺し可能なストッパを貫通するように構成されている。第２の患者側カニューレは、さらに密閉可能なマルチプル試料スリーブを具えている。しかしながら、２本のカニューレの代わりに切欠きを含む１本のカニューレを使用することもできる。他の別なカニューレの構成は、非患者側カニューレの基端を通り、マルチプル試料スリーブを巡って通気孔を通った後、フラッシュバックが起こるように、切欠きの無い１本のカニューレを用いている。基端近傍のハブの外側部分は、一条の外側ねじ山、またはその他の装着構造で形成され、血液

採取針アセンブリを採取管ホルダその他の医療装置に装着することができる。あるいは、このホルダを針アセンブリに予め取り付けておくことができる。

【0010】

一実施形態において、通気機構はハブのフラッシュバックチャンバに配されている。前記２本カニューレ型構造または切欠き付き１本カニューレの使用は、この構成に適している。これによって、通気機構は、ハブを介して流体通路と外部雰囲気とを連通させる。

【0011】

他の実施形態において、通気機構が非患者側カニューレの基端を越えて配され、これは空気が、血液が吸引される非患者側カニューレの基端を通過し、次いで通気孔を通過することを意味する。この場合、切欠きを持たない１本カニューレが適しているが、あらゆるカニューレ構造が使用可能である。詳しくは、空気は針の外側とマルチプル試料スリーブとの間の空間を流れ、流体通路から非患者側カニューレの基端の外に排出される。次に、空気は、非患者側係止突起か、非患者側ハブのねじ山か、非患者側のハブ本体か、マルチプル試料スリーブか、またはその他の非患者側カニューレの基端を越えた位置やこれらの位置を組合せた位置にある通気機構を介して流れる。非患者側カニューレの基端に装着される採取管は、流体通路のみから血液を吸引し、通気空間からは吸引しない。従って、この実施形態は、採取通路全体を通して血液を流すことができる。これは、潜在的に血小板の活性化か、汚染またはその他の望ましくない結果をもたらす血液試料の通気孔への接触も防ぐ。これは、減圧管が装着された場合、空気が流体通路に逆に吸い込まれることも防止する。この実施形態は、通気孔がハブに配された前述の実施形態に比べて、小さな噴出チャンバしか必要でないことにも注目すべきである。

【0012】

本発明の別の実施形態は、少なくとも一部が焼結プラスチック，セラミックまたは金属などの多孔質材料で形成された一体化されたハブからなる通気機構を有している。この多孔質材料は、空気が非患者側カニューレに入る前か、または空気が基端を出てカニューレとマルチプル試料スリーブとの間の空間へと非患者側カニューレを通って流れた後の何れかに、排気が行われるように配置することができる。多孔質材料は空気の通気は行うが、血液の漏洩は阻止する。典型的な実施形態において、この多孔質材料は疎水性である。多孔質材料は、濡れると膨潤する材料をさらに含んでいる。他の通気方法も可能である。内部通路の壁面は、多孔質材料による血液試料の汚染を防ぐシーラントによってコーティングされてもよい。この実施形態は、全採取経路に亙って血液を流すことができる。ねじ山による接続の必要性や不便さを排除するため、必要に応じてハブは恒久的に管ホルダに接合することができる。このホルダへの接合は、溶剤，溶着，加熱，加圧または他の適当な手段、あるいはこれらの組み合せによって行うことができる。このようにして一体化された装置は効率よく製造され、ホルダが針と一緒に廃棄されることによって、医療行為の安全性を高めることができる。

【0013】

さらに別の実施形態において、通気機構はハブに配された側面開口を介して空気を外に排出するが、この開口は、当該開口内にまたは開口に接して機械的に保持されるような形状を有する通気材料によって覆われている。この通気材料は疎水性であることが好ましく、表面張力もまた漏洩を防止するようになっている。この実施形態の通気媒体材料は、ばねのエネルギーが通気材料をこの装置に対して保持するように、弾性的な性質および形状を有していることが好ましい。例えば、形状が捻じれるには通気媒体がハブ上の受け入れ構造の全体に亙って伸びることが必要なＣ字型形状の通気媒体を使用することができる。通気媒体が支持構造体に設置されると、通気媒体に吸収されて悪影響を与えることのあるエポキシなどの接合材料が無くても、それは解放されてそれ自体の弾性を用いて所定の位置に保持される。この実施形態の通気機構は、最初に通気用材料を圧縮し、この材料を開口に置き、そして通気用材料を解放して開口内で拡張させるようにしてもよい。

【発明を実施するための最良の形態】

【0014】

本発明は、血液などの流体の流出を防止すると共に空気の放出を助ける自己通気機構を具えた自己通気型血液採取用針アセンブリであって、患者から血液やその他の流体を１本以上の減圧血液採取管に採取する際、血管への挿入の可視的指示（「フラッシュバック」）を与えるアセンブリを提供するものである。

【0015】

通気媒体は、例えば栓やインサートなどの別の物理的要素か、レーザー穿孔などによって処理されたり全体的または部分的に多孔質材料にて形成される装置の一体部品か、あるいは例えば含浸，被覆，スプレーなどにより装置に対して材料を配することによって形成される膜や層などであってよいことに留意されたい。

【0016】

本発明の一実施形態にかかる血液採取針アセンブリを図１に示す。針アセンブリ１０は、一方の側に流体入口針（第１カニューレ）３６を、反対側に非患者側の流体出口針（第２カニューレ）５２を支えるハブ１２を具えている。第１カニューレから採取された流体はハブ１２を通り、半透明の窓１００を介してフラッシュバックチャンバ内で直ちにに見ることができ、通気機構の助けによる適正な血管穿刺が行われたことの適時な指示を与える。

【0017】

図２～図２８は、血液採取針アセンブリにおける通気機構の種々の構成を含む本発明の種々の実施形態を示す。特に、図２，図３，図４Ａ，図４Ｂおよび図４Ｃは、通気機構がハブの部分に配された実施形態を示している。図５～図１２は、通気機構が非患者側カニューレの基端６０を越えた所に配された実施形態を示している。図１３および図１４は、針のハブの一部が通気媒体として作動する実施形態を示している。図１５は、通気機構が単一化されたハブ１３２である実施形態を示している。図１６～図２６は、通気機構が通気性を有するコードである実施形態を示している。図２７Ａおよび図２７Ｂは、通気機構が逆止め弁である実施形態を示している。図２８は、１つの切欠き付きカニューレを具えた実施形態を示している。２本のカニューレがある以下の各実施形態において、１本の切欠き付きカニューレが同様に使用可能であることに留意されたい。

【0018】

図２，図３，図４Ａ，図４Ｂおよび図４Ｃは、第１カニューレ３６の基端３０１の周囲に通気リング３００を配した通気機構を示している。この通気リングは、フラッシュバックチャンバ３０２の内壁と締まり嵌めを形成する。従って、空気はこの通気リングを介して通気開口３０３から外部雰囲気へ放出できる。これらの開口をハブの末端のどこにでも配することができる。図２および図３において、これらの開口はハブ３０４の末端に配されている。図４Ａ，図４Ｂおよび図４Ｃには、通気開口が通気リング３００の末端側に当接する長手方向の通気窓３０５である別の実施形態が示されている。

【0019】

幾つかの実施形態は、非患者側カニューレの基端６０を越えた所に配した通気機構を具えている。この通気機構は、より小さなフラッシュバックチャンバ２２ａを用い、図２，図３，図４Ａ，図４Ｂ，図４Ｃなどの前述の実施形態に比べて、ハブアセンブリ１２から排気される空気の量を減らすのに有利である。次の実施形態は、より大きな環状フランジ６８ａを用い、より小さなフラッシュバックチャンバ２２ａを作っているが、別な設計でもよい。これらの設計の例は、フラッシュを見やすくするためのハブの表面に近い半透明／透明材料の窓および／またはフラッシュバックチャンバの一部である。特に切欠きの無い１本のカニューレを使用する実施形態の場合、フラッシュバックチャンバまたは窓を空気／血液通路に配することができることに留意されたい。

【0020】

図５の実施形態において、空気は流体通路３０６から非患者側カニューレの基端６０まで流れ、さらに針の外側３０８とマルチプル試料スリーブ６１の内側との間の空間３０７を通って、非患者側の係止突起３１０と空気の流出は許すが血液その他の流体は外部雰囲気へ流出させない通気栓３１１とで構成されている通気孔３０９の位置まで達する。

【0021】
図６，図７，図８Ａ，図８Ｂ，図９Ａ，図９Ｂ，図１０Ａおよび図１０Ｂは、通気機構が非患者側カニューレの基端６０の越えた所に設けられている実施形態を示している。図６および図７の実施形態は、非患者側の係止突起の少なくとも一部としても機能する通気栓３１２を示す。これらの図に示されているように、両方の実施形態では、通気孔の少なくとも一部が外部に接近しており、これを介して空気を排気する。図８Ａおよび図８Ｂは、非患者側の係止突起３１４における切欠き３１３が空気を通気用円板３１５に逃がすように構成された実施形態を示している。図９Ａおよび図９Ｂは、非患者側の係止突起３１４における切欠き３１６が通気栓３１７を含んでいる別の実施形態を示している。図１０Ａおよび図１０Ｂは、通気スリーブ３１９が空気を逃がすように改変された非患者側の係止突起３１８の構成を示している。各実施形態においては、通気機構（およびここに述べられた類似のエレメント）が空気を流出させるが、血液その他の流体が外部雰囲気に流出することは防止している。
【0022】
図１１は、非患者側のカニューレの基端６０を越えた所に設けられた通気機構の別の実施形態を示す。この実施形態によれば、空気は、非患者側のカニューレ５２からの流体の流出を防ぐマルチプル試料スリーブ３２０自体の材料を通って排気される。このマルチプル試料スリーブ３２０は、減圧採取管のストッパによって生じる力に応じて、非患者側カニューレ５２の尖った基端６０によって突き破られるその正常な機能を維持している。スリーブを前述のような多孔質の疎水性材料で形成することにより、通気孔としても機能するマルチプル試料スリーブ３２０を作ることができる。
【0023】
図１２は、空気が非患者側針５２の外側と非患者側係止突起３５４との間の狭い通路３５３を通り、次にベース６４と環状フランジ６８との間を通って通気媒体３５７を収容するハブ３５６のリザーバ３５５内に入り、ハブ３５６と非患者側ハブのベース６４との間の境界８０に設けた通路３５８を介して外部雰囲気に排出される別の実施形態を示している。ハブのインサート３５９がリザーバ３５５を形成している。
【0024】
図１３および図１４は、ハブ３２１または非患者側のねじ山付きアセンブリ３２２が多孔質材料で作られ、従って通気媒体として作用する通気機構を示している。図１３は、空気をハブ３２１の傾斜部２８を通って環状溝２６から周囲の大気中に排出する通気媒体としてのハブ３２１を示している。図１４は、通気媒体としての非患者側のねじ山付きアセンブリ３２２を示している。この実施形態は、空気をフラッシュバックチャンバ２２ａの壁に通し、次に非患者側の係止突起３２４を通して放出させることができる。
【0025】
図１５は、環状溝２６とフラッシュバックチャンバ２２ａの壁を通じ、且つ流体通路３０６を介して空気を逃し、非患者側のカニューレの基端６０から排出する多孔質材料の通気媒体で作られた一体化されたワンピース型のハブ３２５である通気機構を示し、空気はさらに針３０８の外側とマルチプル試料スリーブ６１の内側との間の空間３０７を通り、次いで非患者側係止突起３２６を通って周囲の大気中に流出する。一体化されたハブ３２５の性質によって、このホルダはねじ山を設けず、接合によって予めハブ３２５に装着可能である。しかし、図示のように必要に応じてねじ山を設けてもよい。管ホルダをこの一体型の非患者側のハブ３２５に接合するには、溶剤，溶着，加熱，圧力その他、従来からある手段やそれらの組合せが用いられる。
【0026】
図１６は、マルチプル試料スリーブ６１の密閉表面の内側と非患者側の係止突起３２７との間に設けられた通気性を有する通気可能なコード３２６の通気機構を示している。密閉表面にコードが設けられているので、空気は針３０８の外側とマルチプル試料スリーブ６１の外側との間の空間３０７から排出されるが、コードの材料の性質および／またはコードによって形成される通路の寸法が非常に小さいことによって流体の漏洩が防止される

。この機構を使用した通気は、通気媒体（例えば設置，被覆，処理などの）を流体通路３０６に沿って任意の１つまたは複数の密閉表面の間に位置させることにより行われる。図１７～図２６は、好適な通気性を有するコードの断面を示す。その他の形状やこれらの形状の組み合せも利用可能である。コードは押し出しや紡織などで作られ、そしてワックスなどの疎水性のコーティングを施すことが有利である。

【0027】

他の実施形態において、通気機構は流体通路に沿った何れかに配される逆止め弁を使用している。この弁は、空気を通過させるが真空がもたらされると閉じ、従って減圧採取管が針の先端に取り付けられると、この管は流体通路から血液を吸引するが、空気を吸い込まない。図２７Ａおよび図２７Ｂは、逆止め弁の一例を示す。この通気機構を流体通路３０６に沿った任意の箇所（単数または複数）に設けることができるが、好ましくはハブ３２８に設けられる。この弁３４９自体は、通気孔を被覆するプラスチックフィルム３５０などの薄いフラップ，変形可能なゴムなどのシール，またはプラスチック製ダックビル型の弁，通気孔を覆う変形可能なラップ，他の任意の手段，またはこれらの組み合せであってよい。この弁３４９は、通気孔に対して基端側または末端側に位置している。図２７Ｂに示した実施形態では、薄いプラスチックフィルムの弁３４９が、フィルム３５１の一方の密閉された縁に沿ってハブ３２８に取り付けられ、最初の静脈穿刺の際に、静脈圧力によって流体通路３０６から多孔質通気栓３５２を介して空気が押し出され、プラスチックフィルム３４９の固定されていない縁の下から出て行く。しかし、流体通路３０６に（血液採取管の取り付け部を介して）真空がもたらされると、薄いプラスチックフィルム３４９が多孔質通気栓３５２に対してぴったりと吸い付けられ、通気孔を密閉して空気が流体通路に再び入ることを防止する。こうして、この実施形態は、排気が行われた後でシステム内に空気が再侵入することを防ぐ、主たるまたはバックアップの機能を発揮する。

【0028】

図２８は、１本のカニューレ３６０と非患者側の係止突起として機能する通気栓３６１とを具えた血液採取針アセンブリを示している。このカニューレ３６０は、カニューレ３６０の孔３６５が環状溝２６の位置に設けられ、これとの流体連通を保つように、孔３４に位置している。カニューレ３６０が適正に位置決めされると、カニューレは孔３４と摩擦係合し、または接着剤などによってこれに固定される。静脈穿刺の際には、空気は流体通路３０６から流れ、カニューレの基端３６２から排出され、さらに針３６３の外側とマルチプル試料スリーブ６１の内側との間の空間３０７に流れ、通気栓３６１に達する。

【0029】

当業者ならば理解できるように、１つの装置に１つ以上の通気機構を組み合わせたり、同じ通気機構を１つの装置の１つの箇所に取り付けることが可能である。さらに、本発明の通気機構に種々の通気媒体の任意のものを使用することも可能である。さらに、ここに述べられた通気機構は、血液採取針アセンブリ以外の種々の装置にも適用可能である。

【0030】

ここで使用される通気媒体は、例えば

・水溶性または水を含む物質に接触すると膨潤する親水性材料がコーティングされ，含浸され，またはこれを含む一般的に疎水性の基材またはキャリア材料にて形成され、この膨潤可能な性質によって、血液に接触すると通気孔に密閉機能が与えられる多孔質栓か、

・艶消し仕上げ，微小寸法の通路，レーザー穿設孔，曲りくねった通路、多孔質材料によって設けられるか、または穴，間隙または通路が空気を通すには充分に大きいが、血液の漏洩を防ぐためには充分に小さい、例えばコードにおけるシール面の間に設けられる通気孔か、

・例えば通気孔を塞ぐ凝固および／または細胞の膠着による生物学的現象を利用し、血液と接触すると塞がる多孔質栓か、

・水性流体と接触して膨潤することにより、通気孔を密閉する超吸収性材料か、または

・逆止め弁：例えば通気孔を覆うプラスチックフィルムなどの薄いフラップ，ゴムまたはダックビル型弁の如き変形可能なシール，または通気孔を覆う変形可能なラップ

の何れかまたはこれらの組み合せを含むことができる。

【0031】

好ましくは、多孔質栓は、カルボキシメチルセルロース（ＣＭＣ）またはポリアクリレートなどの親水性材料によって被覆されるか、含浸させられるか、またはこれを含む高密度ポリエチレン（ＨＤＰＥ）などの疎水性材料にて形成される。代わりの疎水性材料として、これに限定されるものではないが、ポリテトラフルオロエチレン（ＰＴＦＥ），超高分子量ポリエチレン（ＵＨＭＰＥ），ナイロン６，ポリプロピレン（ＰＰ），ポリビニリデンフルオライド，またはポリエーテルスルホン（ＰＥＳ）が挙げられる。次にさらに詳細に説明されるように、本発明の通気媒体は、通気機構および装置に好適なものとして、艶消し仕上げされた１つ以上の微小寸法の通路，レーザー穿設孔，通気可能なコード，超吸収性逆止め弁，または他の手段、あるいはこれらの任意の組み合せを代わりに用いることができる。このように、例えば栓などの任意の特定な通気媒体についてここで述べているが、これらに限定するものではなく、他の通気媒体の適当な部材も含むことを意図している。

【0032】

通気媒体の一実施形態は、外壁に形成された微小寸法の孔からなる。これらの孔は空気を通すには充分に大きいが、血液の漏洩を阻止するには充分に小さい。この通気孔は、１つの孔を含む任意の数でよいが、信頼性のある機能のためには複数の孔が好ましい。これらの孔は、レーザーにて穿孔され、即ちこれらは１本以上のレーザービームを用いて壁を焼き切って貫通形成される。基板は普通の材料でよいが、薄いプラスチックフィルムが好ましい。通気機構は前述のように逆止め弁を含むことができる。この通気機構は注射器側または患者側カニューレ，ハブ，または付加された構成部品内の流体通路に沿った都合のよい任意の空間に設けられるが、管の全長に亙ってフラッシュを発生させるには、基端に設けられるのが好ましい。

【0033】

血液と接触すると生物学的現象によって密閉される多孔質栓は、例えば焼結プラスチック，セラミック，または金属の如き多孔質材料を用いるか、あるいは通気可能なコードを用いるか、または部品間の小さな孔や空間に生物学的薬剤を配置することによって用いることができる。この通気孔は従来からある任意の形状であってよい。通気は流体通路の任意の位置（単数および複数）で行われるが、採取装置に近いハブなどの基端が好ましい。通気孔は、凝固しおよび／または固まった細胞が通気孔を通過する流れを阻止するように、血液と相互作用して凝血および／または細胞の膠着を促進する刺激剤で作られ、これを含み、これと隣接し、またはこれと協同することが好ましい。凝血刺激剤の一例は、シリカ，破砕ガラス，またはガラス繊維である。膠着剤の一例はレクチンである。血小板賦活剤の一例はコラーゲンまたはトロンビンである。プロトミンスルフェートなどの抗凝固剤のための中和剤が含まれていてもよい。生物学的刺激剤は、粉末，溶液，懸濁液，スラリー，または他の形状として、都合の良い任意のプロセスを用いて付与することができる。これは乾燥、または真空凍結乾燥したものであってよい。

【0034】

当業者であれば本発明の範囲や精神から逸脱することなく、種々の他の変更や修正を行うことが可能であり、これらの変更や修正は、すべて本発明の範囲に入るものとして意図されるものである。

【図面の簡単な説明】

【0035】

【図1】血液採取針アセンブリの斜視図である。

【図2】本発明の血液採取針アセンブリの別の実施形態の断面図である。

【図3】図２と同様な側断面図であるが、本発明の別の実施形態を示している。

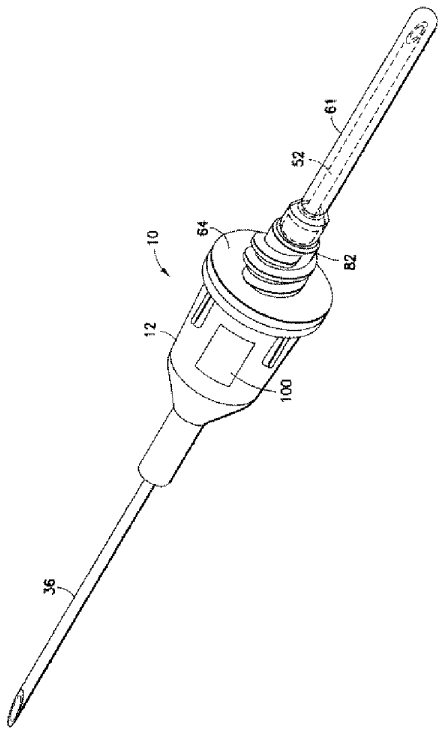
【図4A】図２と同様な側断面図であるが、本発明の別の実施形態を示している。

【図4B】図４Ｂの側面図である。

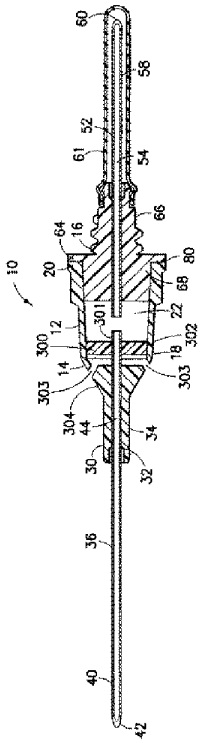
【図4C】Ｒ－Ｒの方向から見た図４ＢＡの正面図である。

【図5】血液採取針アセンブリの一実施形態の断面図である。
【図6】図５と同様な断面図であるが、本発明の別の実施形態を示している。
【図7】図５と同様な断面図であるが、本発明の別の実施形態を示している。
【図8A】図５と同様な断面図であるが、本発明の別の実施形態を示している。
【図8B】Ｘ－Ｘの方向から見た図８Ａの正面図である。
【図9A】図５と同様な断面図であるが、本発明の別の実施形態を示している。
【図9B】Ｙ－Ｙの方向から見た図９Ａの正面図である。
【図10A】図５と同様な断面図であるが、本発明の別の実施形態を示している。
【図10B】領域Ｚから見た図１０Ａの拡大図である。
【図11】血液採取針アセンブリの一実施形態の断面図である。
【図12】血液採取針アセンブリの一実施形態の断面図である。
【図13】血液採取針アセンブリの一実施形態の断面図である。
【図14】血液採取針アセンブリの一実施形態の断面図である。
【図15】血液採取針アセンブリの一実施形態の断面図である。
【図16】血液採取針アセンブリの一実施形態の断面図である。
【図17】通気可能なコードの一実施形態の断面図である。
【図18】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図19】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図20】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図21】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図22】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図23】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図24】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図25】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図26】図１７と同様な断面図であるが、本発明の別の実施形態を示している。
【図27A】血液採取針アセンブリの一実施形態の断面図である。
【図27B】領域Ｒから見た図２７Ａの拡大図である。
【図28】血液採取針アセンブリの一実施形態の断面図である。

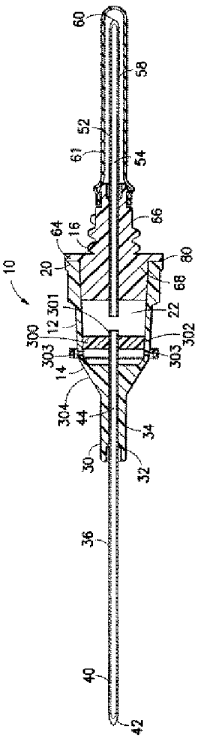
【図1】


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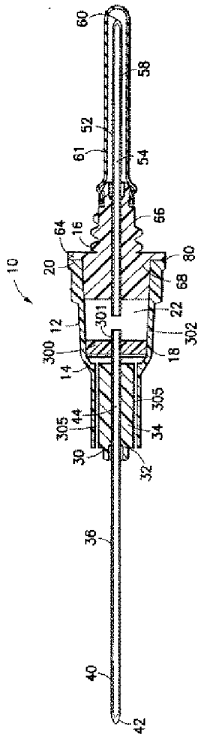
【図2】


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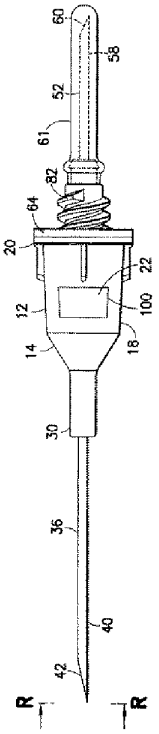
【図3】


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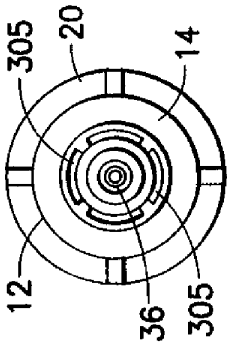
【図4A】


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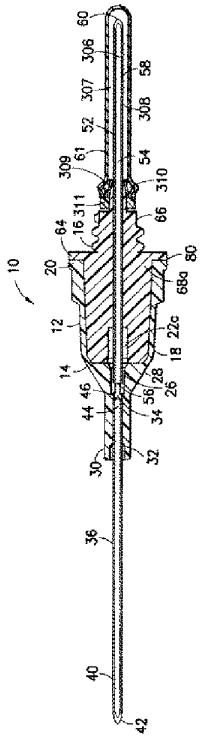
【図4B】


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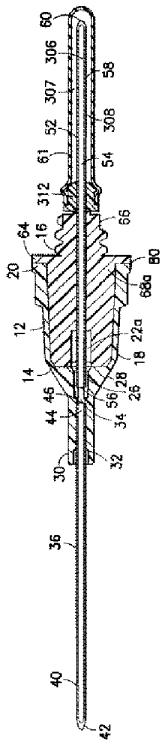
【図4C】


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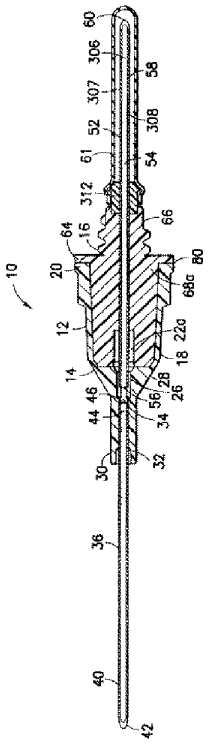
【図5】


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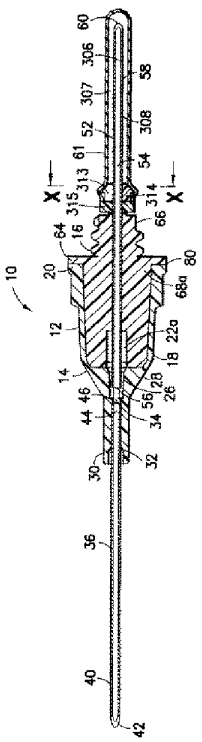
【図6】


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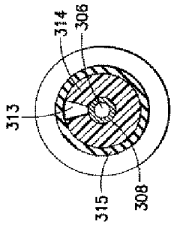
【図7】



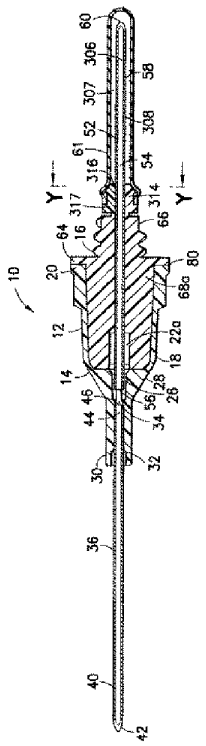
【図8A】



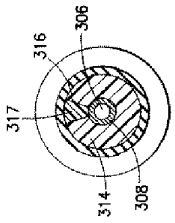
【図8B】



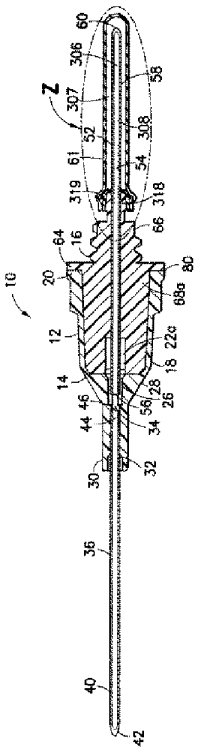
【図9A】



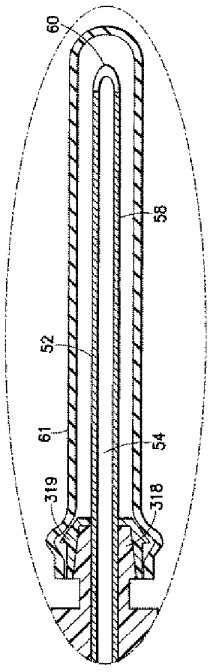
【図9B】



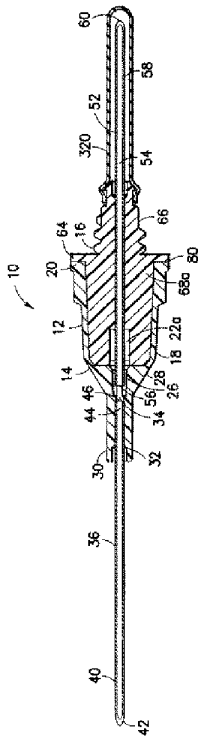
【図10A】



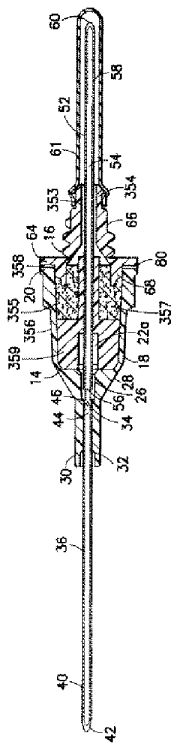
【図10B】



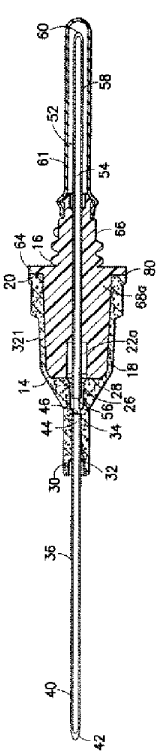
【図11】



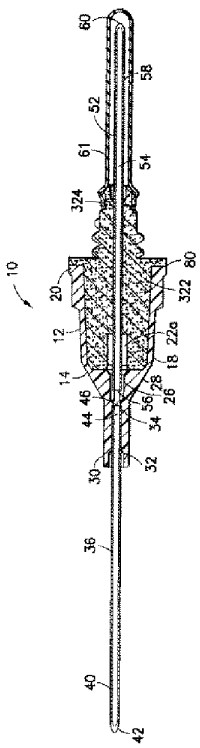
【図12】



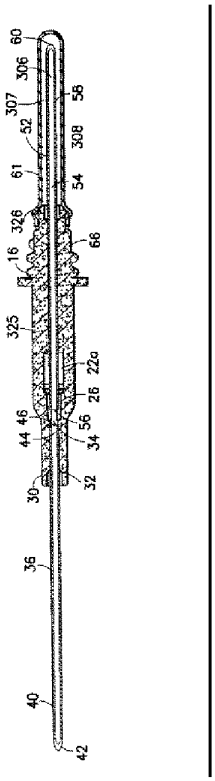
【図13】



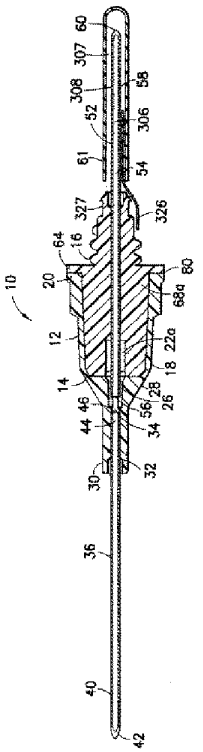
【図14】



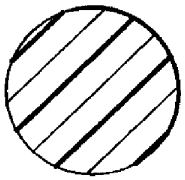
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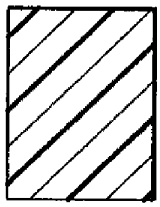
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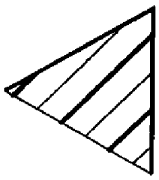
【図17】



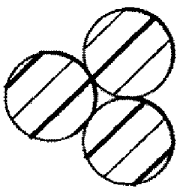
【図18】



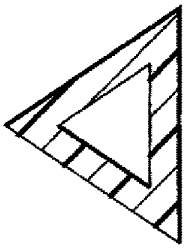
【図19】



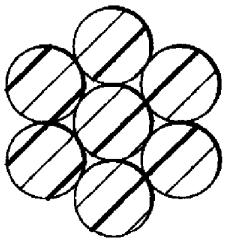
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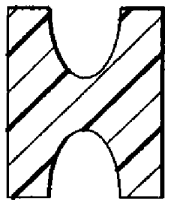
【図21】



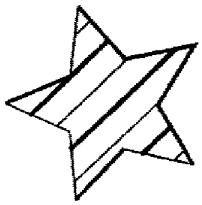
【図22】



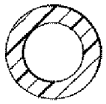
【図23】



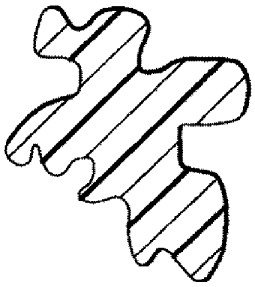
【図24】



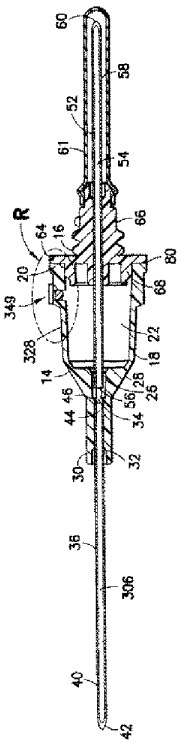
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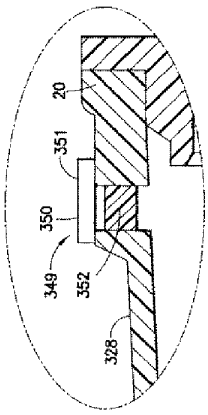
【図26】



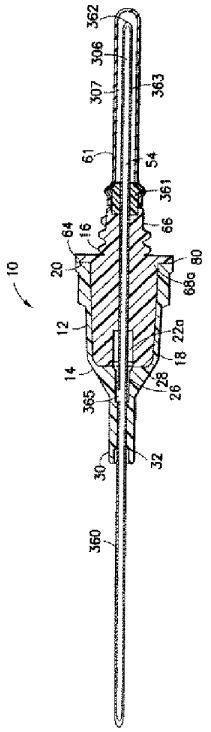
【図27A】



【図27B】



【図28】


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アメリカ合衆国　０７０４５　ニュージャージー州　モントビル　エインズレー　コート　２０
Ｆターム(参考) 4C038 TA06 UJ02
4C066 AA09 BB01 CC01 DD06 FF05 GG12 GG15 KK05 KK06

【外国語明細書】
2005349196000001.pdf

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5736-PCT	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 2015/035870	International filing date *(day/month/year)* 15 June 2015 (15.06.2015)	(Earliest) Priority Date *(day/month/year)* 13 June 2014 (13.06.2014)
Applicant GARRET, Chad et al.		

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. 1

☒ 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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2015/035870

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/15 *(2006.01)*
A61M 25/01 *(2006.01)*
G01N 33/48 *(2006.01)*

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 5/15, A61M 5/19, 25/01 G01N 33/48

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)

PatSearch, Espacenet, USPTO, Google

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 2013/082301 A1 (TELEFLEX MEDICAL, INC.) 06.06.2013 claims, [0006]-[0008], [0037], [0041], [0044]-[0054], fig. 1-5	1-9 10-13, 15-16, 18-19
Y	JP 2009131273 A (CSL BEHRING GMBH) 18.06.2009 abstract	10-13
X Y	EP 2593169 A1 (BECTON DICKINSON CO) 22.05.2013 abstract, [0006]-[0013]	14, 17 15-16, 18-19

☐ 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
19 October 2015 (19.10.2015)	05 November 2015 (05.11.2015)

Name and mailing address of the ISA/RU:	Authorized officer
Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	E. Kazak Telephone No. 8 (495) 531 64 81

Form PCT/ISA/210 (second sheet) (January 2015)

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

To:
HARMS, Donn K.
12702 Via Cortina, Suite 100
Del Mar, CA 92014
United States of America

Date of mailing *(day/month/year)* 05 November 2015 (05.11.2015)	
Applicant's or agent's file reference 5736-PCT	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 2015/035870	15 June 2015 (15.06.2015)	13 June 2014 (13.06.2014)

International Patent Classification (IPC) or both national classification and IPC
A61B 5/15 *(2006.01)*
A61M 25/01 *(2006.01)*
G01N 33/48 *(2006.01)*

Applicant
GARRET, Chad et al.

1. This opinion contains indications relating to the following items:

- [X] 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
- [X] 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/RU:	Date of completion of this opinion	Authorized officer
Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37	19 October 2015 (19.10.2015)	E. Kazak Telephone No. 8 (495) 531 64 81

Form PCT/ISA/237 (cover sheet) (January 2015)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 2015/035870

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established 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)).

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 filed or furnished:
   - 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 in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 2015/035870

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	10-13, 15-16, 18-19	YES
	Claims	1-9, 14, 17	NO
Inventive step (IS)	Claims		YES
	Claims	10-13, 15-16, 18-19	NO
Industrial applicability (IA)	Claims	1-19	YES
	Claims		NO

2. Citations and explanations:

D1 - WO 2013/082301 A1
D2 - JP 2009131273 A
D3 - EP 2593169 A1

D1 can be regarded as the closest prior art of test component for blood according to claim 1.

D1 (claims, [0006] - [0008]) discloses a substrate configured to generate a visually discernable reaction to the presence or a threshold level of a substance in said blood; said substrate adapted for positioning in a fluid communication pathway carrying blood from a flash chamber defined by a surrounding sidewall of a housing of an introducer; and said substrate generating said visually discernable reaction viewable by a user of said introducer, subsequent to a fluid communication of said blood from said flash chamber to said substrate.

Thus, the invention according to claim 1 does not meet the criterion of novelty.

D3 can be regarded as the closest prior art of the inventions according to independent claims 14, 17.

D3 (abstract, [0006] - [0013]) discloses an introducer for the introduction of a catheter into the vein or artery of a patient: said introducer having a needle in axial communication between a distal end and a flash chamber with a housing of said introducer; a testing substrate within a substrate housing, said substrate housing in a fluid communication with said flash chamber through a passage in a sidewall of said flash chamber; said testing substrate configured to generate a visually discernable result, to a substance contained within blood communicated through said needle to said flash chamber; and said testing substrate viewable through a cover of said substrate housing, whereby said user can concurrently introduce a catheter to a patient and view test results for the presence of said substance with said blood from said patient communicated to said flash chamber.

D3 (abstract, [0006] - [0013]) discloses a method of testing a patient's blood for a substance comprising the steps of: placing a substrate having a visually discernable reaction area thereon to a said substance, in a fluid communication with a flash chamber of an introducer employed for the insertion of a catheter into the vein or artery of a patient; puncturing the vein or artery of said patient with a needle engaged to said introducer; allowing blood from said vein or artery to communicate axially through said needle to a flash chamber in said introducer; allowing a portion of said blood to fluidly communicate with said substrate; and viewing said substrate to ascertain said visually discernable reaction.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of V:

Thus, the inventions according to independent claims 14, 17 do not meet the criterion of novelty.

The features of dependent claims 2-4, describing the fluid communication being through the microporous membrane disposed within the flash chamber, are disclosed in D1 ([0037], [0041], [0044], [0054]).

The features of dependent claims 5-6, indicating that positioned within a chamber of a substrate housing, said housing being engageable with an exterior of said sidewall of said substrate housing; and said fluid communication to said substrate communicating through an aperture in said sidewall , are disclosed in D1 ([0054]).

The features of dependent claims 7-9, indicating that substrate housing having a transparent cover in an engagement with a base having a passage aligned with said aperture in said sidewall; and providing for visually discernable reaction are disclosed in D1 ([0054], fig.1-5).

Thus, the invention according to dependent claims 2-9 does not meet the criterion of novelty.

The features of dependent claims 10-13, indicating that a clotting factor on or adjacent to said separation membrane generating a cessation of said fluid communication through said separation membrane subsequent to a duration of time sufficient to clot said blood at said separation membrane are disclosed in D2 (abstract).

The features of dependent claim 15 indicating that a separation membrane interposed between said flash chamber and said substrate: and said separation membrane allowing only blood plasma from said portion of blood therethrough to a said fluid communication with said substrate are disclosed in D1 ([0044], [0054]).

The features of dependent claim 16, indicating a plurality of said testing substrates, each located within separate said substrate housing, each said substrate housing in a fluid communication with said flash chamber through a passage in a sidewall of said flash chamber are also disclosed inD1 ([0044], [0054]).

The features of dependent claims 18, 19, indicating a visually discernable reaction area of substrate positioned in substrate housing are disclosed in D1 ([0044]).

Thus, the invention according to dependent claims 10-13, 15, 16, 18, 19 does not meet the criterion of inventive step.

The inventions according to claims 1-19 meet the criterion of industrial applicability.

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

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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

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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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DISPOSABLE, CLOSED BLOOD SAMPLING SYSTEM FOR USE IN MEDICAL CONDUIT LINE

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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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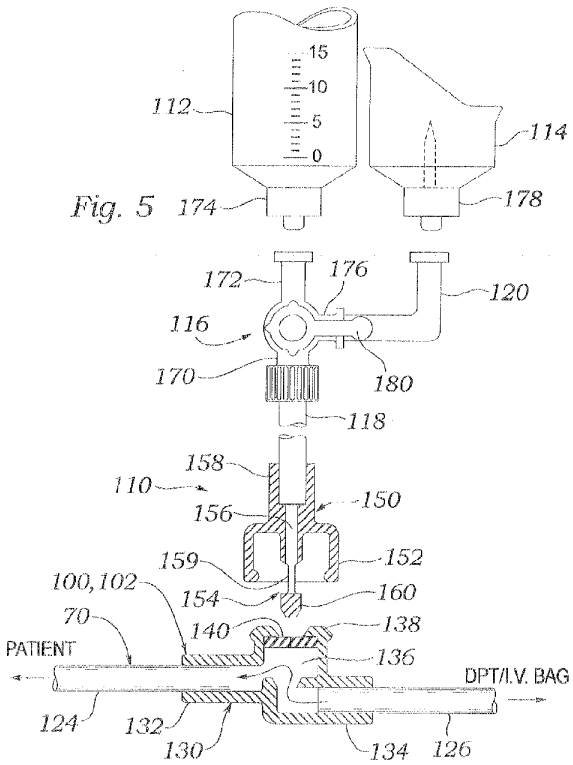


Fig. 5

(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.

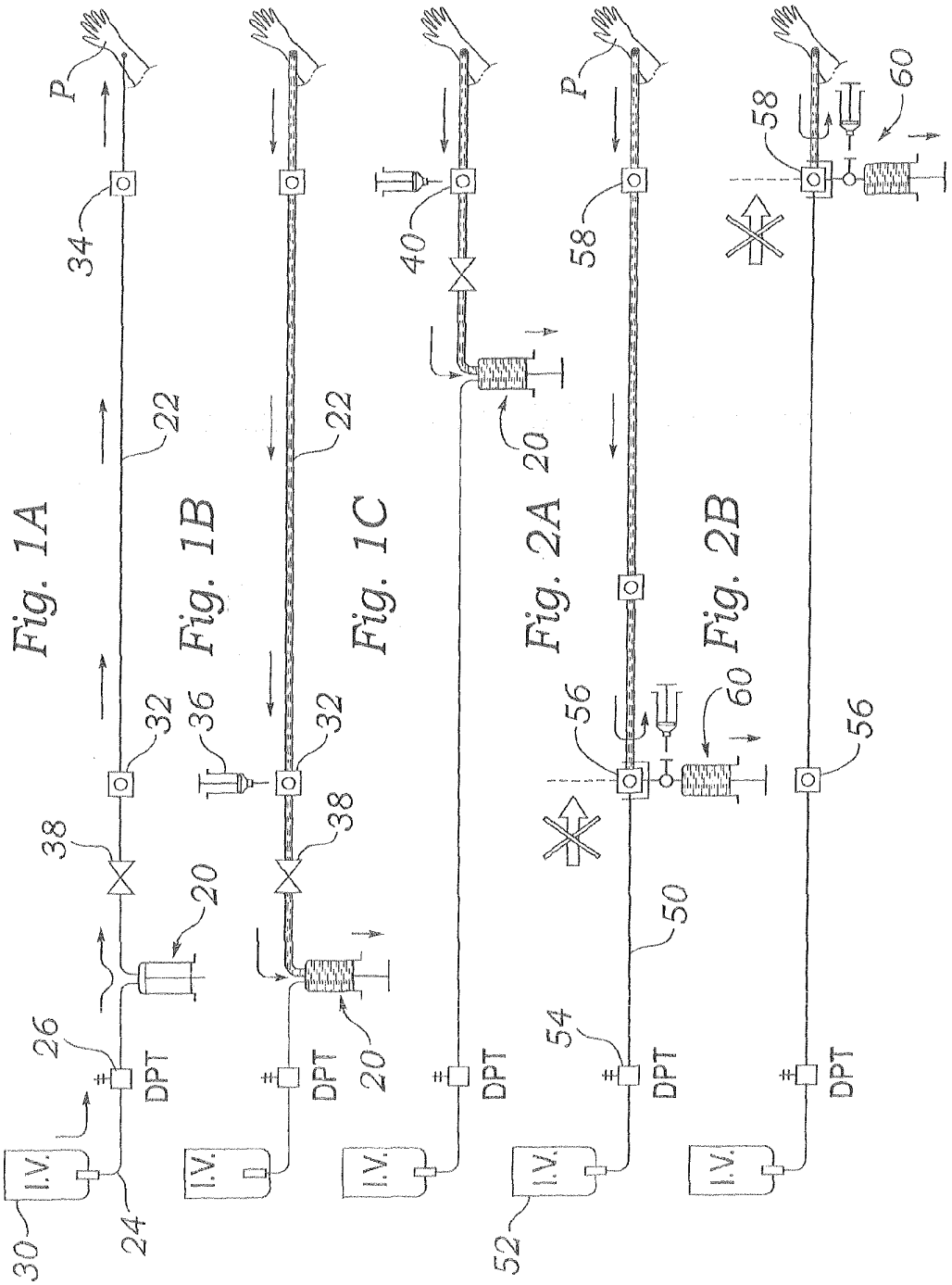
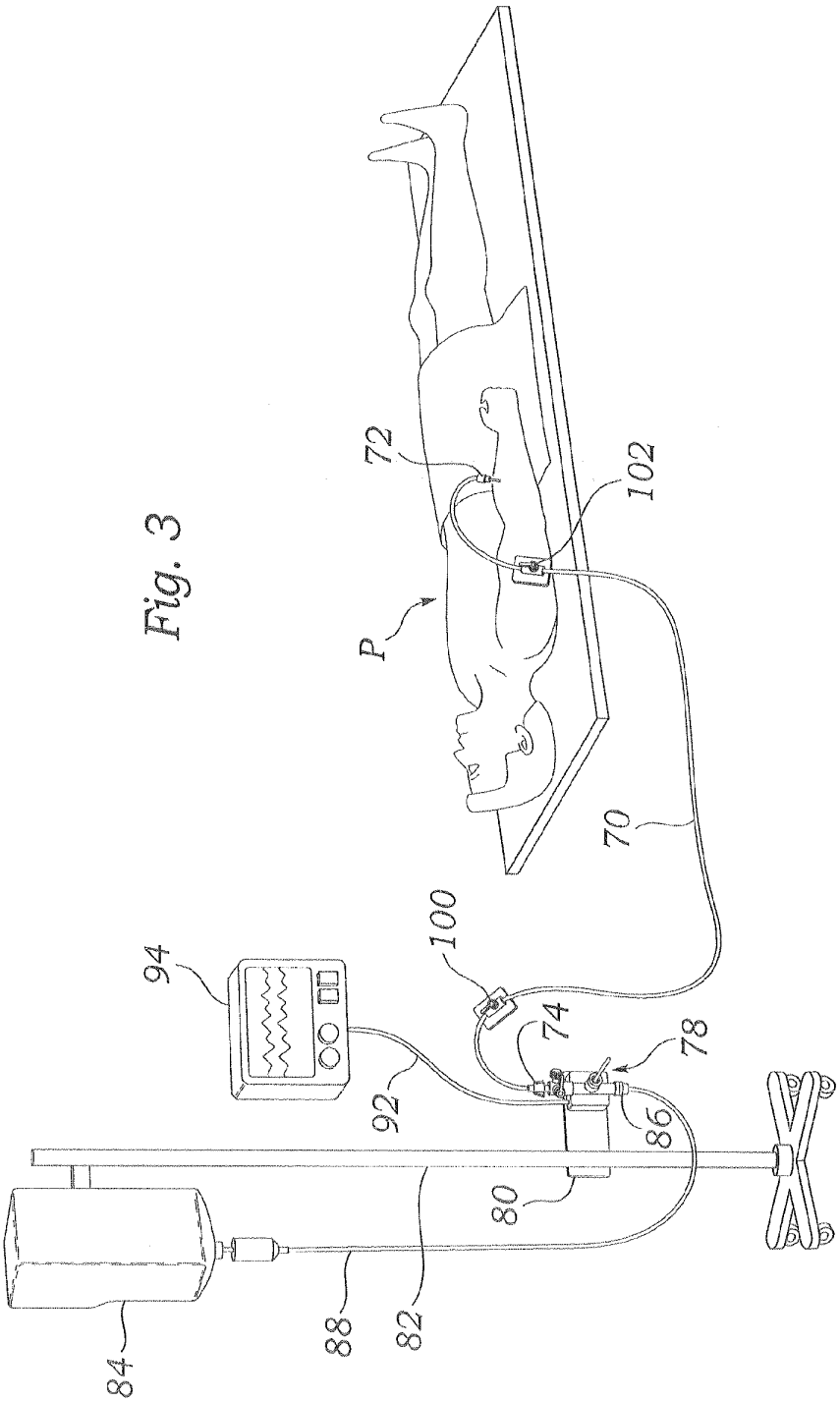

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Fig. 1A
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Fig. 1B
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Fig. 1C
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Fig. 2A
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Fig. 2B

Fig. 3



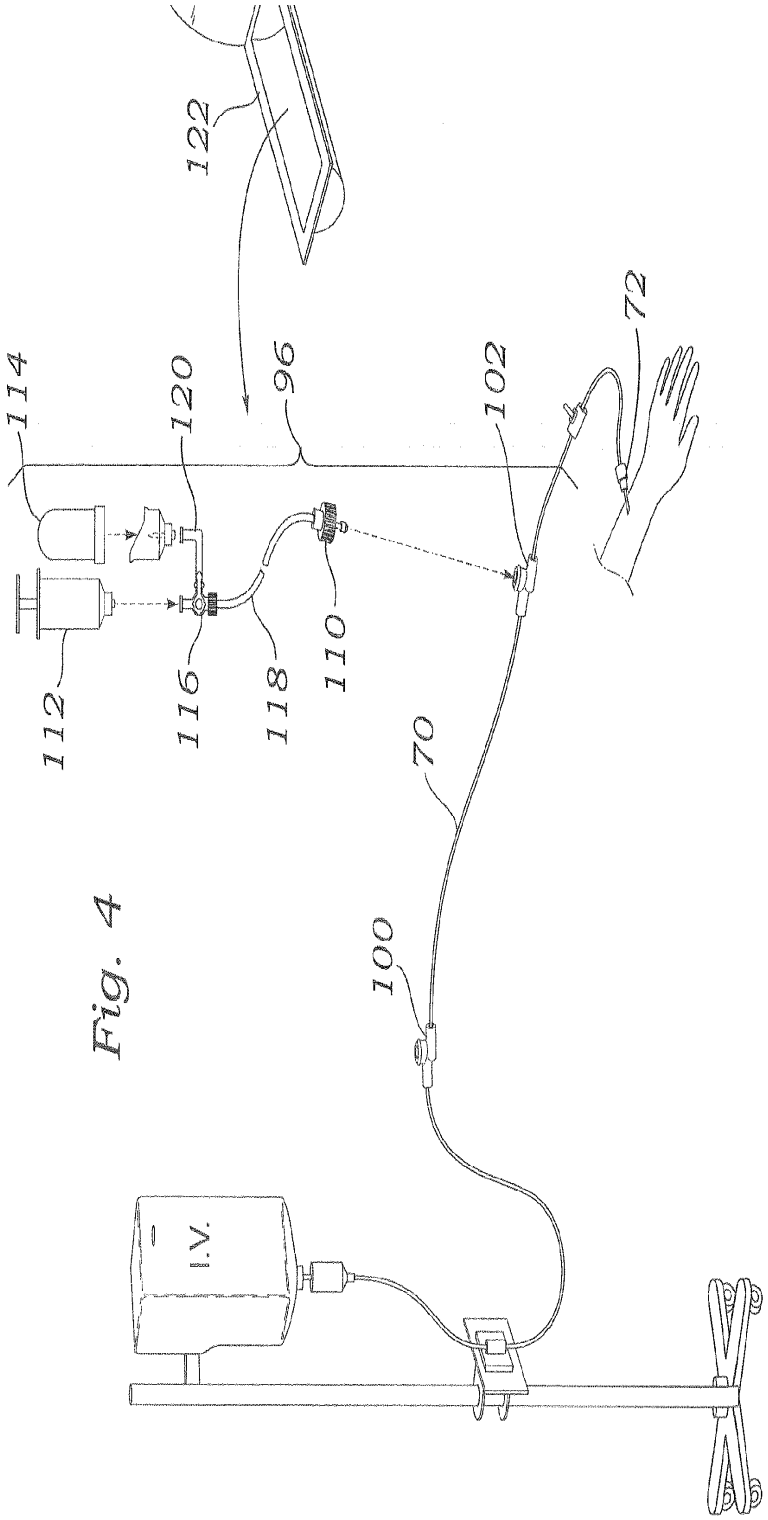


Fig. 4

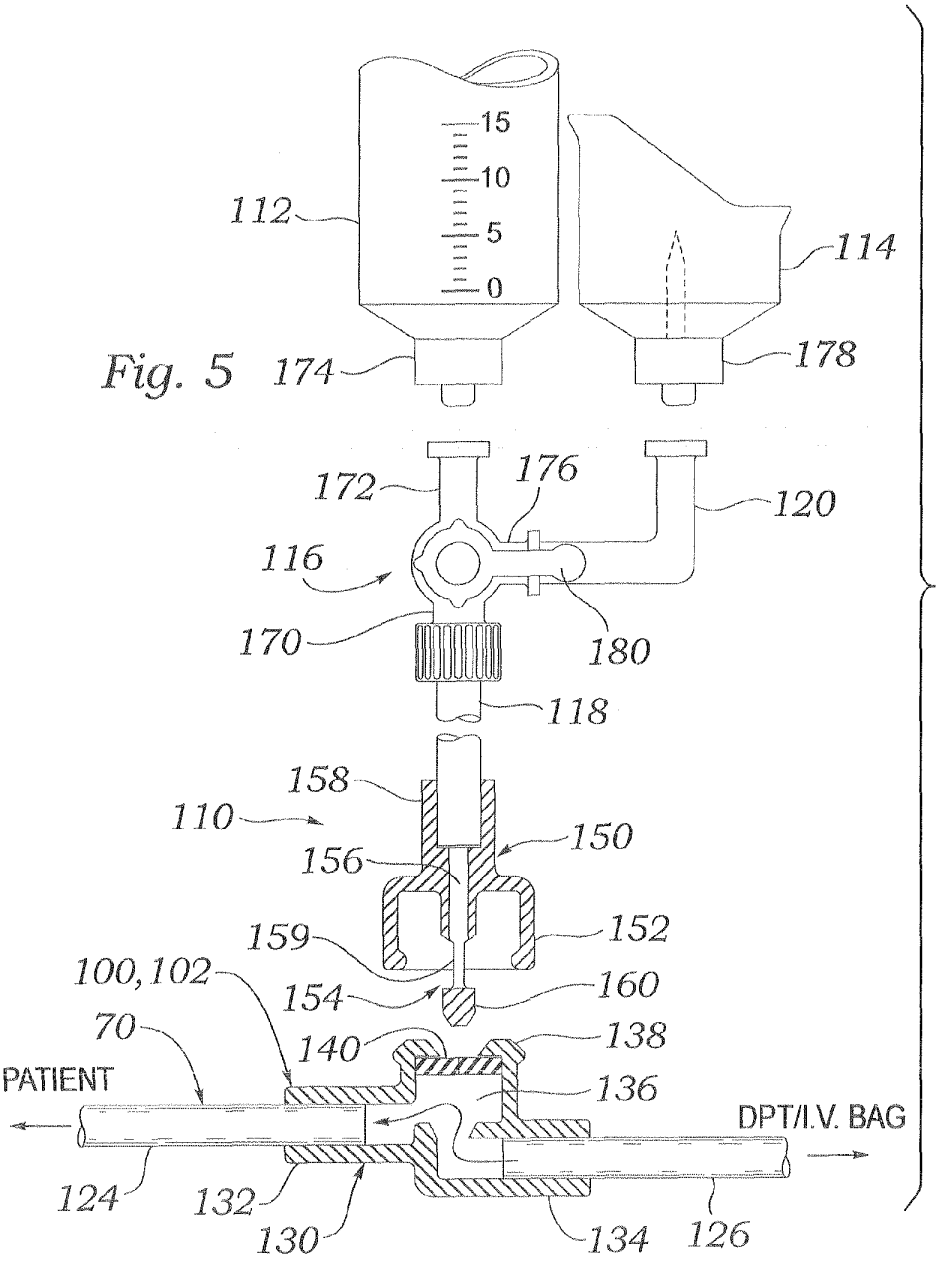

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Fig. 5

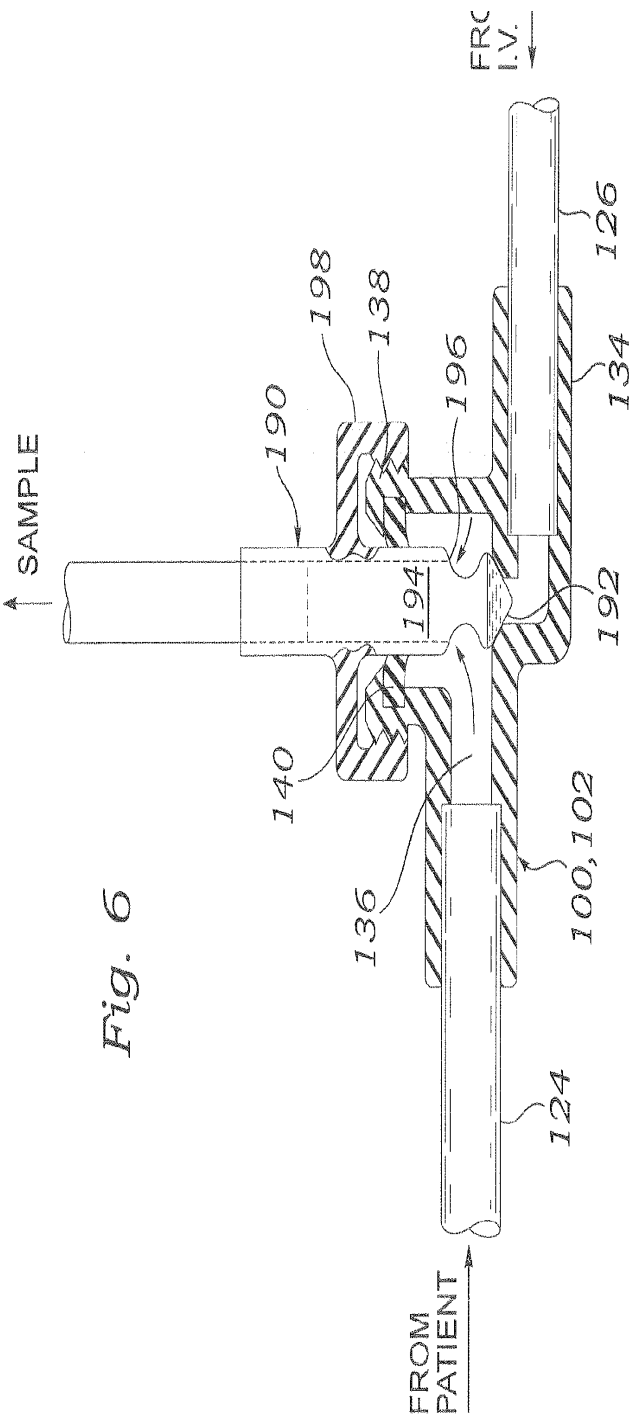

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Fig. 6

Fig. 7A

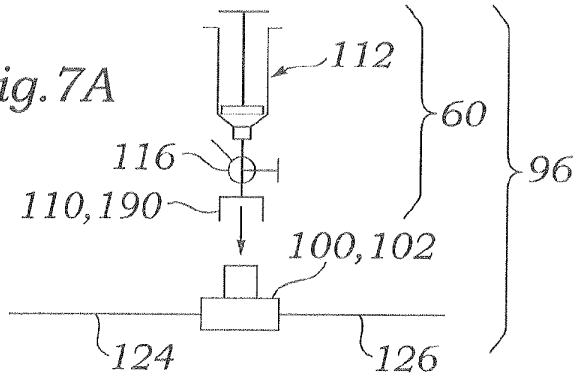


Fig. 7B

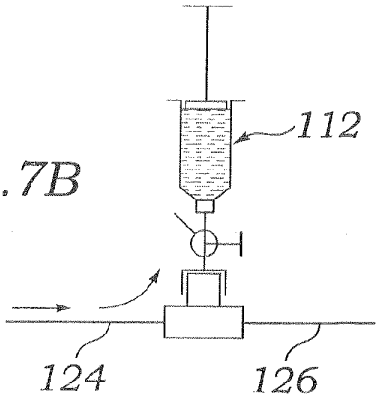


Fig. 7C

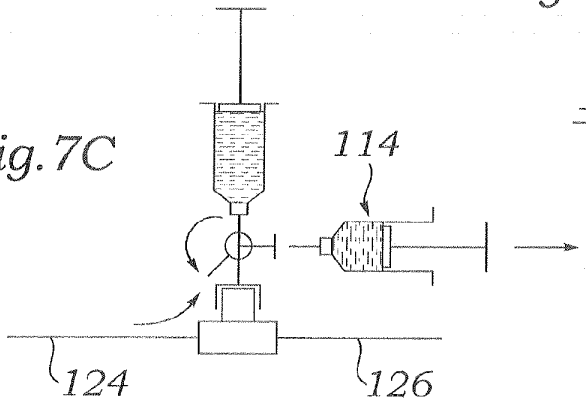


Fig. 7D

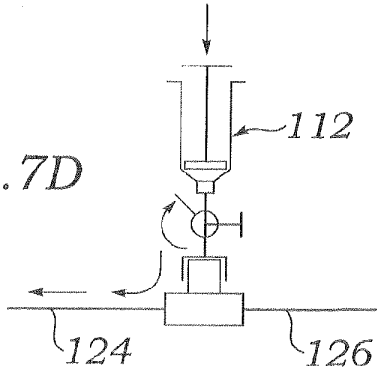


Fig. 7E

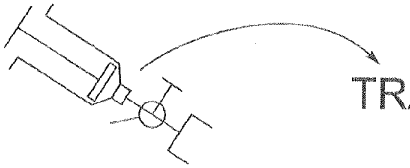




Fig.9A

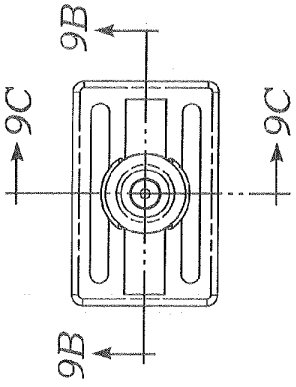


Fig.8B

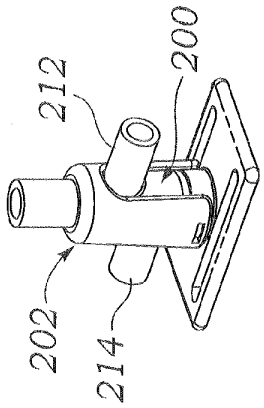


Fig.8A

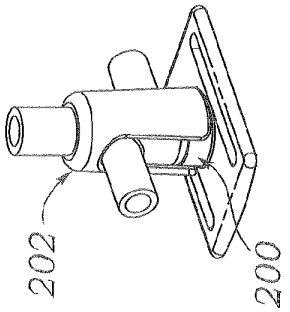


Fig.9C

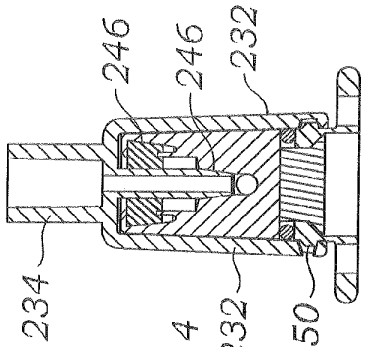


Fig.9B

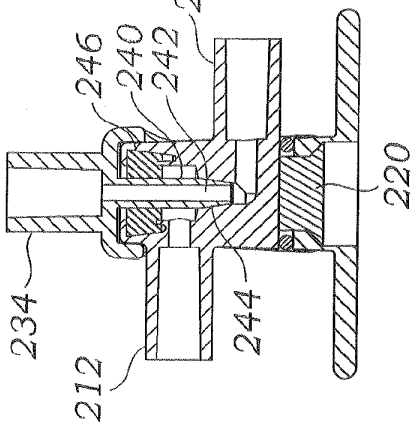


Fig.8C

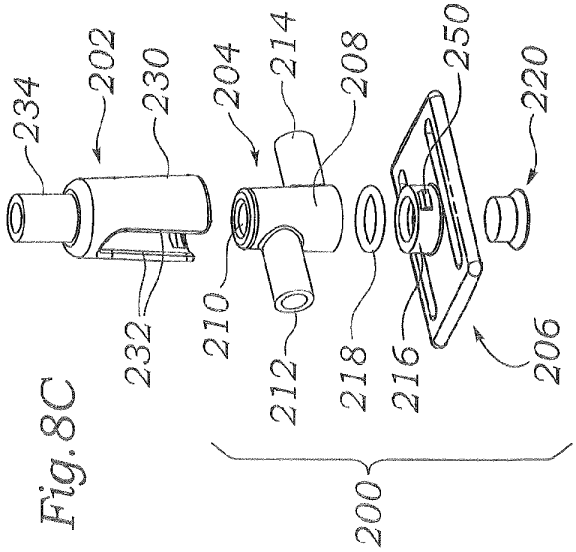


Fig. 10

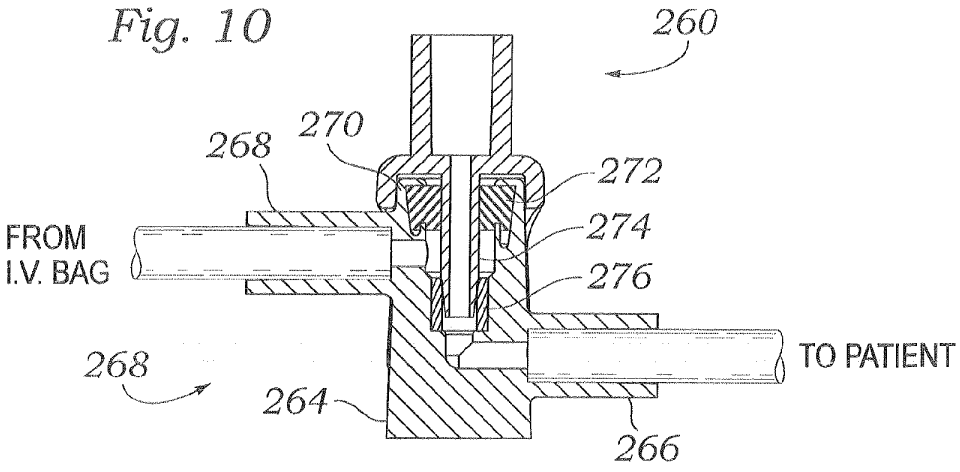

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Fig. 11

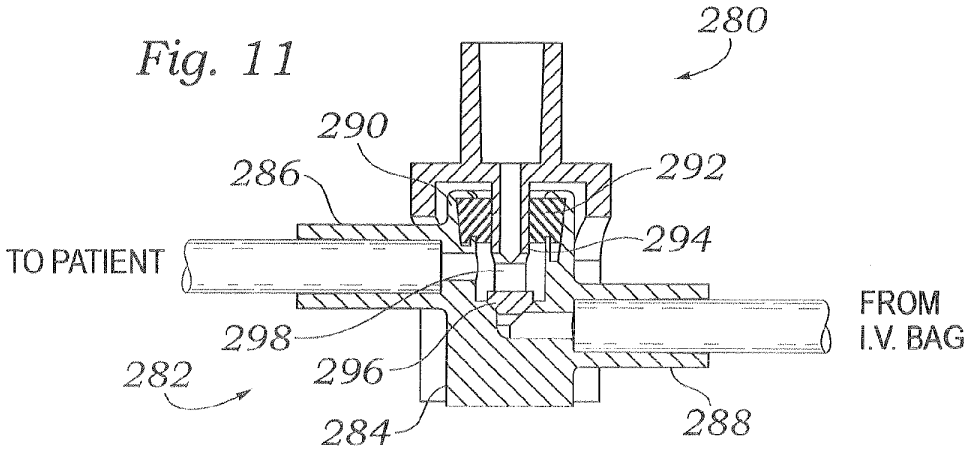

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Fig. 12A

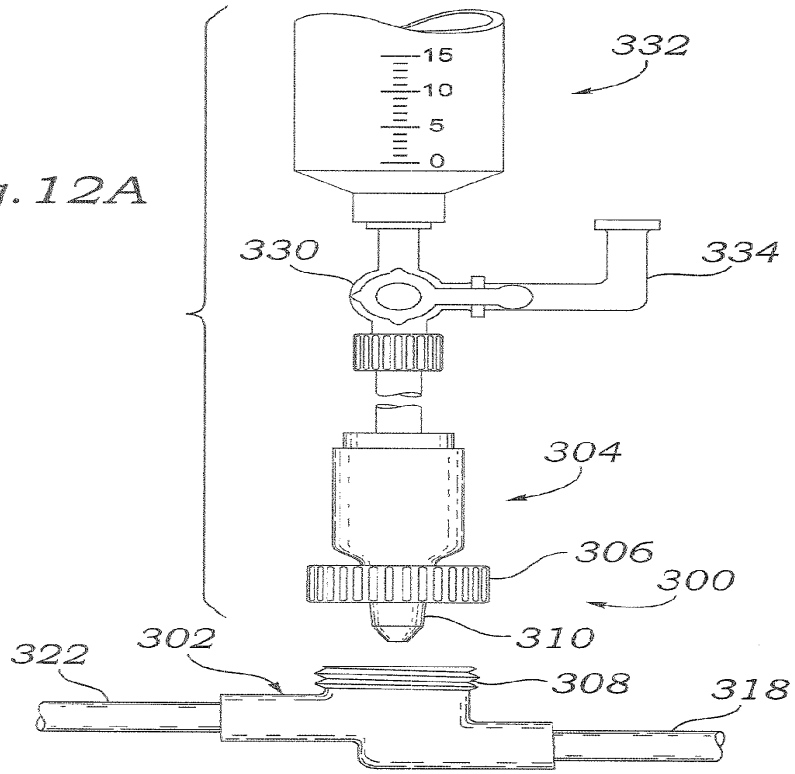
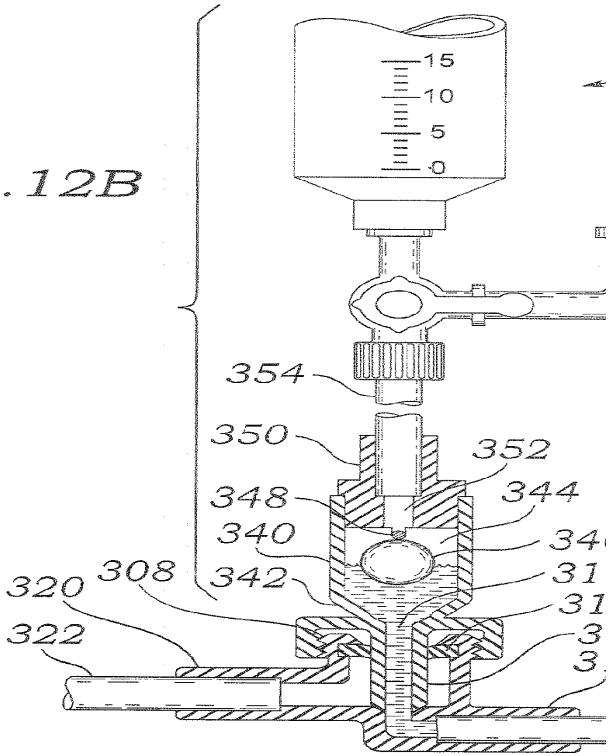


Fig. 12B



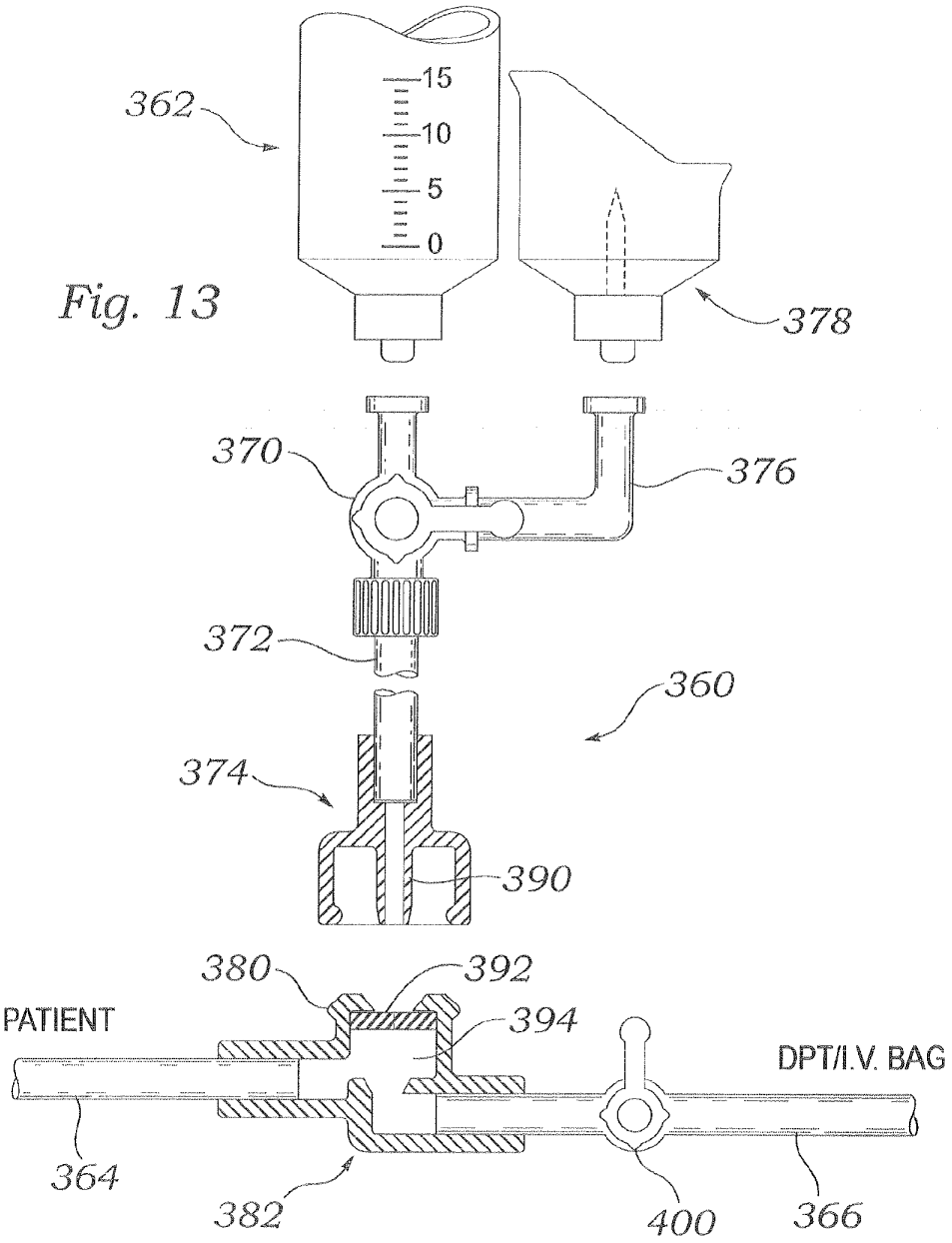

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Fig. 13

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
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		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)

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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:

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(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Published patent publication (A)
(11) [Publication number] Tokuhyo 9-504726
(43) [Publication date] 1997 (1997) May 13
(54) [Title of invention] Closed system blood sampling device
(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
[Total number of pages] 11
(21) [Application number] Japanese Patent Application No. Hei 8-508283
(86) (22) [Filing date] August 22, 1995
(85) [Translation submission date] April 10, 1996 (
86) [International application number] PCT/US95/10702
(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
(33) [Country claiming priority] United States)
(81) [Designated country] EP (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, S
E), AU, CA, JP (71
)) [Applicant]
[Name] Baxter International, Inc.
(72) [Inventor]
[Name] Desekie, Vincent, Shi
(72) [Inventor]
[Name] Browne, Glennie
(74) [Attorney]
[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.

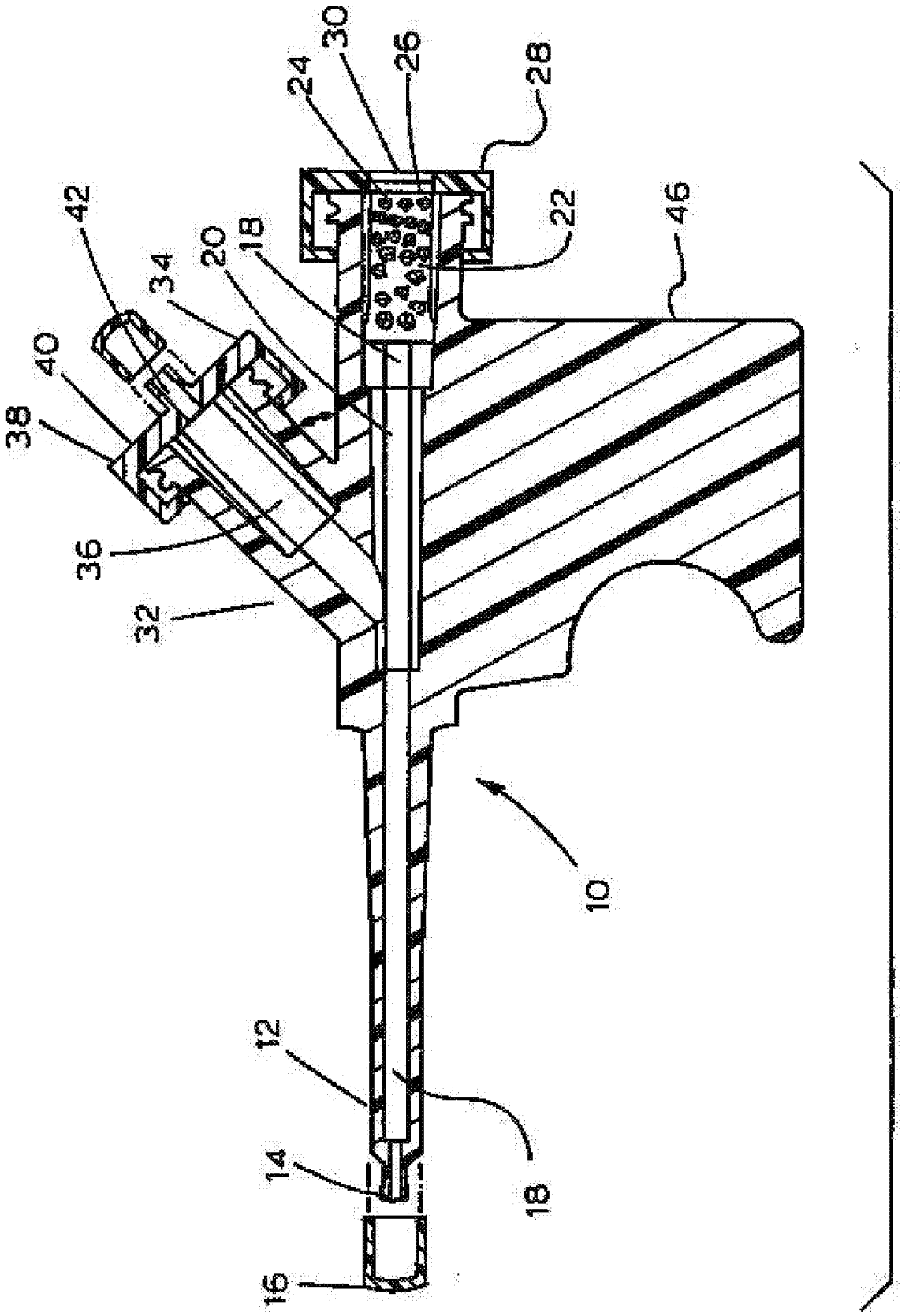


FIG. 1

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]

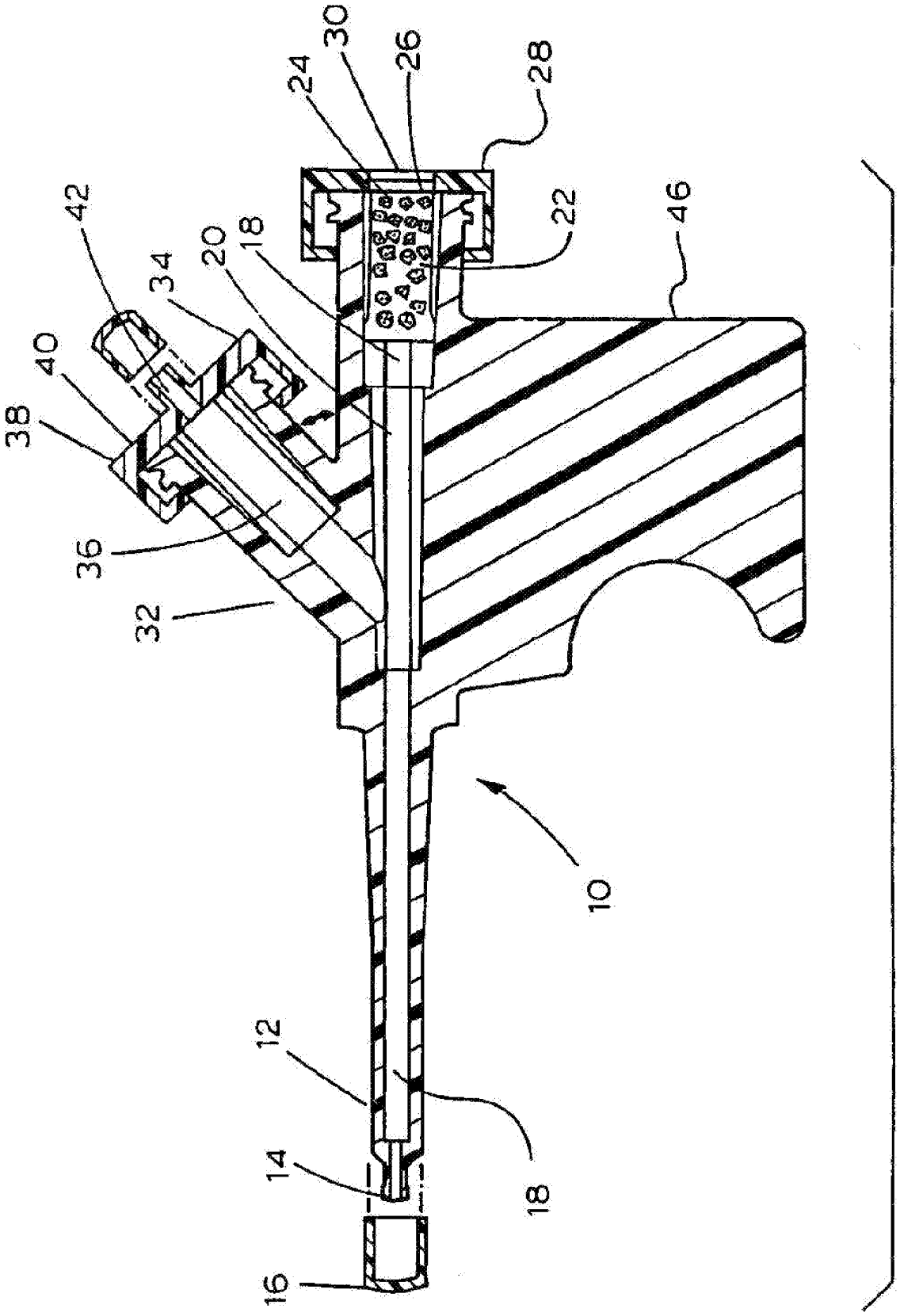


FIG. 1

[Figure 2]

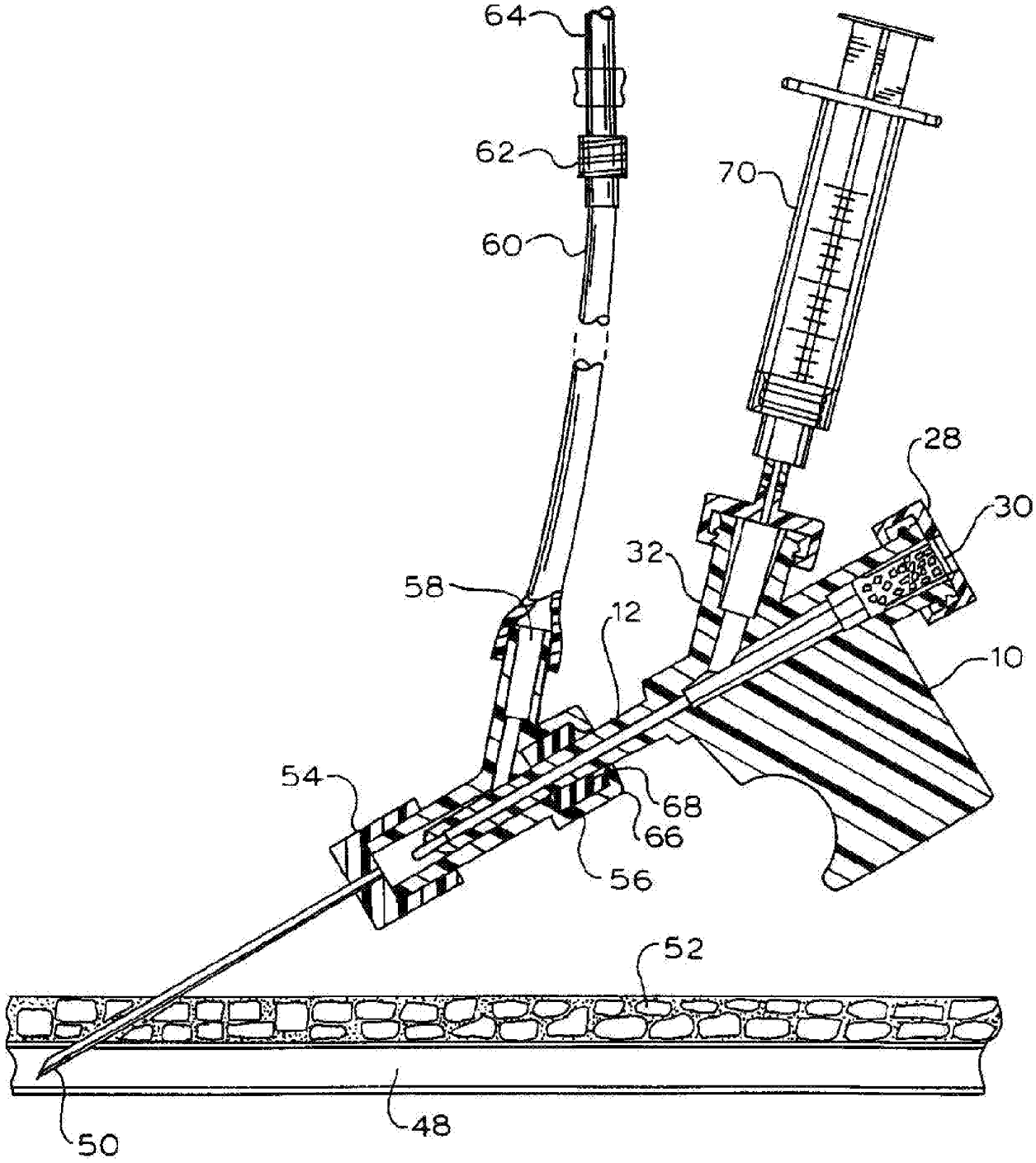


FIG. 2

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

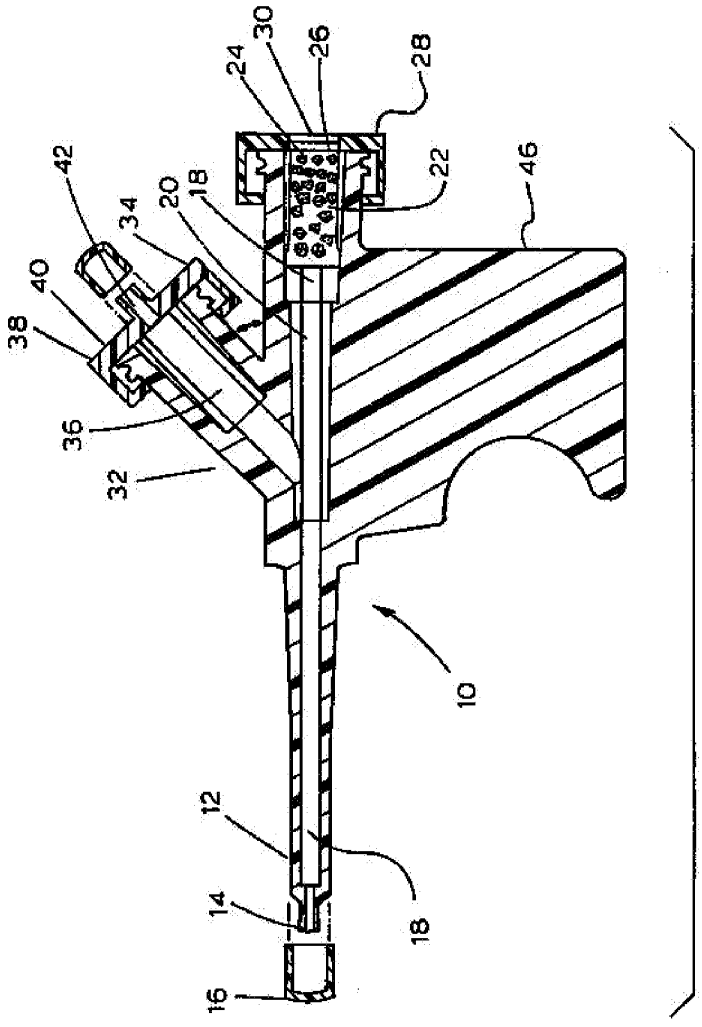


FIG. 1

Representative drawing

1 / 1 display

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(P0200)

Bibliographic data: JPH09504726 (A) — 1997-05-13

CLOSED SYSTEM BLOOD SAMPLING DEVICE

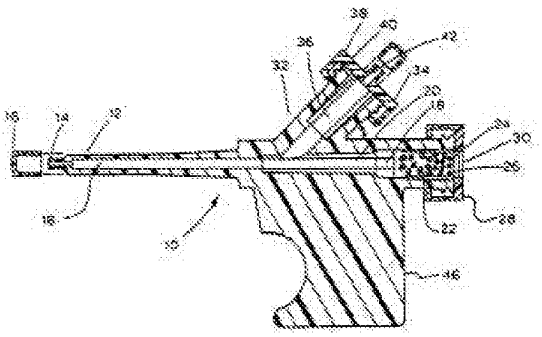
Inventor(s):

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

特表平9－504726

(43)公表日　平成９年(1997)５月13日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ	
Ａ６１Ｂ　5/14	３００	0277－2Ｊ	Ａ６１Ｂ　5/14	３００Ｊ

審査請求　未請求　　予備審査請求　未請求(全 11 頁)

(21)出願番号　特願平8－508283
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(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
(87)国際公開番号　ＷＯ９６／０５８７５
(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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アメリカ合衆国60089イリノイ、バッファローグロウブ、ヒドゥンレークドライブ944
(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。

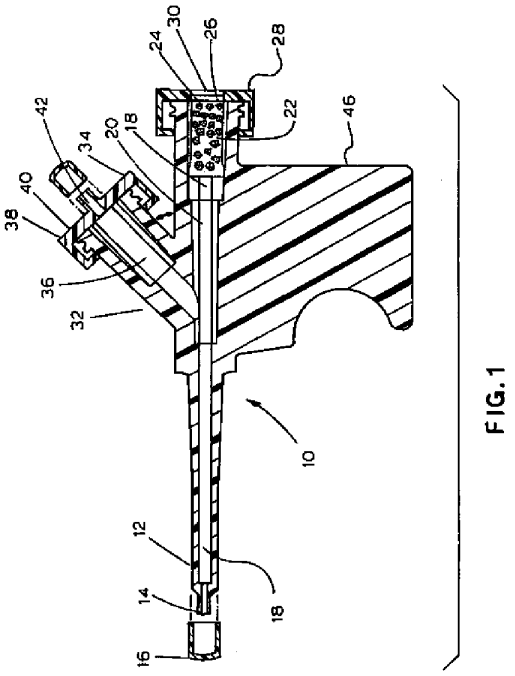


FIG. 1

【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０12ccであるかもしれず、そして血液廃棄室 22の液体容積は約０06cc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５188 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５188 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５300 034中に記述されている。この特許も同じく、この発明の実施中で使用される好まし

い注射部位を記述するおびただしい数の刊行物及び参照文献を詳しく述べている。この特許及びその中に挙げられた刊行物も同じく参照によってここに導入される。

注射部位56はＴ字形コネクター58と連結され、Ｔ字形コネクター58が今度は、雌のルアー継手62を通じて静脈内ライン64へと連結される微細穴チューブと連結される。注射部位56の先端側末端は静脈穿刺装置50の首54へと連結されている。注射部位56の根元側末端66は、該注射部位中へぴったり嵌合するように寸法が与えられた、血液抜取りカニューレ12を受け入れるよう適合させた、予めスリットを入れてある、弾力性のある、再シールする隔壁68と連結されている。第二の枝又はポート32中へと挿入されているのは、ツベルクリン血液吸引注射器のような慣用の注射器70又は動脈血ガス損失抵抗性注射器である。

装置のカニューレ12は、注射部位56の隔壁68を貫通して挿入され、そしてカニューレ12の先端14が静脈穿刺装置に隣接した注射部位中へと完全に挿入されるように配置されるであろう。そのように実施すると、実際のＴ字形ハウジングの残余の体積が血液吸引体積中から、測定可能な要素としては除かれるであろう。動脈圧が、血液をして毛細管作用を通じて該装置へと入りそして該装置を流れ登らせるであろう。血液が該装置の疎水性薄膜30へと上昇するにつれて、空気が上流の疎水性の薄膜30を通して散逸するであろう。該カテーテル中に最初に存在した元々の血液は、該装置中における保持及び最終的な廃棄のためにルアー継手分岐を通り越して押し上げられるであろう。該装置は、血液が満たされた管腔の視覚的確認が形成されるとすぐにＴ字形コネクターから引き抜かれるであろう。ガス抜き除去キャップ44が分岐したルアー継手42から除去され、そして動脈血サンプルを取り除くために吸引されるであろう注射器70によって置き換えられるであろう。分岐の上流の残余血液体積が、その後の廃棄のために該装置中に残るであろう。

【図１】

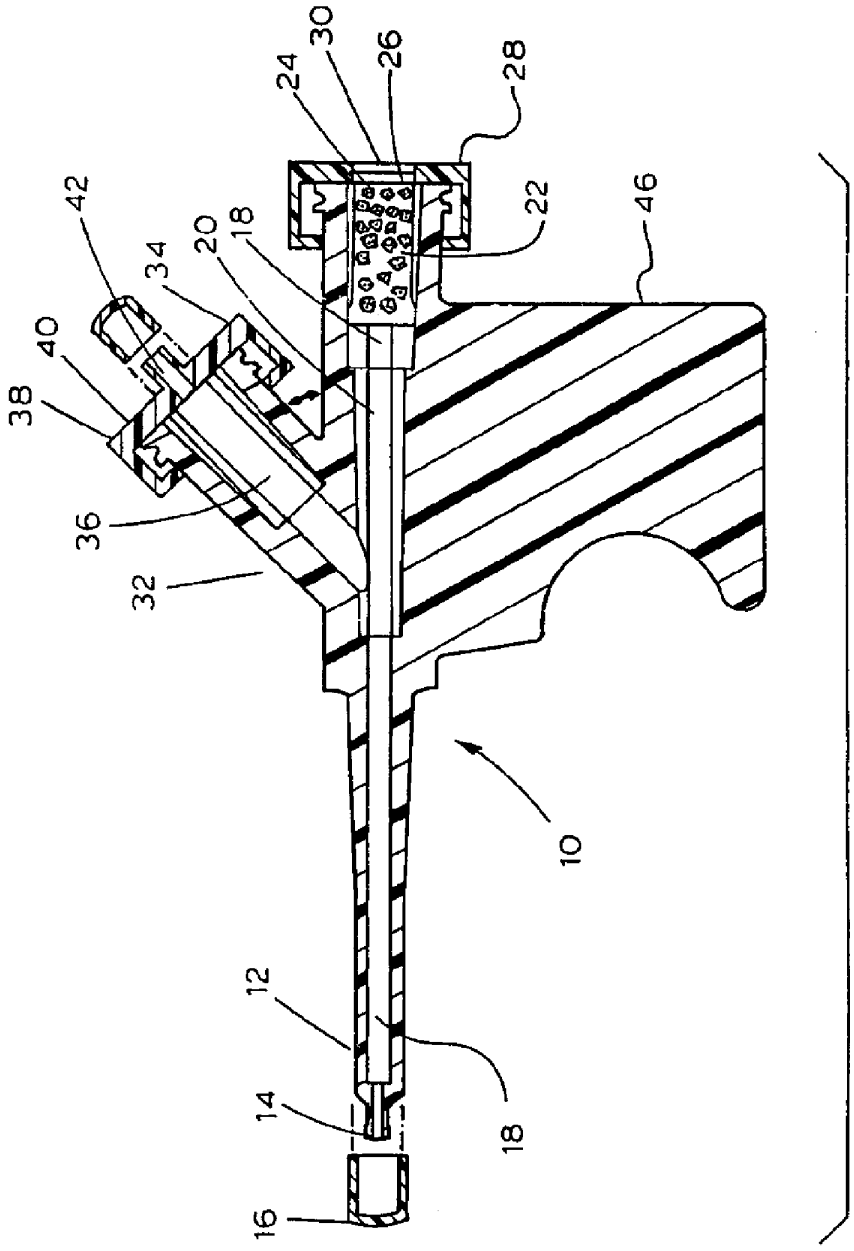


FIG. 1

【図２】

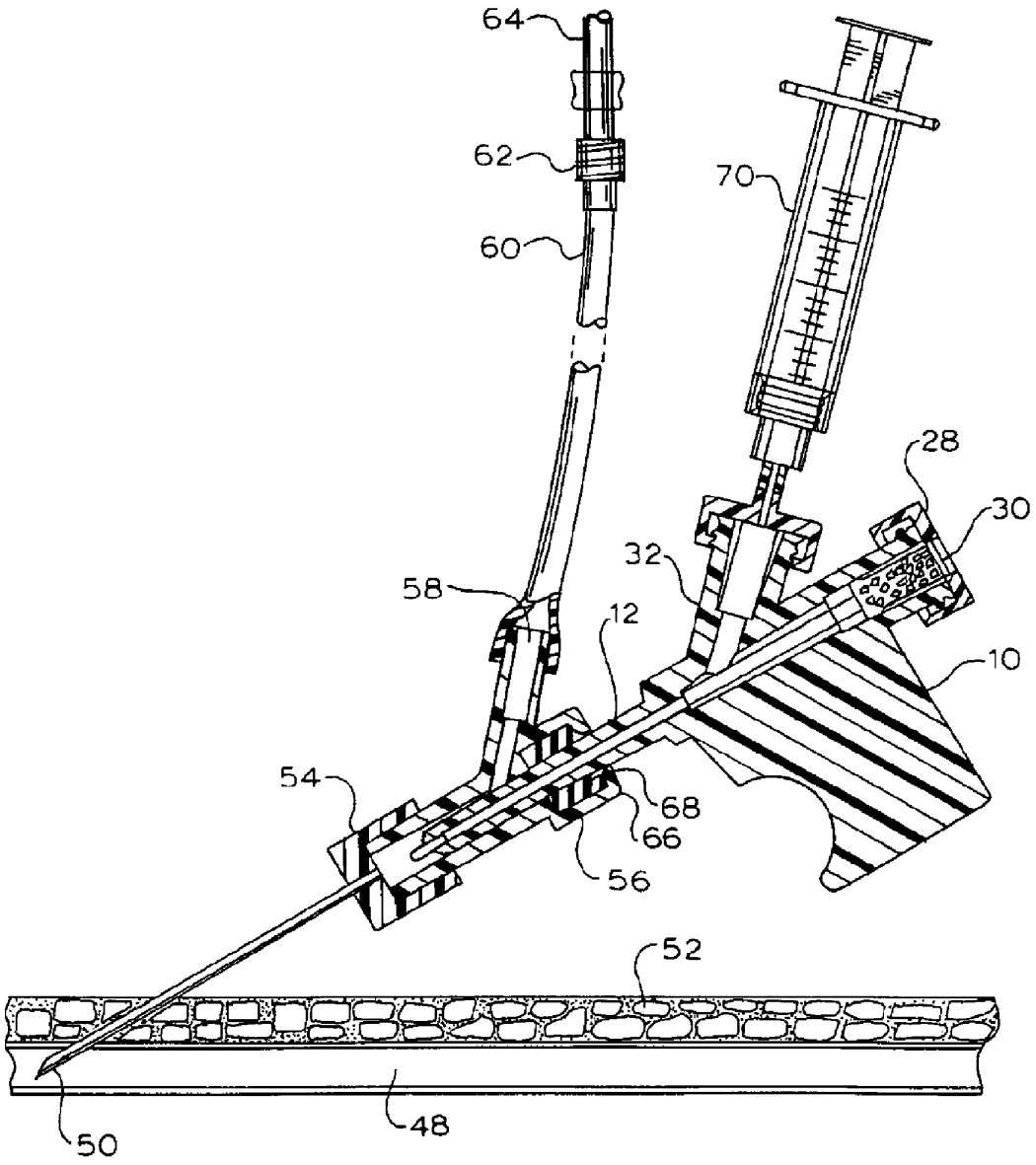


FIG. 2

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/10702

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A 61M 5/00
US CL. : 604/122
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 604/122, 35, 125, 126, 128, 256, 258, 283, 284
128/ 760, 762, 767, 768

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US, A, 4,531,937 (Yates) 30 July 1985, See Entire Reference	1-7,9-15 --- 8,16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 DECEMBER 1995	Date of mailing of the international search report 04 JAN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No.	Authorized officer SAM RIMELL Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet)(July 1992)*

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:

IPC:

CPC: A61B5/15003, A61B5/150213, A61B5/150251, A61B5/150389, A61B5/150488, A61B5/150992, A61B5/153, A61B5/150274, A61B5/1535, A61B5/1545, A61B5/157

FI/F-TERMS:

KEYWORDS OR OTHER ELEMENTS FEATURING THE INVENTION:

EPO FORM P04A42

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/068569

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154 A61B5/157
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 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

-/--

[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
29 March 2018	25/04/2018

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	Nielsen, Michael

1

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/068569

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

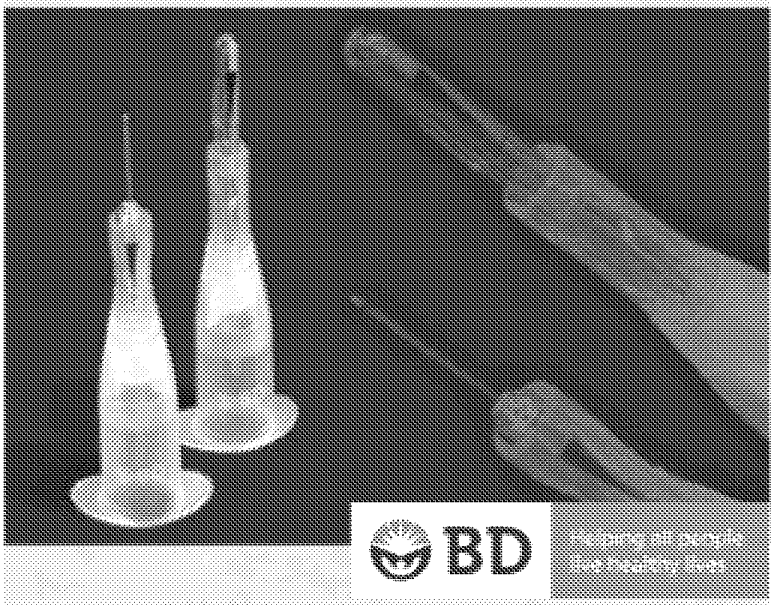
International application No
PCT/US2017/068569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014039348 A1	06-02-2014	US 2014039348 A1	06-02-2014
		US 2016113560 A1	28-04-2016
		WO 2014022275 A1	06-02-2014
US 2014107564 A1	17-04-2014	EP 2906269 A1	19-08-2015
		US 2014107564 A1	17-04-2014
		US 2015367069 A1	24-12-2015
		WO 2014058945 A1	17-04-2014
US 4813433 A	21-03-1989	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
WO 2013181352 A1	05-12-2013	AU 2013267448 A1	18-12-2014
		AU 2017216493 A1	07-09-2017
		CA 2875118 A1	05-12-2013
		CN 104902817 A	09-09-2015
		CN 107736901 A	27-02-2018
		EP 2854643 A1	08-04-2015
		EP 3173021 A1	31-05-2017
		JP 6242386 B2	06-12-2017
		JP 2015519145 A	09-07-2015
		JP 2018034009 A	08-03-2018
		US 2014155781 A1	05-06-2014
		US 2015351679 A1	10-12-2015
		WO 2013181352 A1	05-12-2013

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

Venous Blood Collection

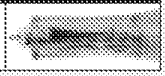
BD Vacutainer® Passive Shielding Blood Collection Needle

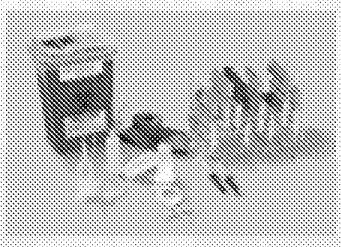


A New Generation of Safety from BD, the leader in safety-engineered technology

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				
[redacted]	Passive Shielding Blood Collection Needle	21g x 1" needle	25/Box 200/Case	
[redacted]	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

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Franklin Lakes, NJ 07417

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

Dirk de Korte, Joyce Curvers, Wim L.A.M. de Kort, Tiny Hoekstra, Cees L. van der Poel, Erik A.M. Beckers, and Jan H. Marcelis

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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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.

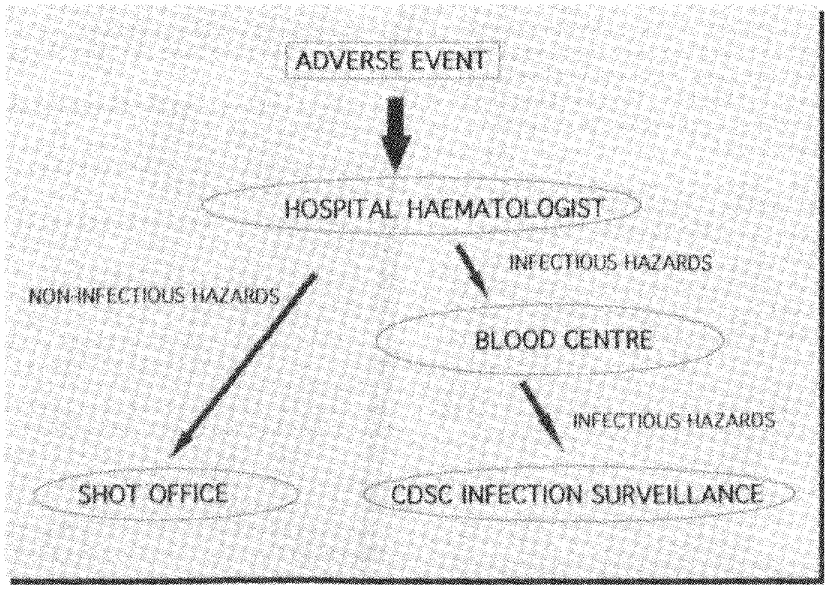
Risks of transfusion and new approaches to reducing the risks

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/bbr2). Recommendations on strategies for the avoidance of transfusion are in preparation. Specific measures which could be considered in critical care practice include better compliance with evidence-based triggers for transfusion, greater use of near patient testing to determine the need for transfusion, and minimising blood loss due to sampling. ■

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Blood extractor for patient has extraction container with needle housing to receive retractable hollow needle to extract blood

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- **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

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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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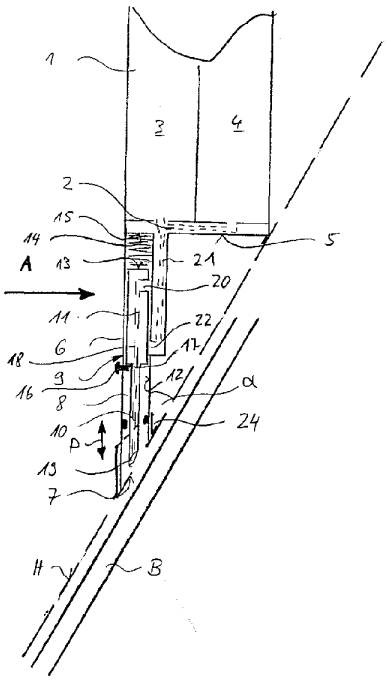
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Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(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.

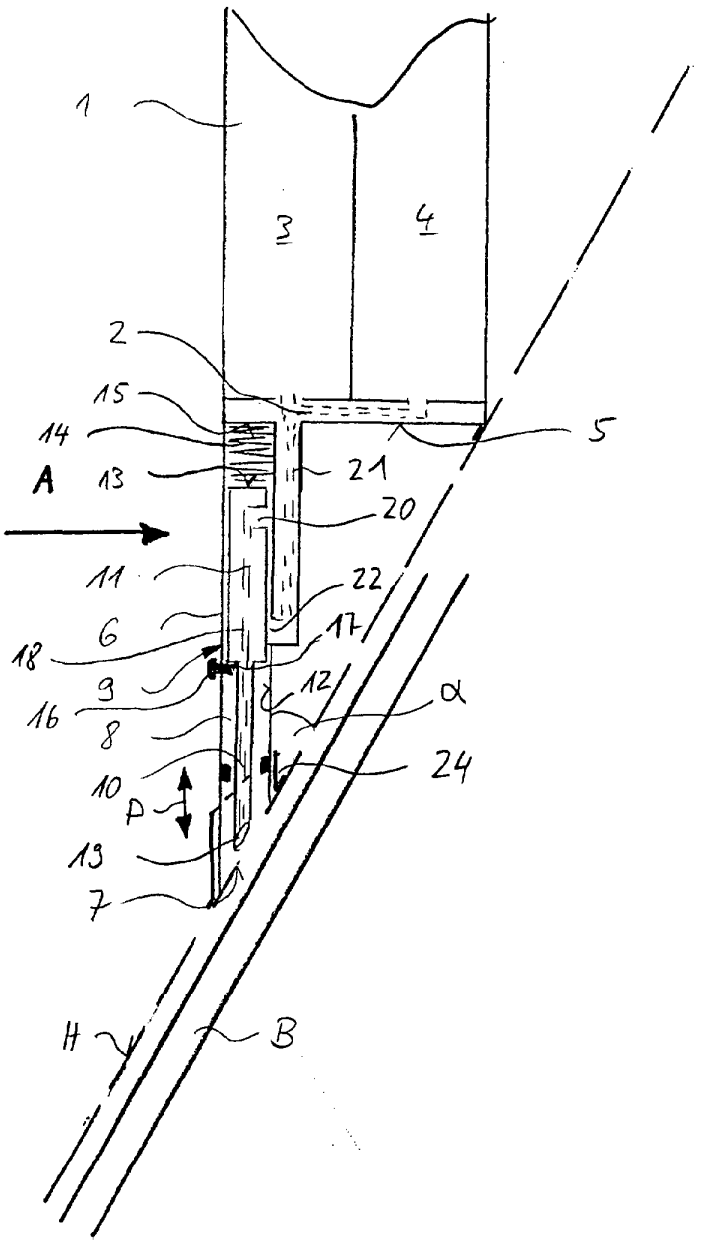
17. Vorrichtung nach Anspruch 15, dadurch gekennzeichnet, daß die Innenvolumina (**31**, **32**, **33**) oder die Behälter parallel miteinander kommunizieren.

Hierzu 6 Seite(n) Zeichnungen

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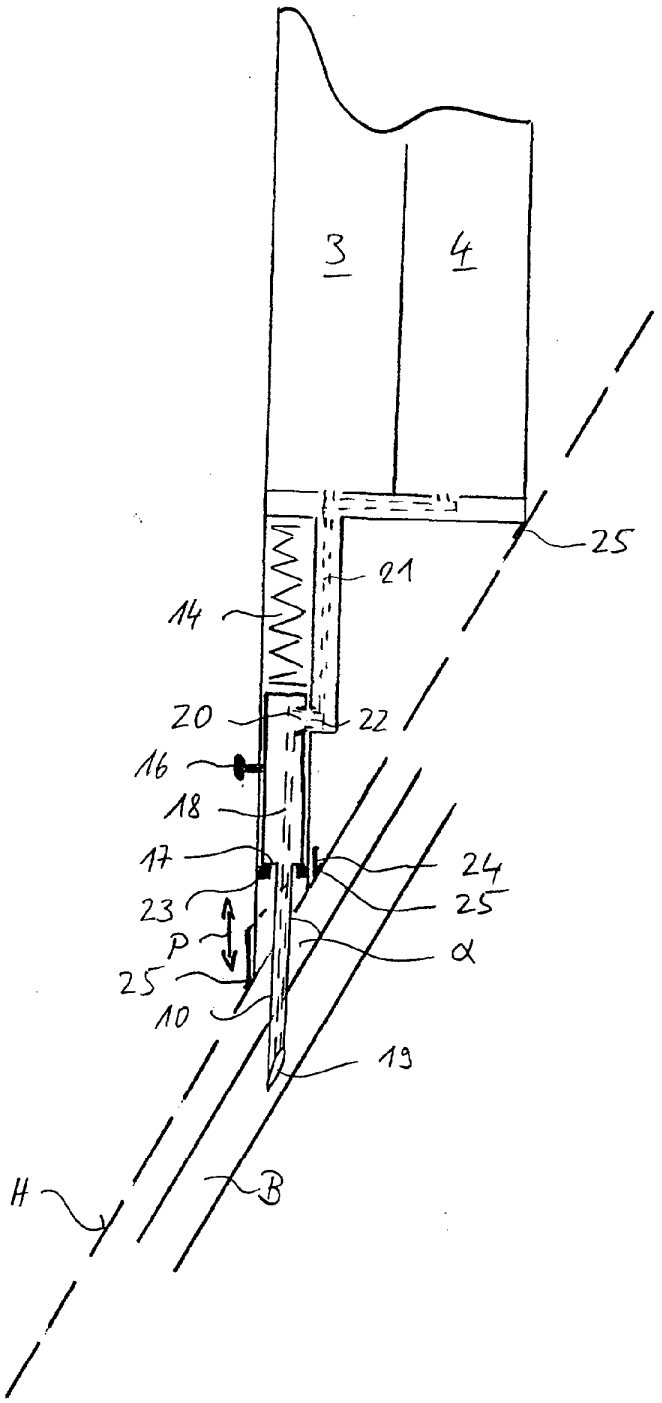
Nummer: **DE 100 38 026 A1**
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Fig. 1



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Fig. 2



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Fig. 3

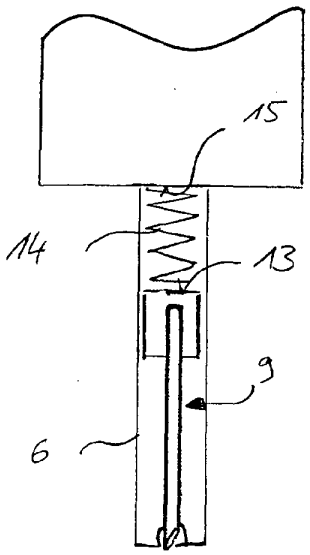
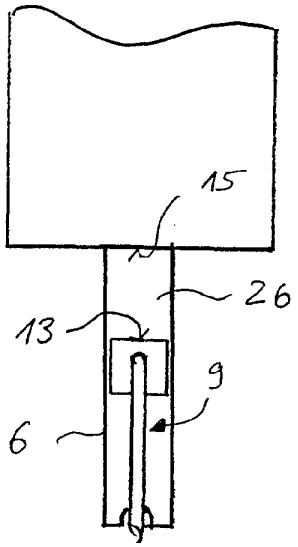


Fig. 4



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Fig. 5

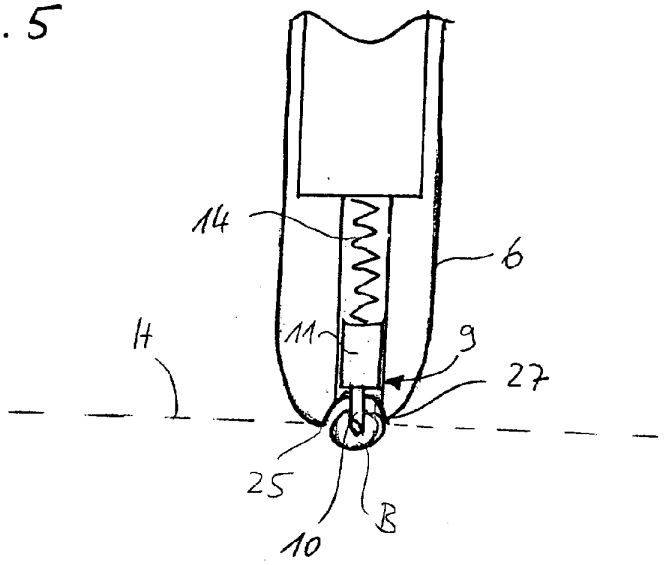
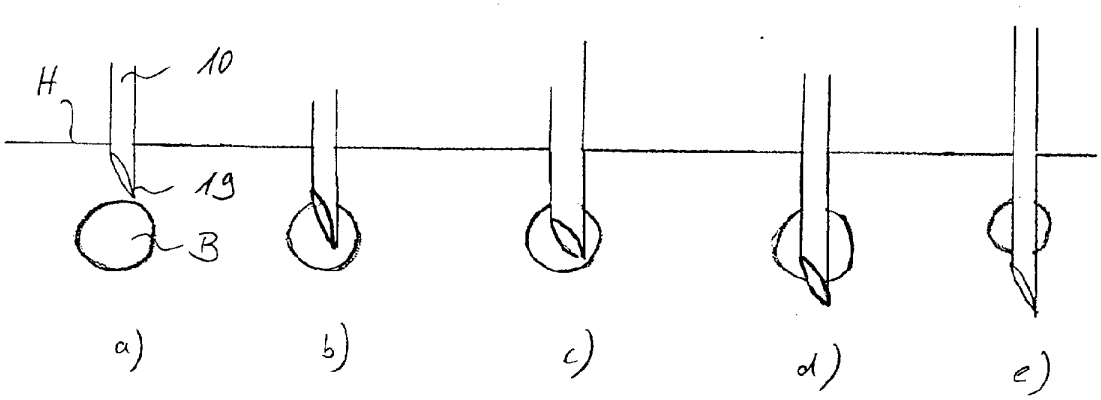


Fig. 6



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Fig. 7

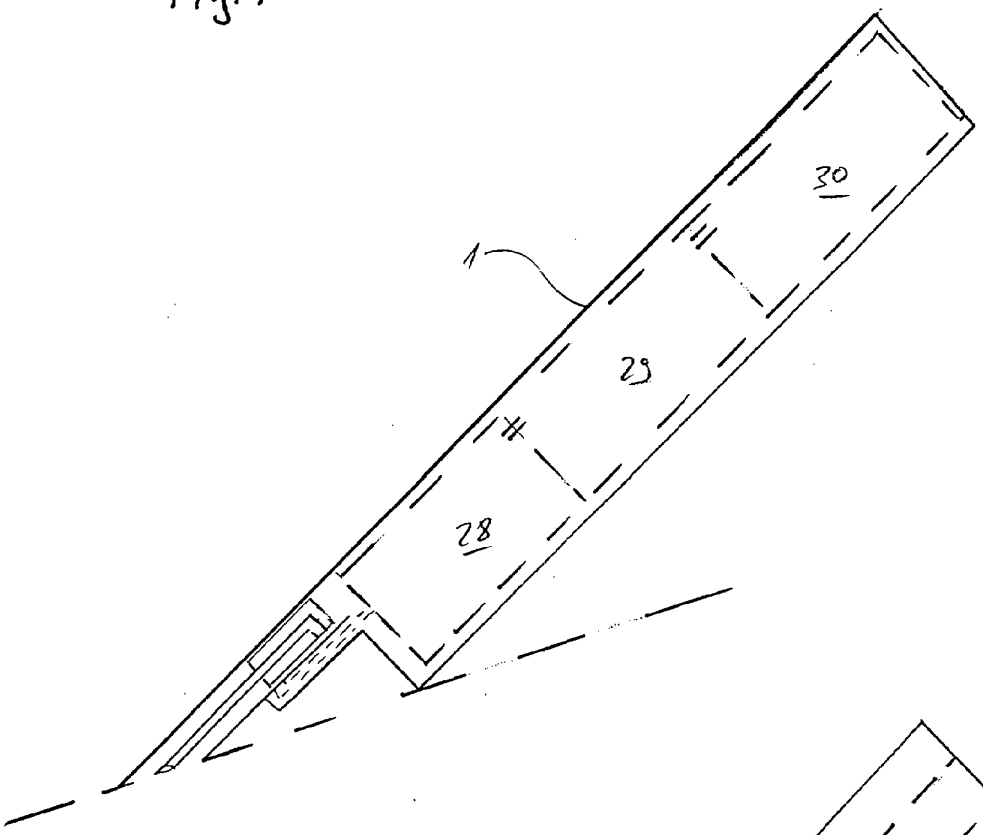
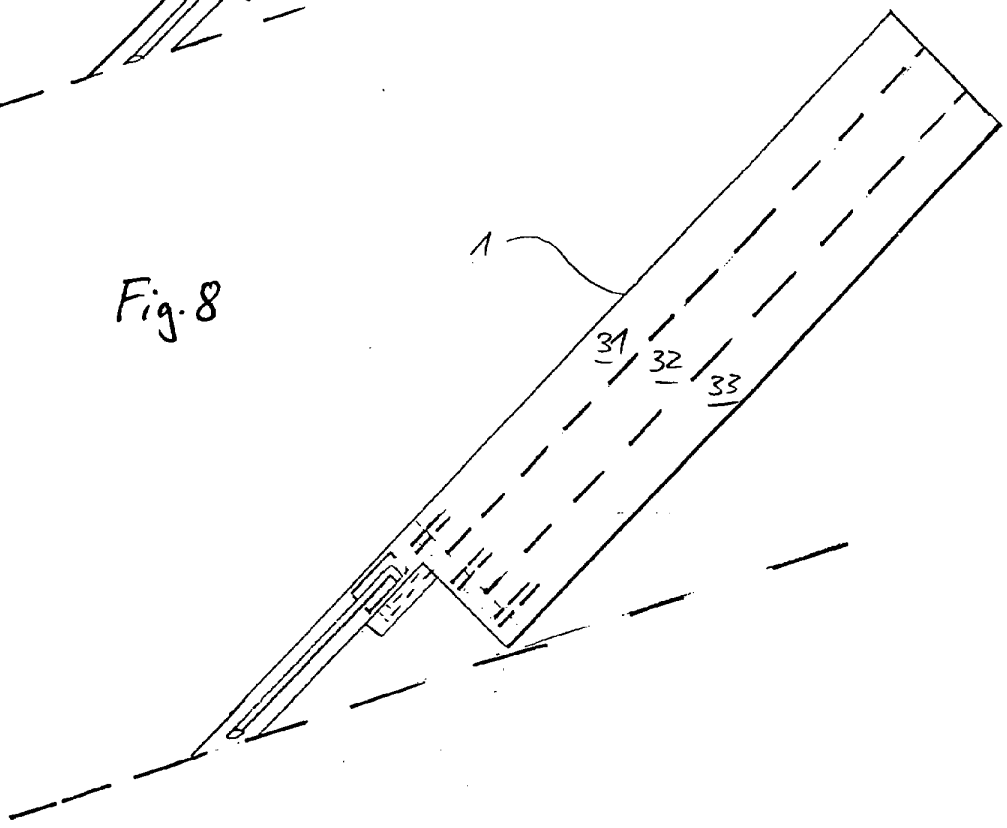
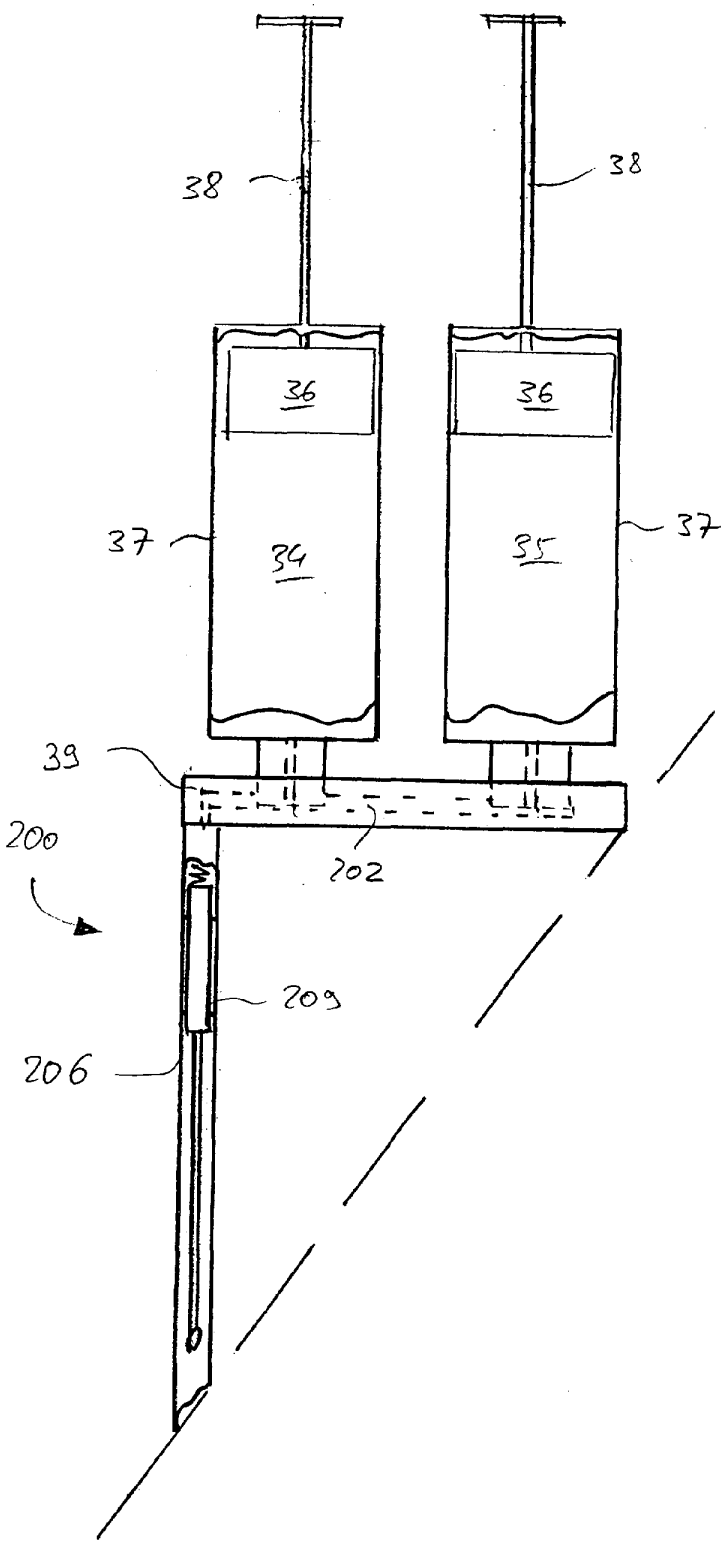


Fig. 8



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Fig. 9



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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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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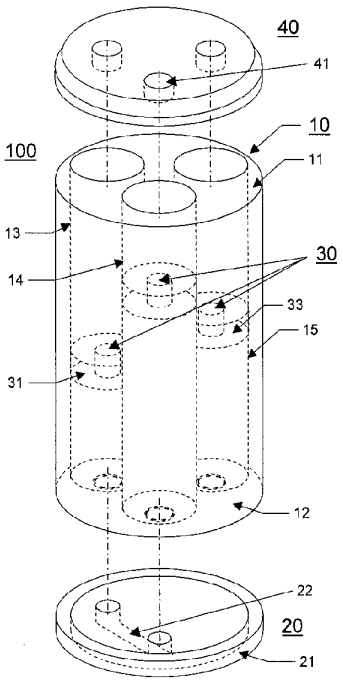
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DE 298 05 538 U1
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(54) Vorrichtung und Verfahren zur Blutpräparation

(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

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Int. Cl.[7]: **A 61 M 1/00**
Veröffentlichungstag: 26. Juni 2003

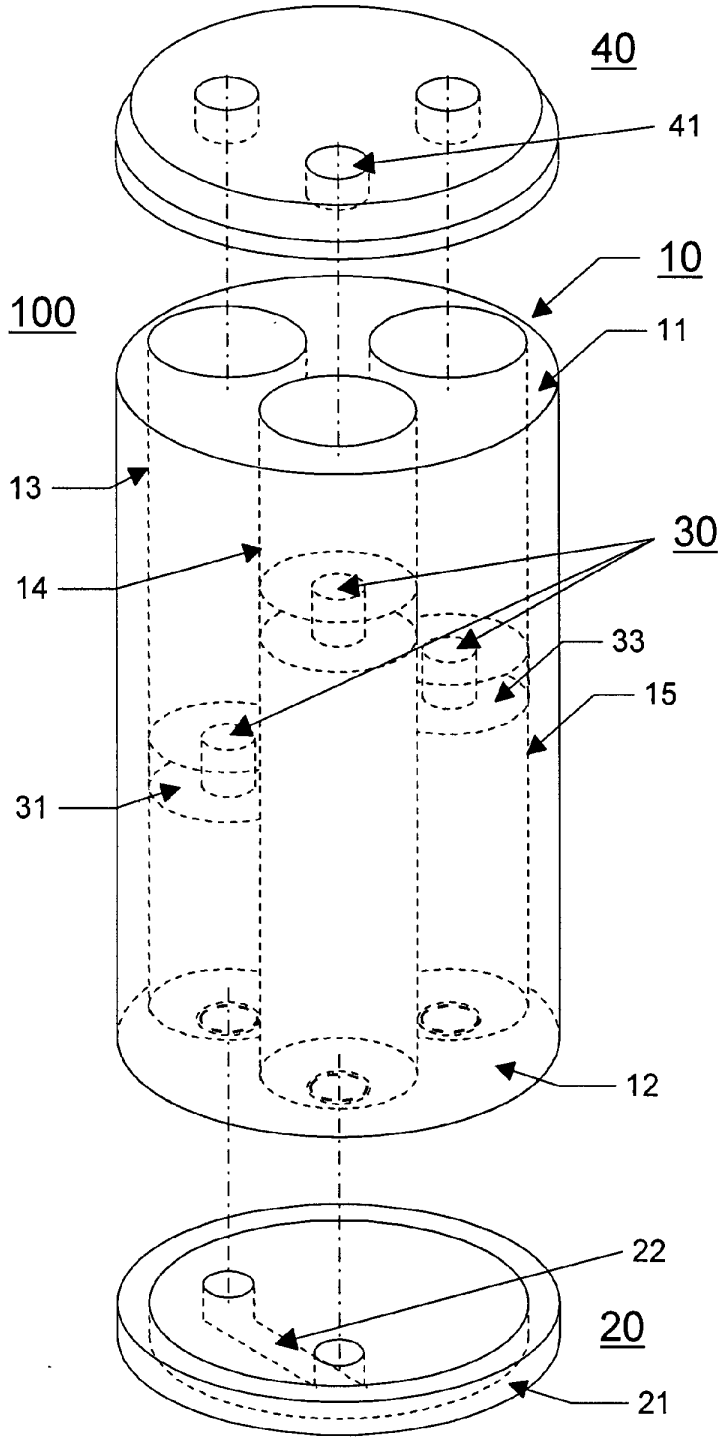


Fig. 1

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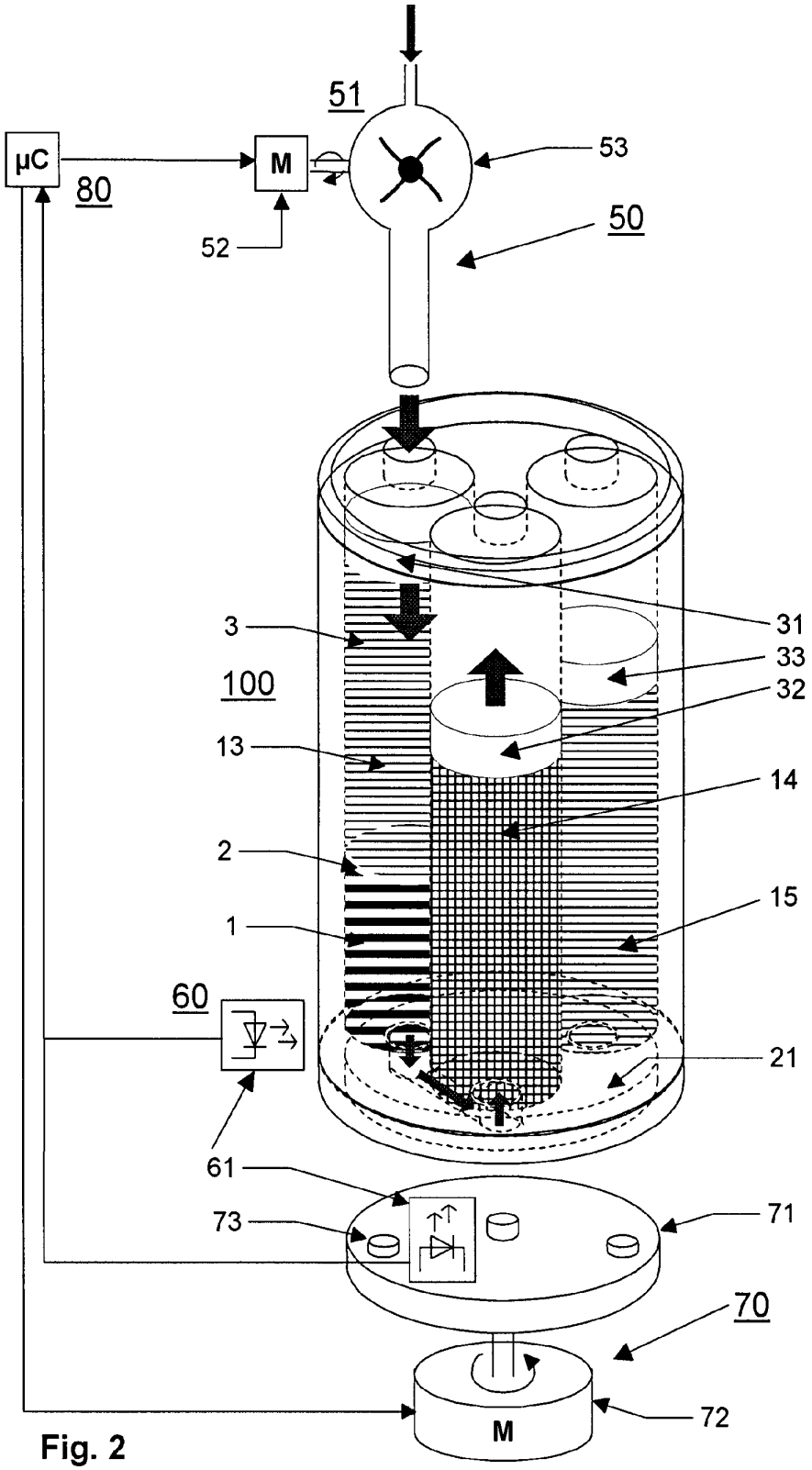


Fig. 2

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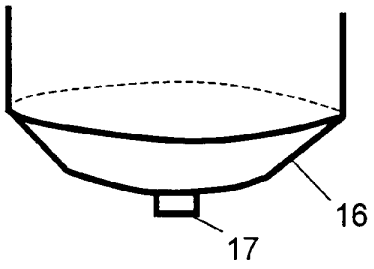


Fig. 3

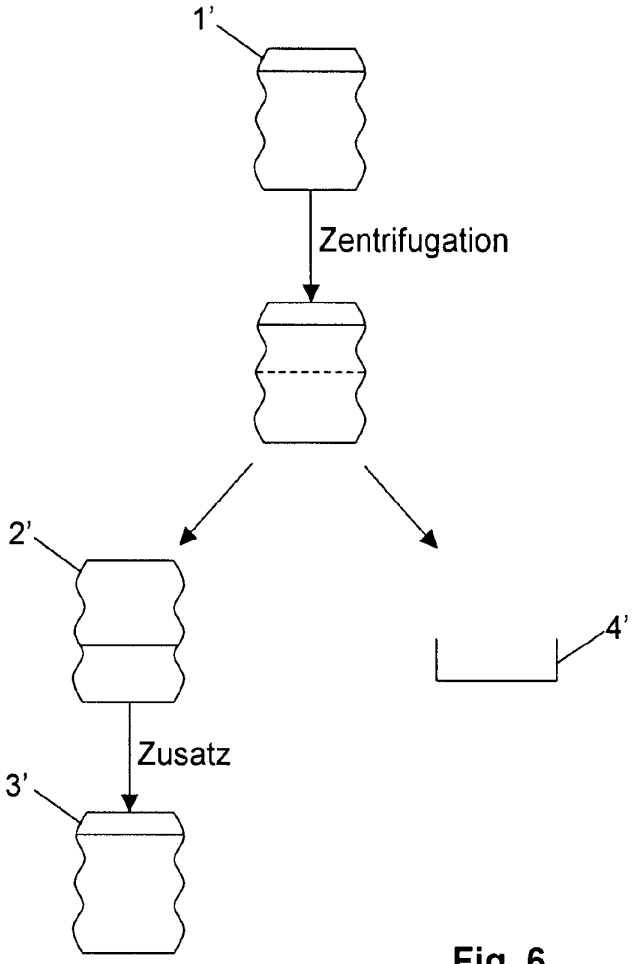
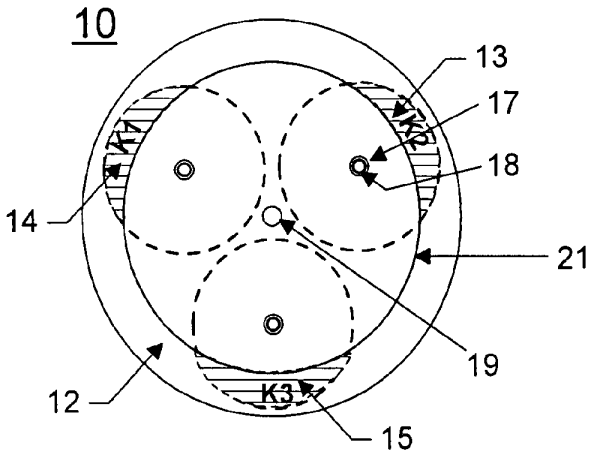
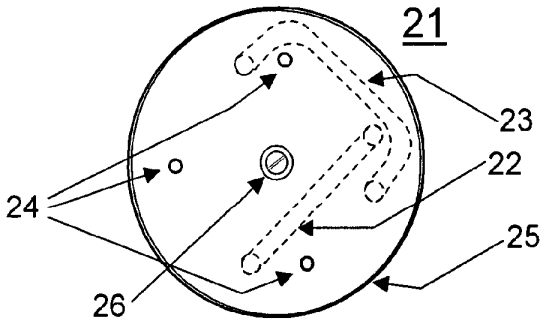


Fig. 6
(Stand der Technik)

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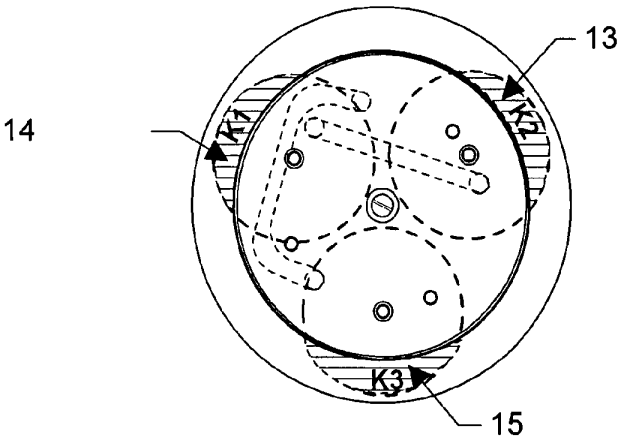


Fig. 4

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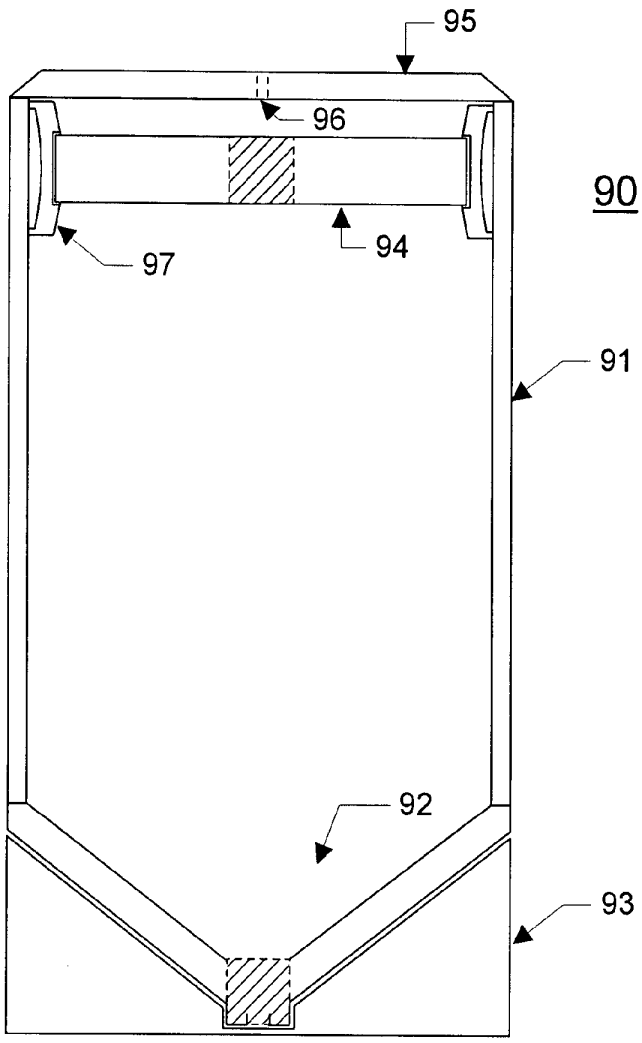


Fig. 5

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Fibronectin (cold insoluble globulin) in the neonate

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FIBRONECTIN (referred to in older literature as cold insoluble globulin), a ubiquitous glycoprotein, participates in cellular, vascular, and plasma coagulant functions.[1] Acting as a nonspecific opsonin, plasma fibronectin potentiates reticuloendothelial clearance of intravascular debris to protect against organ dysfunction secondary to microvascular occlusion and altered vascular permeability.[1] Found on cell surfaces, fibronectin is important in wound healing and embryogenesis.[2] Fibronectin is a substrate for thrombin, plasmin, and activated fibrin–stabilizing factor (factor XIII), and can be lysed by granulocyte and other proteases.[3]

Fibronectin has potentially important roles in hemostasis and control of infection in the neonate. Decreased plasma values of fibronectin, measured by Laurell immunoelectrophoresis, have been reported in apparently healthy full-term infants.[4] We present the fibronectin values measured by immunoelectrophoresis in reference full-term and preterm infants and in neonates with sepsis of early onset.

MATERIALS AND METHODS

For adult reference values, blood samples were collected from healthy laboratory personnel who were not receiving any medication (including birth control pills or aspirin), had no chronic or recent acute illness, and had not exercised vigorously just prior to blood sampling.

Cord blood samples were collected from 18 healthy full-term infants (gestational age mean 40 weeks, range 37 to 41 weeks) and 15 healthy preterm infants (gestational age mean 35 weeks, range 32 to 36 weeks). Infants met the following criteria: (1) definite maternal dates that agreed within two weeks with the Dubowitz score; (2) Apgar scores at 1 minute of ≥ 7 and at 5 minutes of ≥ 8 in preterm infants (32 to 36 weeks gestational age), and Apgar scores of ≥ 8 at 1 minute and ≥ 9 at 5 minutes in full-term infants; (3) appropriate weight for gestational age; (4) no hypoxia, acidosis, hypotension, or hypothermia by gestational and postnatal age-appropriate definitions; (5) healthy during the first 48 hours of life; (6) inborn; (7) no family history of bleeding disorders; (8) the mothers had not received medications during pregnancy except vitamins, iron, inhibitors of uterine activity, steroids for maturation of fetal lung, and local, general, or epidural anesthesia; (9) the mothers had uncomplicated pregnancies; (10) the mothers of full-term infants delivered by cesarian section did not have labor.

Other preterm infants studied (gestational age mean 35 weeks) did not fit the above criteria because of intrauterine growth retardation (seven infants) or diabetic mothers (two infants). These infants had otherwise uncomplicated, uneventful perinatal courses. The eight ill neonates studied (mean gestational age 33 weeks) had birth asphyxia or hypotension.

Because adults with sepsis have decreased plasma values for fibronectin,[5] we studied infants with early-onset sepsis. In all infants blood cultures were positive for either β-hemolytic streptococcus (two infants) or *Listeria monocytogenes* (four infants) (mean gestational age 37 weeks, range 30 to 40 weeks).

This study was approved by the Hospital and University Ethical Review Committees. Informed parental consent was obtained prior to collection of blood specimens.

All blood samples tested were collected by the two-syringe technique, in which the first 0.5 ml blood drawn

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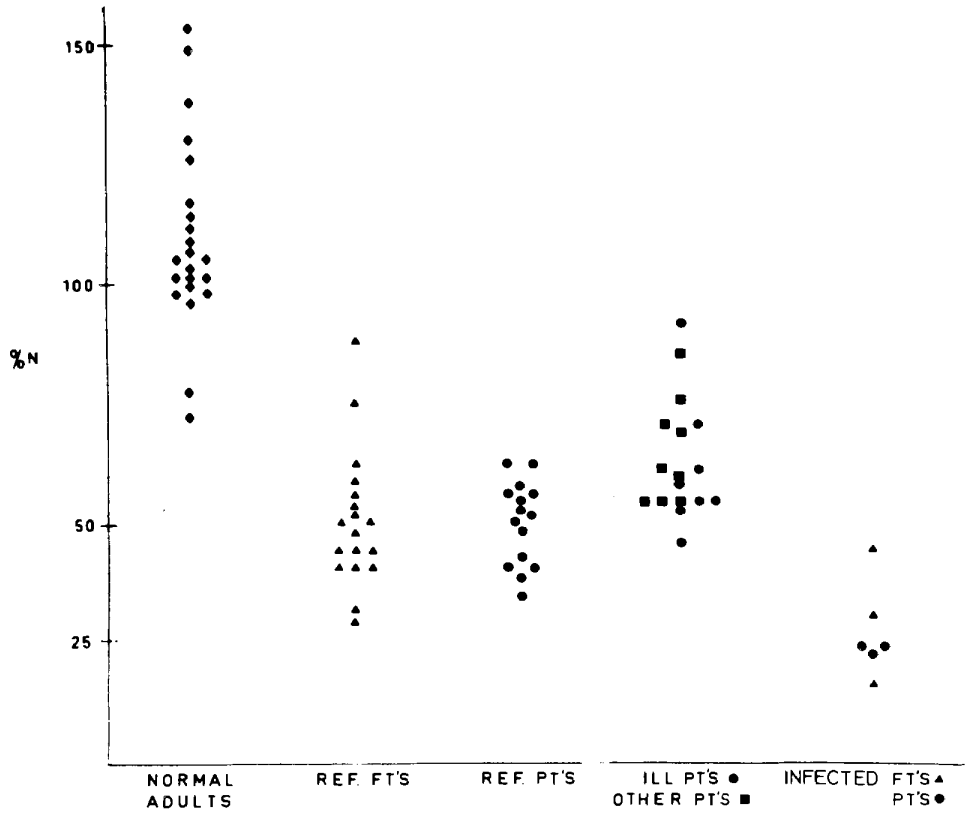


Figure. Fibronectin values in adults, in infected infants, and in healthy infants. *FT*, Full-term; *PT*, preterm.

into a dry syringe was discarded or used for other tests (to prevent contamination of the test sample by tissue thromboplastin). The test sample was then drawn into a syringe containing the anticoagulant to give a ratio of 1 volume anticoagulant to 9 volumes blood. To rule out in vitro artifact from platelet release or thrombin or protease action, the anticoagulant used was buffered citrate (anticoagulant A) or buffered citrate with inhibitors (anticoagulant B). Inhibitors added to the buffered citrate were: theophylline, an inhibitor of platelet release reaction, 1.8 mg/ml (Sigma Chemical, St. Louis); hirudin, an inhibitor of thrombin, 2 antithrombin units/ml (Sigma); and aprotinin, an inhibitor of plasmin and protease, 100 Kunitz IU/ml (Boehringer-Mannheim, Canada).

Cord blood samples were drawn from the umbilical vein of double-clamped cords obtained before placental separation. Samples were collected randomly, first into anticoagulant A or B. Immediately after collection, plasma was separated by refrigerated centrifugation at 5000 *g* for 20 minutes, respun to remove all platelets, and kept frozen at −80°C until assayed. Pooled plasma from normal adults (obtained from George King Ltd., Kansas) was used as control plasma. Our samples were collected by venipuncture, but conceivably samples could be obtained by heelstick using anticoagulated Miale pipettes.

Fibronectin was measured by Laurell immunoelectrophoresis.[5] Plasma samples were diluted with barbital-EDTA buffer (0.03 M barbiturate, 1.0 gm sodium ethylenediaminetetraacetate, 0.1 gm sodium azide in 1000 ml distilled water). The same buffer was used to make 1% agarose (Seakem Marine Colloids, Lockland, Me.). Rabbit antiserum to human fibronectin (lot 153955) was obtained from Cappell Laboratories (Cochranville, Pa.). Glass slides (7.5 cm × 5 cm) were prepared with 4 ml agarose per slide (antiserum concentration approximately 1.675%). Eleven holes (2 mm diameter) were punched per slide. Three lambda samples were applied to each well. The standard curve was made with 100%, 50%, and 25% normal pooled plasma. A normal control plasma was run in duplicate at 50% on each slide. The chamber buffer was a 0.75 M barbital (pH 8.6, 2.07 gm diethylbarbituric acid, 13.14 gm sodium barbitone, 1.0 gm EDTA, 0.1 gm sodium azide in 1000 ml distilled water). Slides were electrophoresed at 15 mamp (constant current) for two hours.

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Normally, slides were washed for 24 hours in 0.5 M sodium chloride and subsequently rinsed in tap water. However, slides can be washed and stained immediately. Interassay coefficient of variation was ±8%.

The paired and unpaired t tests were used for statistical analysis.

RESULTS

Plasma values for fibronectin in 18 reference full-term infants were decreased, compared with values in 22 reference adults (Figure). Measurements of plasma fibronectin in 15 reference preterm infants 32 to 36 weeks gestational age were not statistically different from those in 18 reference full-term infants. Cord blood fibronectin concentrations from nine other preterm infants were not different from values found in the 15 reference preterm infants. The eight ill neonates had cord plasma fibronectin measurements comparable to those of the reference preterm infants. In contrast, six infants, at the time of diagnosis of early-onset sepsis, had decreased plasma values of fibronectin when compared with healthy neonates.

There was no statistical difference by paired t test in plasma fibronectin measurements in paired samples randomly collected first into buffered citrate (anticoagulant A) or into buffered citrate plus inhibitors (anticoagulant B) (53 ± 2% versus 55 ± 2%, mean ± SD).

DISCUSSION

Several thorough reviews have been published recently stressing potential physiologic roles for fibronectin.[1, 2, 7, 8]

Our results confirm the previously reported decreased plasma fibronectin values measured by immunoelectrophoresis in plasma of cord blood from 22 healthy neonates (adult 101 ± 27%, neonates 39 ± 6%).[4] Fibronectin measurements by immunoelectrophoresis were decreased in plasma obtained from cord blood samples of newborn infants when compared with measurements of plasma fibronectin in normal adults; values for normal full-term and healthy preterm infants were not statistically different. Three healthy, extremely premature infants (gestational age 29 weeks) had cord plasma fibronectin values of 27%, 35%, and 45%, respectively (D. Barnard, unpublished data). Because samples collected randomly first into buffered citrate or buffered citrate plus additional inhibitors were not statistically different, the decreased plasma fibronectin measurements in neonates are not related to in vitro proteolysis.

The six full-term and preterm neonates with early-onset sepsis (mean age 14 hours, range 4 to 20 hours at testing) had depressed fibronectin concentrations in plasma from venous blood collected into anticoagulant B. The two infants who died had the lowest plasma fibronectin values measured. Decreased survival[9] has been reported in adults with sepsis and persistently low plasma fibronectin values. In an uncontrolled study, adult patients with sepsis and pulmonary dysfunction (ventilation-perfusion imbalance and presumed increase of lung water) improved after infusion of cryoprecipitate containing approximately 1 gm fibronectin.[10] Decreased levels of fibronectin in neonates may increase their susceptibility to and morbidity from septicemia.

Intrauterine growth retardation, maternal diabetes, and birth asphyxia or hypotension apparently do not affect plasma cord values of fibronectin.

Low plasma fibronectin measurements in adults with trauma, disseminated intravascular coagulation, or sepsis are thought to result from utilization of fibronectin in reticuloendothelial system clearance function, consumption by incorporation into intravascular thrombin, proteolytic destruction by granulocyte or tissue protease, binding to areas of tissue damage or denatured collagen, or decreased synthesis.[1] The cause of the decreased plasma values of fibronectin in neonates is speculative.

We acknowledge the excellent cooperation of the nurses and physicians of the Grace Maternity Hospital in obtaining cord blood specimens, and Drs. R. A. Bortolussi, A. Allen, D. Stinson, and E. Rees for blood specimens from septic infants.

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CARTRIDGE AND TEST INFORMATION

i-STAT® sensors are available in a variety of panel configurations. Sensors are contained in cartridges with microfluidic components and, in some cartridges, calibration solution. i-STAT cartridges are used with the i-STAT 1 Analyzer* for the simultaneous quantitative determination of specific analytes and coagulation parameters in whole blood.

CARTRIDGE SPECIFICATIONS

Shelf Life:

Refrigerated at 2 to 8 °C (35 to 46 °F) until expiration date.

Refer to the cartridge box for room temperature storage requirements.

Preparation for Use:

Individual cartridges may be used after standing five minutes at room temperature. An entire box of cartridges should stand at room temperature for one hour.

All cartridges should be used immediately after opening pouch. If the pouch has been punctured, the cartridge should not be used.

Sample Type:

Fresh whole blood from arterial, venous, or skin punctures.

(Note: Skin puncture is NOT a recommended sample type for ACT, cTnI, CK-MB, ß-hCG or BNP testing.)

cTnI, ß-hCG and CK-MB cartridges require the use of heparinized whole blood or plasma, or non-heparinized whole blood tested within one minute of patient draw.

BNP cartridges require the use of EDTA whole blood or plasma samples.

Sample Volume:

17 µL, 20 µL, 40 µL, 65 µL, or 95 µL depending on cartridge type.

Test Timing:

Immediately after collection

- Samples for the measurement of ACT, PT/INR and Lactate

Within 3 minutes after collection

- Samples collected in capillary tubes with balanced heparin anticoagulant
- Samples collected in evacuated or non-evacuated tubes and syringes without anticoagulant

Within 10 minutes after collection

- Samples collected with anticoagulant for the measurement of pH, PCO_2, PO_2 and iCa. Maintain anaerobic conditions. Remix before filling cartridge.

Within 30 minutes after collection

- Sodium, potassium, chloride, glucose, BUN/urea, creatinine, hematocrit, troponin I, CK-MB, ß-hCG and BNP. Remix thoroughly before testing.

Abbott Point of Care

Art: 714258-01O Rev. Date: 15-Aug-16

* The cTnI, CK-MB, ß-hCG and BNP cartridges can only be used with the i-STAT 1 analyzer bearing the  symbol.

Analysis Time:

- ACT cartridge: to detection of end point - up to 1000 sec (16.7 min)
- PT/INR cartridge: to detection of end point – up to 300 sec (5 min)
- cTnI, ß-hCG and BNP cartridges: 600 sec (10 min)
- CK-MB cartridge: 300 sec (5 min)
- Other cartridges: typically 130 to 200 sec

Cartridges	Collection Options			
	Syringes	Evacuated Tubes	Capillary Tubes	Directly from Skin Puncture
Cartridges which measure ionized calcium	• Without anticoagulant • With balanced heparin anticoagulant (syringe must be filled to labeled capacity)	• Without anticoagulant • With lithium heparin anticoagulant (tubes must be filled to capacity)	• With balanced heparin anticoagulant	• Not recommended • Not recommended for blood gas analysis; arterial specimens are preferred
Cartridges which perform ACT	• Without anticoagulant ONLY • Syringes must be plastic	• Without anticoagulant, clot activators, or serum separators ONLY • Tubes must be plastic • Devices used to transfer sample to cartridge must be plastic	• Not recommended	• Not recommended
Cartridges which perform PT/INR	• Without anticoagulant ONLY • Syringes must be plastic	• Without anticoagulant, clot activators, or serum separators ONLY • Tubes must be plastic • Devices used to transfer sample to cartridge must be plastic	• Not recommended	• Recommended
Cartridges which measure Troponin I or CK-MB	• With sodium or lithium heparin anticoagulant (syringe must be filled to labeled capacity) • Without anticoagulant if tested within one minute of patient draw	• With sodium or lithium heparin anticoagulant (tubes must be filled to capacity) • Without anticoagulant if tested within one minute of patient draw	• Not recommended	• Not recommended

Cartridges	Collection Options			
	Syringes	Evacuated Tubes	Capillary Tubes	Directly from Skin Puncture
Cartridges which measure Total ß-hCG	• With sodium or lithium anticoagulant (syringe must be filled to labeled capacity) • Without anticoagulant if tested within one minute of patient draw • Syringes must be plastic	• With sodium or lithium heparin anticoagulant (tubes must be filled to capacity)	• Not recommended	• Not recommended
Cartridges which measure BNP	• With EDTA anticoagulant (syringe must be filled to labeled capacity) • Syringes must be plastic	• With EDTA anticoagulant (tubes must be filled to capacity) • Tubes must be plastic	• Not recommended	• Not recommended
All other cartridges	• Without anticoagulant • With lithium or balanced heparin anticoagulant (syringe must be filled to labeled capacity)	• Without anticoagulant • With lithium heparin anticoagulant (tubes must be filled to capacity)	• With balanced heparin anticoagulant • With lithium heparin if labeled for the measurement of electrolytes	• While a sample can be transferred directly from a skin puncture to a cartridge, a capillary tube is preferred • Not recommended for blood gas analysis; arterial specimens are preferred

Note Regarding System Reliability

The i-STAT System automatically runs a comprehensive set of quality checks of analyzer and cartridge performance each time a sample is tested. This internal quality system will suppress results if the analyzer or cartridge does not meet certain internal specifications (see Quality Control section in System Manual for detailed information). To minimize the probability of delivering a result with medically significant error the internal specifications are very stringent. It is typical for the system to suppress a very small percentage of results in normal operation given the stringency of these specifications. If however the analyzer or cartridges have been compromised, results may be persistently suppressed, and one or the other must be replaced to restore normal operating conditions. **Where unavailability of results while awaiting replacement of analyzers or cartridges is unacceptable, APOC recommends maintaining both a backup i-STAT System analyzer and cartridges from an alternate lot number.**

EXPECTED VALUES

Measured:

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
Sodium/Na	mmol/L (mEq/L)	100 – 180	138 – 146	138 – 146
Potassium/K	mmol/L (mEq/L)	2.0 – 9.0	3.5 – 4.9	3.5 – 4.9
Chloride/Cl	mmol/L (mEq/L)	65 – 140	98 – 109	98 – 109
Glucose/Glu	mmol/L mg/dL g/L	1.1 – 38.9 20 – 700 0.20 – 7.00	3.9 – 5.8 70 – 105 0.70 – 1.05	3.9 – 5.8 70 – 105 0.70 – 1.05
Lactate/Lac	mmol/L mg/dL	0.30 – 20.00 2.7 – 180.2	0.36 – 1.25 3.2 – 11.3	0.90 – 1.70 8.1 – 15.3
Creatinine/Crea	mg/dL µmol/L	0.2 – 20.0 18 – 1768	0.6 – 1.3 53 – 115	0.6 – 1.3 53 – 115
pH		6.5 – 8.2	7.35 – 7.45	7.31 – 7.41
***P*CO$_2$**	mmHg kPa	5 – 130 0.67 – 17.33	35 – 45 4.67 – 6.00	41 – 51 5.47 – 6.80
TCO$_2$ (on the CHEM8+ cartridge only)	mmol/L (mEq/L)	5 – 50	23 – 27	24 – 29
***P*O$_2$**	mmHg kPa	5 – 800 0.7 – 106.6	80 – 105 10.7 – 14.0	
Ionized Calcium/iCa	mmol/L mg/dL	0.25 – 2.50 1.0 – 10.0	1.12 – 1.32 4.5 – 5.3	1.12 – 1.32 4.5 – 5.3
Urea Nitrogen/BUN **Urea**	mg/dL mmol/L mg/dL g/L	3 – 140 1 – 50 6 – 300 0.06 – 3.00	8 – 26 2.9 – 9.4 17 – 56 0.17 – 0.56	8 – 26 2.9 – 9.4 17 – 56 0.17 – 0.56
Hematocrit/Hct	%PCV Fraction	15 – 75 0.15 – 0.75	38 – 51 0.38 – 0.51	38 – 51 0.38 – 0.51
Celite Activated Clotting Time / ^{Celite}ACT *The range from 80 - 1000 seconds has been verified through method comparison studies.*	seconds	50 – 1000	74 – 125 (Prewarm) 84 – 139 (Nonwarm)	74 – 125 (Prewarm) 84 – 139 (Nonwarm)
Kaolin Activated Clotting Time / ^{Kaolin}ACT *The range from 77 - 1000 seconds has been verified through method comparison studies.*	seconds	50 – 1000	74 – 137 (Prewarm) 82 – 152 (Nonwarm)	74 – 137 (Prewarm) 82 – 152 (Nonwarm)
Prothrombin Time / PT *Performance characteristics have not been established for INRs above 6.0.*	INR	0.9 – 8.0		
Troponin I / cTnI	ng/mL (µg/L)	0.00 – 50.00		0.00 – 0.03* 0.00 – 0.08**
Performance characteristics have not been established for cTnI values above 35.00 ng/mL. ** Represents the 0 to 97.5% range of results.* *** Represents the 0 to 99% range of results.*				
Creatine Kinase MB / CK-MB ****Represents the 0 to 95% range of results.*	ng/mL (µg/L)	0.0 – 150.0		0.0 – 3.5***

EXPECTED VALUES (CONT.)

Measured: (CONT.)

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
B-Type Natriuretic Peptide / BNP	pg/mL (ng/L)	15 – 5000		<15 – 50#
# Represents the 0 to 95% range of results.				
Total Beta-Human Chorionic Gonadotropin /ß-hCG	IU/L	5.0 – 2000.0		<5.0

Calculated:

TEST	UNITS	REPORTABLE RANGE	REFERENCE RANGE (arterial)	REFERENCE RANGE (venous)
Hemoglobin/Hb	g/dL	5.1 – 25.5	12 – 17	12 – 17
	g/L	51 – 255	120 – 170	120 – 170
	mmol/L	3.2 – 15.8	7 – 11	7 – 11
TCO_2 (on all cartridges but the CHEM8+)	mmol/L (mEq/L)	5 – 50	23 – 27	24 – 29
HCO_3	mmol/L (mEq/L)	1.0 – 85.0	22 – 26	23 – 28
BE	mmol/L (mEq/L)	(-30) – (+30)	(-2) – (+3)	(-2) – (+3)
Anion Gap/AnGap	mmol/L (mEq/L)	(-10) – (+99)	10 – 20	10 – 20
sO_2	%	0 – 100	95 – 98	

CARTRIDGE CONFIGURATIONS AND SAMPLE VOLUME

i-STAT EC8+ (65µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
pH
PCO_2
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Hematocrit (Hct)
TCO_2*
HCO_3*
BE*
Anion Gap* (Angap)
Hemoglobin* (Hb)

i-STAT 6+ (65µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT EC4+ (65µL)
Sodium (Na)
Potassium (K)
Glucose (Glu)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT E3+ (65µL)
Sodium (Na)
Potassium (K)
Hematocrit (Hct)
Hemoglobin* (Hb)

i-STAT G (65µL)
Glucose (Glu)

i-STAT CREA (65µL)
Creatinine (Crea)

i-STAT EG7+ (95µL)
Sodium (Na)
Potassium (K)
Ionized Calcium (iCa)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT EG6+ (95µL)
Sodium (Na)
Potassium (K)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT G3+ (95µL)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*

i-STAT CG4+ (95µL)
pH
PCO_2
PO_2
Lactate
TCO_2*
HCO_3*
BE*
sO_2*

i-STAT TOTAL ß-hCG (17µL)
Total Beta-Human Chorionic Gonadotropin

Calculated

i-STAT CG8+ (95µL)
Sodium (Na)
Potassium (K)
Ionized Calcium (iCa)
Glucose (Glu)
Hematocrit (Hct)
pH
PCO_2
PO_2
TCO_2*
HCO_3*
BE*
sO_2*
Hemoglobin* (Hb)

i-STAT CeliteACT (40µL)
Celite® ACT

i-STAT KAOLINACT (40µL)
Kaolin ACT

i-STAT PT/INR (20µL)
Prothrombin Time

i-STAT cTnI (17 µL)
Troponin I

i-STAT CK-MB (17µL)
Creatine Kinase MB

i-STAT BNP (17µL)
B-type Natriuretic Peptide

i-STAT CHEM8+ (95µL)
Sodium (Na)
Potassium (K)
Chloride (Cl)
Urea Nitrogen (BUN)/Urea
Glucose (Glu)
Creatinine (Crea)
Ionized Calcium (iCa)
TCO_2
Hematocrit (Hct)
Anion Gap* (Angap)
Hemoglobin* (Hb)

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REVIEW Open Access

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

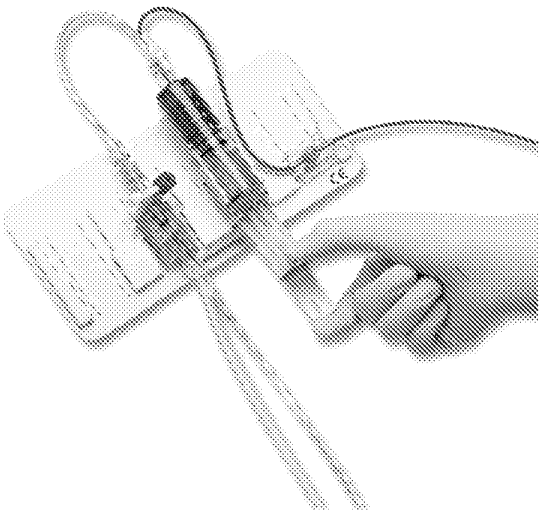


Figure 1 Edwards VAMP system. The port to the right of the image is the sampling port, which is accessed by a needless device. The middle syringe is the reservoir where the previous "discarded" blood is held before being reinfused back into the patient. Picture submitted with permission from Edwards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

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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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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.

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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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Differential Quantitative Blood Cultures in the Diagnosis of Catheter-Related Sepsis in Intensive Care Units

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The aim of this prospective study was to compare differential blood cultures and quantitative catheter tip cultures for the diagnosis of catheter-related sepsis. Over a period of 2 years, 283 central venous catheters were inserted in 190 adult patients. Catheters were removed when they were no longer needed or when infection was suspected. Immediately before removal of the central venous catheters, blood cultures were performed, with blood drawn simultaneously from the catheter and the peripheral vein. After removal, quantitative catheter culture was performed according to the Brun-Buisson modified Cleri technique. Fifty-five quantitative catheter cultures were positive. They were classified as contaminated (n = 18), colonized (n = 23), or infected (n = 14). Differential blood cultures correctly identified 13 infections. With a catheter/peripheral cfu ratio of 8, differential blood cultures had a sensitivity of 92.8% and a specificity of 98.8%. When the catheters were removed because of suspected infection, differential blood cultures had a sensitivity of 92.8% and a specificity of 100%. Differential blood culture, a technique that does not necessitate catheter removal, seems effective in the diagnosis of catheter-related sepsis in patients in the intensive care unit.

Infection is the main complication related to the use of central venous catheters (CVCs). Catheter-related infection (CRI) is a major cause of nosocomial infection and may be life-threatening [1]. The diagnosis of CRI remains difficult. Clinical signs lack sensitivity and specificity. It is widely accepted that when a patient in the intensive care unit (ICU) becomes febrile, infection of the CVC is suspected and it is removed [2]. However, 70%–85% of CVCs are removed unnecessarily [2–4]. Moreover, the insertion of a new CVC is not without complications, especially mechanical [5]. Therefore, a technique allowing the diagnosis of CRI without removal of the catheter would be of great interest.

Differential quantitative blood cultures (DBCs) of blood withdrawn from the CVC and from a peripheral vein have been evaluated in hematology and oncology patients and in patients receiving long-term parenteral nutrition [6–10]. The few studies comparing this technique to a "gold standard" have given conflicting results [11–14]. Moreover, few data are available concerning ICU patients. The aim of our study was to compare DBC with a reference technique for the diagnosis of CRI in patients treated in ICUs.

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Informed consent was obtained from all patients or their next of kin.
This study followed the guidelines of the Institutional Review Board.
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Patients and Methods

The study was approved by the hospital's Institutional Review Board. Informed consent was obtained from all patients or their next of kin. Patients hospitalized in a surgery-trauma ICU and in a medical ICU were included during the 25-month period of November 1992 through November 1994. Patients were eligible if a CVC (either single or multiple lumen) inserted while the patient was in the ICU was scheduled to be removed. Several CVCs inserted in the same patient could be included in the study. Many patients in the study units were not eligible because they entered the units with a CVC inserted elsewhere or were discharged with their CVC still in place. People who died in the units with their CVC in place were not included. Arterial and pulmonary catheters were excluded, but introducer sheaths were included. All inserted CVCs were polyurethane. The insertion site was the jugular, subclavian, or femoral vein. None of the CVCs were tunneled.

Physicians of both ICUs inserted the CVCs after surgical hand-washing and the donning of masks, sterile gowns, and gloves. The puncture site was prepared first with a solution of quaternary ammonium, then ether, and then iodine/alcohol. The surrounding areas were covered with sterile drapes. After insertion of the CVC, an occlusive gauze dressing was placed following application of povidone-iodine. The dressings were changed every 48 hours.

When it was decided to remove the CVC, the connection of the CVC and the venous line were externally disinfected with iodine/alcohol. Then the line was disconnected and a sterile syringe was inserted in order to withdraw 5 mL of blood. For multiple-lumen CVCs, blood was withdrawn from each port.

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Immediately after, 5 mL of blood was obtained from a peripheral vein by standard venipuncture and placed in a heparinized tube. Then each intravascular device was removed aseptically after sterilization of the skin-puncture site. The distal segment of the catheter tip (5 cm) was cut off with sterile scissors, dropped into a tube, and sent to the laboratory.

The catheter tip was cultured according to the technique described by Brun-Buisson et al. [15], adapted from Cleri et al. [16]. In brief, 1 mL of sterile water was added into the tube containing the catheter tip. The contents were mixed for 1 minute, and 0.1 mL was sampled and plated on the surface of 5% horse blood agar. The agar plates were incubated at 37°C for 5 days. If colonies were observed, the number was recorded. The culture was considered positive when bacterial growth was observed. Identification and antimicrobial susceptibility assessment were conducted according to standard laboratory methods.

Blood withdrawn from the CVC and the peripheral vein was treated with use of the pour-plate technique [6–12]: 1 mL of nondiluted blood and 1 mL of serial blood dilutions (10^{-1}, 10^{-2}, 10^{-3}) were added to 19 mL of melted brain-heart infusion agar cooled to 45°C and poured into petri dishes. All plates were incubated for 5 days, and cfu were counted. When no growth was observed, the count was taken as 1 for the calculation of catheter/peripheral ratio. The DBC was considered positive when the catheter/peripheral cfu ratio was greater than 1.

Catheter findings were divided into three categories [4–15]. Catheter contamination was defined as the presence of $<10^3$ cfu/mL by the quantitative catheter-tip technique, without any local or general sign of infection. Catheter colonization was defined as the presence of $>10^3$ cfu/mL by the quantitative technique, without any local sign of infection. In this category, general signs of infection might be present and related to a remote septic focus, and clinical sepsis did not resolve within 48 hours after catheter removal. CRI was defined as a positive tip culture with a bacterial count of $>10^3$ cfu/mL, in association with general signs of infection (which disappeared after catheter removal), without any focus of infection with the same microorganism. The CRI could be accompanied by bacteremia.

Statistical Analysis

Published studies were analyzed to estimate the sample size for catheters. Assuming a prevalence of CRI in ICU patients of 5%–10%, and using data from a preliminary study indicating sensitivity of 90% and specificity of 94%, we decided 250–300 catheters would be required to obtain a positive predictive value between 60% and 80% with a precision of 5% α level. Thus, 300 catheters were included.

Using the quantitative catheter-tip culture as a reference, the sensitivity, specificity, and positive and negative predictive values were calculated at different catheter/peripheral cfu ratios. Sensitivity was plotted against specificity with use of a receiver operating characteristic (ROC) curve [17]. Quantitative results were expressed as mean ± standard deviation. Categorical results were given with their 95% confidence interval.

Results

During the 2 years, 283 CVCs were inserted in 190 adult patients.

Quantitative cultures of the catheter tip. One hundred and fifteen patients were hospitalized in the surgical unit and 75 in the medical unit. They were comparable with respect to age (45.9 ± 19.2 vs. 56.6 ± 19.6 years), sex, simplified acute physiologic score (SAPS) (11 ± 5 vs. 14 ± 4) [18], length of ICU stay (24 ± 16 vs. 21 ± 22 days), and antibiotic treatment (112/115 vs. 73/75).

Of the 283 studied catheters, 55 (19%) were positive in quantitative catheter-tip cultures. Of these positive results, 18 were considered contaminations; 23, colonizations; and 14, infections (table 1). The organism distribution pattern was similar among contaminated, colonized, and infected catheters, with a large predominance of staphylococci (76% of all isolates).

Fourteen catheters from different patients were considered infected. These catheters were inserted in 14 patients (age, 56.9 ± 18.4 years; SAPS, 13 ± 5; ICU stay, 36 ± 18 days), of whom 12 were treated with antibiotics for a remote septic focus. Bacteremia was associated with nine of these catheters. None of the bacteria were susceptible to the antibiotics previously prescribed. For the patients with infected catheters, the quantitative cultures, indicative of infection, were positive within 18–36 hours.

Differential blood cultures. Among the 283 catheters, 19 (from 19 patients) were DBC-positive (table 2). Among the catheters, 8 were inserted in the jugular vein, 7 in the femoral vein, and 4 in the subclavian vein. Of the 14 CRIs according to the quantitative catheter-tip cultures, 13 were associated with a positive DBC.

ROC curve analysis was carried out by varying the catheter/peripheral cfu ratio (figure 1). The combined sensitivity and specificity were most satisfactory at a ratio of 8. With use of this threshold, the DBCs were positive for 16 catheters as well as for the 13 catheters previously considered infected. Sensitivity, specificity, and predictive values are reported in table 3.

Discussion

When CRI is suspected in ICU patients, the removal of the catheter is generally proposed. However, as many as 80% of the catheters removed will be sterile [4]. Furthermore, the insertion of a new catheter carries its own risk of complications, especially mechanical. In a study of 160 ICU patients, insertion of CVCs at new sites has been shown to lead to complications such as pneumothorax or arrhythmias in 9% of patients [5].

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Table 1. Characteristics of the catheters removed from ICU patients and analyzed in the study.

	Positive in catheter tip culture			Negative in culture (n = 228)	All catheters (n = 283)
	Contaminated (n = 18)	Colonized (n = 23)	Infected (n = 14)		
Insertion site					
Jugular	13	15	6	143	177
Subclavian	4	3	2	46	55
Femoral	1	5	6	39	51
Mean (±SD) duration of stay (d)	10 ± 5	10 ± 3	13 ± 5	10 ± 6	10 ± 5
Reason for catheter removal					
Infection suspected	7	11	14	86	118
No longer useful	11	12	0	142	165
Organism(s) identified					
Staphylococcus aureus	5	8	7		
Coagulase-negative staphylococci	8	10	4		
Other gram-positives	3	1	1		
Enteric gram-negatives	2	4	2		

Therefore, a technique allowing for the diagnosis of CRI without catheter removal would be useful in clinical practice. The ideal technique should have good specificity to prevent the removal of sterile catheters, but, more important, it should have good sensitivity. Indeed, this technique needs to be safe, presenting minimal risk of leaving an infected catheter in place. False-negative results should be minimized.

In 1979 Wing et al. first had the idea of performing cultures of blood withdrawn from the CVC and from a peripheral vein [6]. They compared both results and could establish the diagnosis of CRI in a patient. This observation led to the development of differential blood cultures for the diagnosis of CRI.

The aim of our study was to evaluate DBCs for ICU patients. As the ''gold standard'' for the microbiological diagnosis technique, we chose that proposed by Brun-Buisson et al. [15], adapted from Cleri et al. [16]. This technique allows for the detection of colonization of the external surface of the catheter tip and of its internal lumen. To identify false-negatives in the

Table 2. Data concerning the 19 positive differential blood cultures.

Catheter classification	Insertion site	Isolate	Differential blood cultures: cfu/mL in indicated specimen		
			CVC	P	CVC/P ratio
Sterile	Jugular	*Klebsiella oxytoca*	10^2	<1	10^2
Sterile	Subclavian	*Klebsiella oxytoca*	16	<1	16
Sterile	Femoral	*Enterobacter cloacae*	10^2	<1	10^2
Sterile	Subclavian	*Staphylococcus epidermidis*	2	<1	2
Colonized	Jugular	*Staphylococcus aureus*	2	<1	2
Colonized	Jugular	*Escherichia coli*	4.4×10^3	<1	4.4×10^3
Infected	Jugular	*Staphylococcus aureus*	10^4	20	5×10^2
Infected	Jugular	*Staphylococcus aureus*	5×10^3	10	5×10^2
Infected	Femoral	*Staphylococcus aureus*	10^4	3	3.3×10^3
Infected	Jugular	*Staphylococcus aureus*	4.6×10^3	<1	4.6×10^3
Infected	Subclavian	*Staphylococcus aureus*	7×10^2	90	8
Infected	Femoral	*Staphylococcus aureus*	3×10^5	2×10^3	1.5×10^2
Infected	Femoral	*Staphylococcus epidermidis*	8×10^2	<1	8×10^2
Infected	Femoral	*Staphylococcus epidermidis*	4×10^6	10^3	4×10^3
Infected	Femoral	*Staphylococcus epidermidis*	1.5×10^6	<1	1.5×10^6
Infected	Jugular	*Staphylococcus epidermidis*	5×10^2	<1	5×10^2
Infected	Subclavian	*Escherichia coli*	4×10^3	<1	4×10^3
Infected	Jugular	*Escherichia coli*	3.5×10^3	<1	3.5×10^3
Infected	Femoral	*Corynebacterium* species	6×10^4	<1	6×10^4

NOTE. CVC = central venous catheter; P = peripheral vein. When the number of cfu in the peripheral vein was <1, it was considered as 1 for the calculation of the CVC/P ratio.

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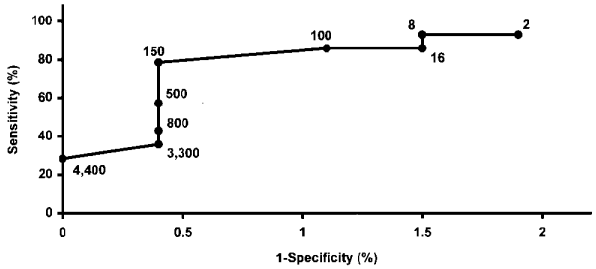


Figure 1. Receiver operating characteristic curve for ratio of bacterial counts in culture of the blood withdrawn from the catheter and culture of blood from a peripheral vein. The numbers on the curve are respective cutoffs in the differential blood cultures.

microbiological techniques, local and general signs of infection were noted at the time of the sepsis suspicion and after catheter removal. The reason for removal could be either that infection was suspected because of local signs (local inflammation or infection) or general signs (fever, chills, etc.), or else that the catheter was no longer needed.

We found a rate of 4.9% of infected catheters and 7.3% of patients with CRI. Bacteremia followed catheter infection in 3.1% of catheterized patients. *Staphylococcus aureus* was the predominant organism associated with bacteremia. This is in accordance with findings in other studies of ICU patients [11, 12, 15]. Although yeast may be responsible for CRI in the ICU, especially in immunocompromised patients, no fungal infection was identified.

DBCs have been evaluated in several studies, including a comparison with another microbiological technique. In a group of 24 patients receiving parenteral nutrition, Fan et al. found that DBC correctly identified seven of nine infected catheters [12]. They used an arbitrary threshold of seven for the catheter/peripheral cfu ratio. Sensitivity was 77.8% and specificity was 100%, with no false-positive results.

These interesting findings were brought into question by the results from Paya et al. [13]. In a study including 44 patients in a surgical ICU with suspected CRI, 15 catheters were considered infected according to a semiquantitative technique; DBC identified only 7 of these catheters. In that study, with regard to six catheters classified as DBC-false-negative, high organism concentrations (>100 cfu/mL) were observed in the blood withdrawn from the catheter and from the vein. In fact, a dilution of these samples might have yielded a positive DBC. In addition, the investigators did not include any clinical information in the definition of CRI. Thus, it was impossible to separate colonizations and infections of the catheters.

Finally, bacteria responsible for CRI were different from those found in other studies, including ours. *Pseudomonas aeruginosa* was found in more than half of the CRIs, and *S. aureus* accounted for only 6% of the isolated organisms. This difference may be explained by variations in the pathogenesis of the infections and may reflect differences in the efficiency of DBC.

In another study of patients hospitalized in internal medicine and surgical wards and the ICU, 107 catheters were evaluated, and DBCs identified 16 of 17 CRIs. DBC was found to be reliable, with a sensitivity of 94% and a specificity of 100% [11]. Recently, in patients with cancer (n = 31) and in the ICU (n = 27), DBC identified correctly 30 of 36 CRIs; the 6 remaining cases were false-negatives because removal of these catheters led to resolution of clinical signs of infection [14]. It is interesting that 16 patients with CRI had a negative tip culture, and CRIs were found to be related to hub infection. If this finding is confirmed, the efficacy of DBC as compared with that of tip cultures would be reinforced.

In all of these studies the catheter/peripheral cfu ratio was chosen arbitrarily. The range of this ratio was wide, between 2 and 30. In our study, the ROC curve technique was used to determine the ratio of the DBC that gives the best performance in diagnosis of CRI. With a threshold of 8, sensitivity was maximal, decreasing the number of false-negatives with the technique. This value is close to those chosen arbitrarily in other studies [11–14]. With this cutoff, sensitivity and specificity of DBC were very high. The few false-positive results led to the removal of sterile catheters, but these cases are few in contrast to the large number of catheters that can be safely left in place.

The DBC technique may have some potential drawbacks. First, the one false-negative result of the study raises an important issue because an infected catheter may remain inserted. All the studies of DBC have found false-negative results, but sensitivity remained up to 80%. These results may be explained by strictly external contamination of the catheter, missed by the DBC. However, to our knowledge, a method of diagnosis of CRI with 100% sensitivity and 100% specificity does not

Table 3. Sensitivity, specificity, and predictive values of differential blood cultures for all catheters and for catheters removed for a suspected infection. (Percentages and 95% confidence limits are given.)

Catheters removed	Sensitivity	Specificity	PPV	NPV	Accuracy
All (n = 283)	92.8 ± 3.0	98.8 ± 1.2	81.2 ± 4.5	99.6 ± 0.7	98.5 ± 1.4
For suspected infection (n = 118)	92.8 ± 3.0	100	100	99.0 ± 0.9	99.1 ± 1.7

NOTE. NPV = negative predictive value; PPV = positive predictive value.

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exist. In all circumstances, the results of the technique must be interpreted cautiously and clinical evaluation must remain the first criterion of CRI diagnosis, leading to the removal of the catheter if there is any doubt.

The second problem is related to the time necessary to obtain results from quantitative cultures, generally between 24 and 48 hours. In some circumstances, this delay will be too long for a patient with signs of severe infection. In this case, the catheter has to be removed. In our study, the catheters were cultured over 5 days to be certain not to miss late bacterial growth. However, no culture was positive after 48 hours.

Finally, the technique of DBC has a cost. However, this is balanced by the savings due to the limitation in wasting sterile catheters. In our study, 14 of 118 patients with a suspected CRI had a positive DBC, so 104 catheters were removed unnecessarily. Their replacement could have been avoided. A cost-benefit evaluation of the DBC technique must be done.

In conclusion, for ICU patients, DBC may be considered a useful tool for diagnosis of CRI without removal of the catheter. The possibility of false-negative results, although uncommon, must be kept in mind, and the persistence of sepsis syndrome without any evidence of other sources of infection must lead to the removal of the catheter. The technique cannot be used for all ICU patients, especially because of the time lag in obtaining culture results. However, this technique seems to decrease the waste of sterile catheters removed when ICU patients become febrile.

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[Application form] OL
[Application in foreign language]
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[Theme code (reference)]
4C038
[F term (reference)]
4C038TA01
4C038TA03
4C038UJ02

wrap up close

(57) [Summary] (Modified)
[Problem] To provide a cheaper and simpler phlebotomy needle that facilitates visualization of flashbacks.
A central portion (106) of the needle (100) includes a hole or opening (110) that communicates with the flow path defined by the needle (100), and a transparent housing (112) covers the opening (110). Positioned around to facilitate visualization of blood flow through needle 100 . A material that allows passage of air and provides an indication of blood flow through needle

100 is positioned over opening 110 . The material is in the form of plugs or alternatively in th e form of patches or collars. The phlebotomy needle includes a needle 100, a housing 112 hav ing a passive vent, and an observation area for visualizing blood flow in the housing 112. FIG. [Selection drawing] Fig. 2-1

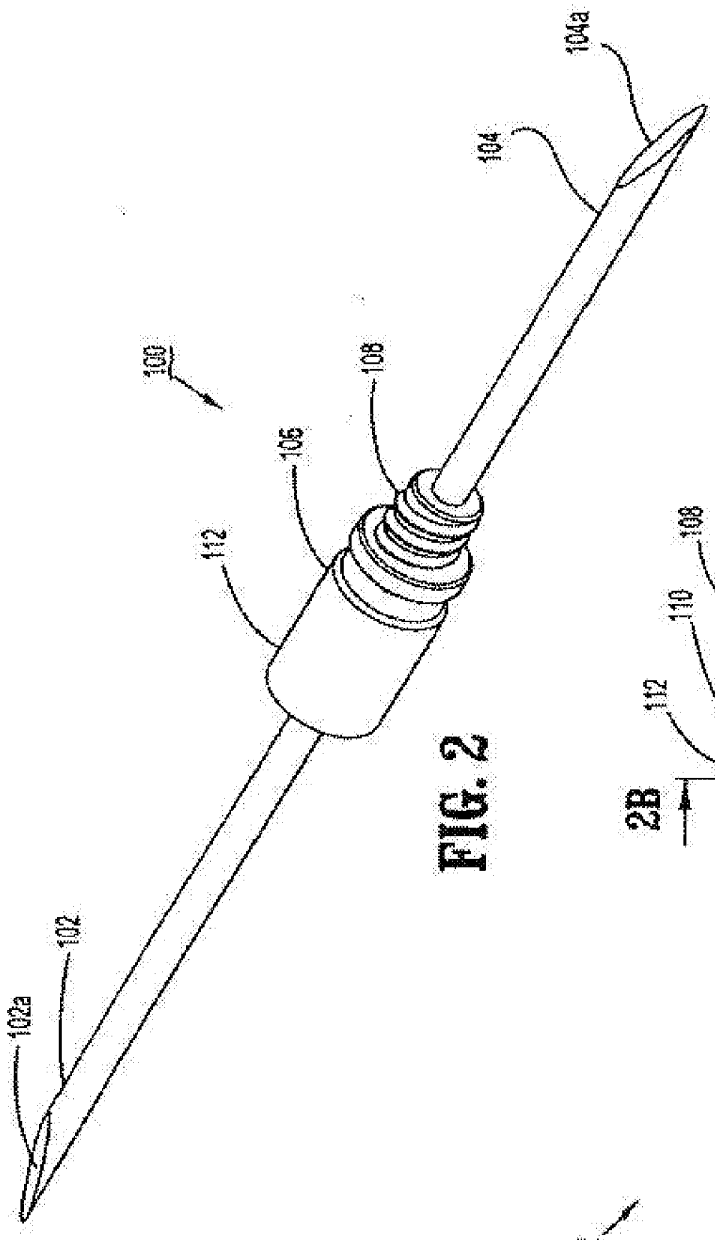


FIG. 2

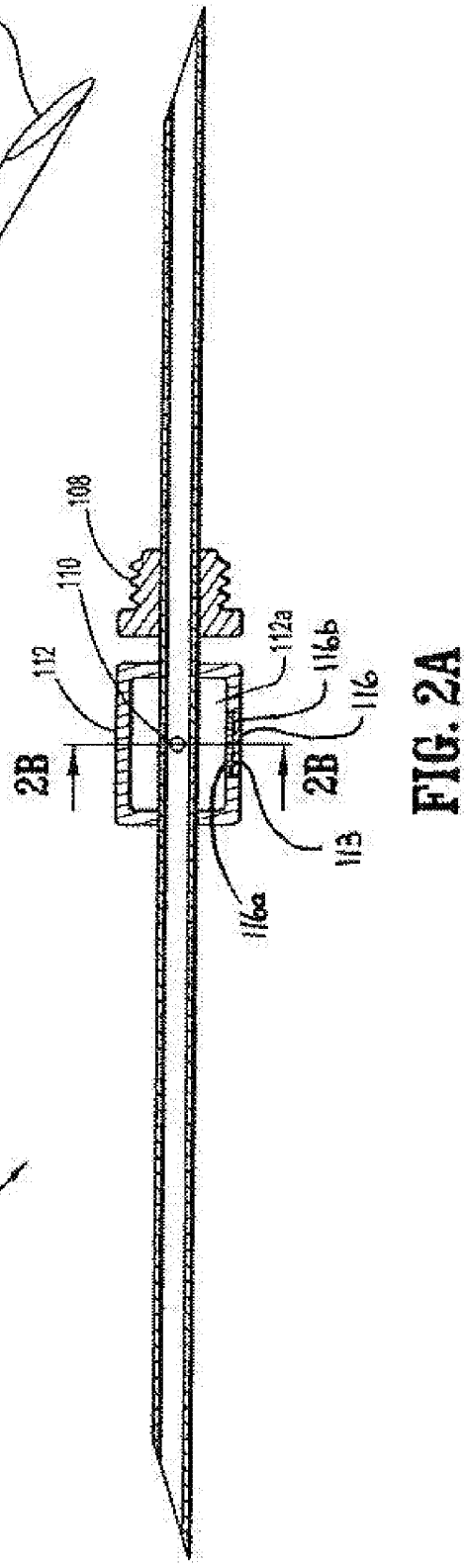


FIG. 2A

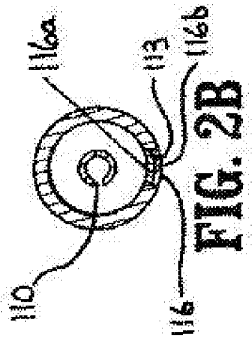


FIG. 2B

The scope of the claims open ----

Claims:

1. A

phlebotomy needle: a distal needle portion

having a sharpened distal end configured to pierce tissue; and a distal needle portion configured to pierce a stopper of a blood collection tube. a proximal needle portion having a sharpened proximal end, the distal needle portion and the proximal needle portion defining a fluid channel; a housing supported over the needle

; a housing, comprising a passive vent, the housing defining a viewing area for viewing blood in the housing; and an elastomeric shield positioned about the proximal needle portion

, A phlebotomy needle comprising an elastomeric shield and an elastomeric shield wherein the proximal needle portion defines a fluid flow path into the housing.

2. The phlebotomy needle of claim 1

, further comprising a fluted member positioned within said housing, said fluted member defining a plurality of fluid channels.

3.

The phlebotomy needle of claim 2, wherein said fluted member extends distally beyond said elastomeric shield.

4.

The phlebotomy needle of claim 2, wherein the fluid channel of the fluted member is configured to allow the passage of blood.

5.

The phlebotomy needle of claim 2, further comprising a hydrophilic material supported within said housing. 6. The phlebotomy of claim 5, wherein said flow path directs blood from the proximal end of said needle into the fluid channel of said fluted member and into contact with said hydrophilic material

.

needle.

[Claim 7]

6. The phlebotomy needle of claim 5, wherein a portion of said fluted member is surrounded by said hydrophilic material.

8. The method of claim

5, wherein a proximal end of said fluted member is surrounded by said elastomeric shield and a distal end of said fluted member is surrounded by said hydrophilic material. Phlebotomy needle.

9.

The phlebotomy needle of claim 5, wherein the proximal portion of the housing includes an inwardly extending annular rib.

10.

The elastomeric shield has an open distal end including an annular flange, and an annular rib of the housing engages the flange to extend the distal end of the elastomeric shield into the housing. 10. The phlebotomy needle of claim 9, held in the

11.

The phlebotomy needle of claim 10, wherein the elastomeric shield flange is positioned adjacent to the hydrophilic material.

12.

The phlebotomy needle of claim 1, wherein the distal end of said elastomeric shield is received in said housing and the proximal end of said elastomeric shield extends proximally from said housing.

detailed description open ----

Description: BACKGROUND 1.

Technical Field The present disclosure relates to medical needles having structures that facilitate visualization of flashback. More particularly, the present disclosure provides vented phlebotomy needles that include structures that facilitate visualization of flashback.

Regarding. 2. Background of Related Art

Medical devices for drawing blood from a patient are well known. These devices include standard needle-syringes, butterfly needle sets, and phlebotomy needles. A butterfly needle set typically includes a hollow needle having a sharpened distal end and a proximal end secured to a needle hub. A proximal portion of the needle hub is connected to flexible tubing. The needle hub defines a fluid conduit in communication with the tubing and includes a pair of flexible, radially extending wings that facilitate grasping of the butterfly needle set by a medical practitioner. Generally, the flexible tubing is formed of a transparent material that allows medical personnel to visualize blood flow, or flashback, through the tubing proximate to the needle hub. Flashback visualization allows medical personnel to confirm that the needle has been correctly inserted into the patient. [0003] Some clinicians utilize a hypodermic needle-syringe with a clear needle hub to take blood samples. During insertion, these clinicians usually observe flashb

acks in the needle hub. Phlebotomy needles generally do not include structures for visualizin g flashback. The lack of a flashback visualization feature on the phlebotomy needle is not a m ajor drawback for more experienced HCWs, but for HCWs with little experience of drawing blo od with a phlebotomy needle, the needle may be a problem. Not having any means of confirm ing proper positioning in the patient can increase the time required to draw blood and can incr ease patient discomfort. [0005]

In an attempt to overcome the above disadvantages, US Pat. No. 6,200,300 to Norris et al. discloses a phlebotomy needle, which is attachable to a blood collection tube, comprises an ou ter needle, an inner needle, and a valve (bulb). The valve is transparent, allowing medical pe rsonnel to visualize the blood when the outer needle is correctly positioned within the patien t's vein. The valve also includes a button that can be depressed by a medical practitioner to v ent air from within the needle. Air in the needle prevents blood from flowing through the need le and must be vented.
[0006]
[
0006] US Pat.
No. 5,450,856 . SUMMARY OF THE INVENTION [0007] The Norris phlebotomy needle is a H owever, a cheaper and simpler phlebotomy needle that facilitates flashback visualization is de sired. SUMMARY OF THE INVENTION The present disclosure relates to a phlebotomy needle having a sharpened distal end configured to penetrate tissue.

a proximal needle portion having a sharpened proximal end configured to penetrate a blood c ollection tube stopper; and a central needle portion defining an opening. The distal needle por tion, the proximal needle portion and the central needle portion define a fluid channel in com munication with the opening. A material is positioned adjacent to the opening. The material is

of a type that allows air to exit the fluid channel through the openings while preventing the pa ssage of blood. In one embodiment, the material provides a visual indication of blood flow, or flashback, adjacent the opening.

[0009]

In one embodiment, the material comprises a hydrophobic material. In alternative embodim ents, the material comprises a hydrophilic capillary action material. In yet another embodime nt, the material includes hydrophobic plugs. Alternatively, the material may define a collar pos itioned around the opening.

[0010]

In one embodiment, the opening is circular. Alternatively, the openings are envisioned to be of various configurations, such as rectangular or slot-shaped.

[0011]

In one embodiment, a transparent housing is positioned around the opening to facilitate visu alization of the flashback. A housing may also be positioned to contain the material and may i nclude a vent for venting air from the needle.

[0012]

In one embodiment, the phlebotomy needle includes engagement structure configured to en gage the needle holder.

In one

embodiment, a check valve is provided to prevent air from entering the fluid channel throug h the opening. In yet another embodiment, the phlebotomy needle includes a needle holder. For example, the present invention provides the following items.

(Item 1)

A phlebotomy needle,

a distal needle portion having a sharpened distal end configured to penetrate tissue and a sh arpened

proximal end configured to pierce a stopper of a blood collection tube. and a central needle p ortion

defining an opening, wherein the distal needle portion, the proximal needle portion and the c entral needle portion are in fluid communication with the opening a central needle portion defi ning a channel;

A material positioned adjacent to the opening of a type that allows air to exit the fluid chann el through the opening while preventing the passage of blood to reduce blood flow.

A phlebotomy needle comprising a material that further enables visual indication .

(Item 2)

The phlebotomy needle of item 1, wherein the material comprises a hydrophobic material.

3.

The phlebotomy needle of claim 1, wherein said material comprises a hydrophilic capillary ac tion material.

4.

The phlebotomy needle of claim 1, wherein said material comprises an inner layer of hydrophilic material facing towards said opening and an outer layer of hydrophobic material.

(Item 5)

The phlebotomy needle according to item 1, wherein the opening is circular.

6.

The phlebotomy needle of claim 1, wherein the opening defines an elongated slot.

7.

The phlebotomy needle of claim 1, further comprising a transparent housing positioned around the opening. Clause 8.

The phlebotomy needle of clause 1, further comprising an engagement structure supported by the phlebotomy needle, the

engagement structure configured to engage a needle holder.

9.

The phlebotomy needle of claim 1, wherein the material defines a collar covering the opening and positioned about the needle.

10.

The phlebotomy needle of claim 9, further comprising a transparent housing positioned around the collar material.

11.

The phlebotomy needle of claim 1, further comprising a check valve for preventing air from entering the fluid channel through the opening.

12.

The phlebotomy needle of claim 1, further comprising a needle holder.

13.

The phlebotomy needle of claim 1, wherein the material provides a visual indication of blood flow through the opening.

(Item 14)

A phlebotomy needle, a

distal needle portion having a sharpened distal end configured to penetrate tissue and a

sharpened proximal end configured to pierce a stopper of a blood collection tube. and a central needle portion

defining an opening, wherein the distal needle portion, the proximal needle portion and the central needle portion are in fluid communication with the opening A central needle portion defining a channel and

a hydrophobic material positioned adjacent the opening to permit air to exit the fluid channel through the opening while allowing blood to exit the fluid channel. A hydrophobic material of a type that prevents passage and further permits visual indication of blood flow, a

transparent housing positioned around the opening, and

an engagement supported by the phlebotomy needle. A

phlebotomy needle comprising: a structure, and an engagement structure configured to eng age the needle holder .

(Item 15)

The phlebotomy needle of item 14, further comprising the needle holder.

(Item 16)

A phlebotomy needle,

a distal needle portion having a sharp distal tip configured to penetrate tissue;

a proximal needle portion having a sharpened proximal end configured to penetrate a blood collection tube stopper; and a central needle portion

defining an opening, the distal needle portion, the proximal The needle portion and the centr al needle portion define a fluid channel in communication with the opening, a hydrophilic

capillary action material positioned adjacent the central needle portion and the opening, whe rein air flows into the a hydrophilic capillary active material of a type that allows exiting the fl uid channel through the opening while preventing the passage of blood, further permitting a v isual indication of blood flow; and the opening

. and an engagement structure supported by the phlebotomy needle

, the engagement structure configured to engage a needle holder

.

(Item 17)

The phlebotomy needle of item 16, further comprising the needle holder.

(Item 18)

A phlebotomy needle, the phlebotomy needle

penetrating a distal needle portion having a sharpened distal end configured to penetrate tis sue and a stopper of a blood collection tube. a proximal needle portion having a pointed proxi mal end configured to define a fluid channel

; a housing that includes a passive vent and

defines an observation area for visualizing blood in the housing

.

(Item 19)

19, further comprising an elastomeric shield positioned about the proximal needle portion, th e elastomeric shield and the proximal needle portion defining a fluid flow path into the housin g; Phlebotomy needle as described.

(Item 20)

20. The phlebotomy needle of any one of items 18 and 19, further comprising a fluted memb er positioned within the housing, the fluted member defining a plurality of fluid channels.

(Item 21)

The phlebotomy needle according to any one of items 18 to 20, further including a hydrophili c material supported within the housing.

22.

The phlebotomy needle of any one of items 18-21, wherein the needle has a central portion defining an opening into the housing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

An embodiment of the presently disclosed vented phlebotomy needle with a flashback chamber is disclosed herein with reference to the drawings.

1 is a perspective view, with parts separated, of a "prior art" phlebotomy needle with a needle holder, a protective needle cover and a blood collection tube shown in phantom; FIG.

1A is a side cross-sectional view of an assembled "prior art" phlebotomy needle, needle holder, and blood collection tube shown in phantom, with the distal portion of the phlebotomy needle positioned within a vein; It is

2-1 is a side perspective view of one embodiment of the presently disclosed phlebotomy needle; FIG . 2A is a cross-sectional view of the phlebotomy needle shown in FIG. 2; FIG . 2B is a cross-sectional view along section line 2B-2B of FIG. 2A.

2-2C is a side cross-sectional view of another embodiment of a phlebotomy needle of the present disclosure; FIG.

3 is a side cross-sectional view of an alternate embodiment of the phlebotomy needle of the present disclosure; FIG . FIG. 3A is a cross-sectional view taken along section line 3A--3A of FIG.

FIG. 4 is a side perspective cutaway view of another embodiment of the phlebotomy needle of the present disclosure; FIG . FIG. 4A is a cross-sectional view along section line 4A--4A of FIG.

FIG. 5 is a side perspective cutaway view of another embodiment of the phlebotomy needle of the present disclosure; FIG.

6 is a side cross-sectional view of another embodiment of the phlebotomy needle of the present disclosure; FIG.

7 is a cross-sectional view along section line 7-7 of FIG. 6; FIG. DETAILED DESCRIPTION OF EMBODIMENTS

Embodiments of vented phlebotomy needles of the present disclosure with flashback chambers will now be described in detail with reference to the drawings

, In the drawings, like reference numbers indicate identical or corresponding elements in each of the several drawings. FIG . 1 shows a known phlebotomy needle 10, needle holder 12, and needle covers 14 and 16. As shown in FIG. A blood collection tube 17 is shown in phantom. Phlebotomy needle 10 includes a distal needle portion 20 , a proximal needle portion 22 and an intermediate needle hub 23 with an engaging portion 24 . Engaging portion 24 is provided to facilitate connecting phlebotomy needle 10 to needle holder 12 . In one embodiment, the engaging portion includes a male fitting 24 a configured to engage a female fitting or engaging member 26 , which engages the distal end of needle holder 12 . provided to Alternatively, oth

er engagement structures may be used, including screws, snap-type connectors, and the like. An elastomeric shield 28 is positioned over the proximal needle portion 22 to seal the proxima l needle portion 22, as described in further detail below . [0017]

Needle holder 12 includes a substantially cylindrical body 30 having a distal end including en gagement member 26 and a proximal end including a pair of flange members 32 . Flange me mber 32 facilitates grasping and insertion of blood collection tube 17 by medical personnel. Cy lindrical body 30 defines cavity 34 (FIG. 1A) for receiving blood collection tube 17 . Blood coll ection tube, usually
17 is sealed by a penetrable stopper 17a to define a low pressure cavity 17b (FIG. 1A). The di stal end of holder 12 defines an opening 36 through engagement member 26 , opening 36 siz ed to receive proximal needle portion 22 . In use, needle 10 is secured to the distal end of n eedle holder 12 via engagement portion 24 and engagement member 26, as shown in FIG. 1A .
When needle 10 is secured to needle holder 12 , proximal needle portion 22 is positioned with in cavity 34 of body 30 of needle holder 12 and elastomeric shield 28 is positioned over proxi mal needle portion 22 . be. A blood collection tube 17 (shown in phantom) containing a penet rable stopper 17a is then positioned within cavity 34 . When blood collection tube 17 is inserte d into cavity 34 , proximal needle portion 22 engages stopper 17 a and penetrates shield 28 . Shield 28 is compressed downward (FIG. 1A) so that proximal needle portion 22 penetrates st opper 40 and enters cavity 17b of blood collection tube 17 . Once the distal needle portion 20 is properly positioned in the patient's vein 38 and the blood collection tube 17 is positioned wi thin the cavity 34, blood is typically flowed through the needle 10 and into the blood collection tube 17. The blood collection tube 17 is maintained under vacuum. When the blood collection tube 17 is removed from the needle holder 12 , the resilient elastomeric shield 28 returns to it s original configuration, covering and sealing the proximal needle portion 22 .
[0019]
FIGS. 2 and 2A illustrate one embodiment of the phlebotomy needle of the present disclosur e with a flashback chamber, generally indicated as 100. FIG. Needle 100 includes distal end 1 02 , proximal end 104 and central portion 106 . Distal end 102 has a pointed end 102a config ured to penetrate patient tissue, and proximal end 104 is configured to pierce stopper 17a of blood collection tube 17 (see FIG. 1A). It has a sharp edge 104a. Central portion 106 includes an engagement member 108, as discussed above, which is configured to engage a needle hol der (FIG. 1). Central portion 106 also includes an opening or hole 110 and a translucent or tra

nsparent housing 112 positioned around central portion 106 of the portion defining opening 1 10 . Although opening 110 is shown as circular, other configurations are envisioned, such as r ectangular, square, oval, elongated slot 39 (FIG. 5), and the like. A transparent housing 112 d efines a blood reservoir 112a. Vent openings 113 are preferably formed in transparent housin g 112 . Vent opening 113 facilitates venting needle 100 and allows blood flow through needle 100 . As discussed below, the vent opening 113 of the housing 112 may be covered with a ma terial that allows passage of air but not liquid, such as blood, for example. Referring to FIGS. 2A and 2B, vent opening 113 may be covered with filter 116

.

Filter 116 preferably includes an inner layer 116a of hydrophilic material and an outer layer 1 16b of hydrophobic material. Preferably, at least one of layers 116a and 116b has a pore size of less than 0.45 microns. Such a pore size allows air to pass through but prevents bacteria fr om entering the housing 112 .

[0021]

Referring to FIG. 2C, in an alternative embodiment, filter 116 may be replaced by a hydroph obic check valve, such as flap valve 150, for example. As shown, flap valve 150 is configured t o flex outward from housing 112 to expose vent opening 113 and vent housing 112 when bloo d begins to flow into housing 112 . be.

A hydrophobic sheet 152 is positioned over opening 113 to prevent blood from exiting vent op ening 113 when the check valve is open . Prior to blood beginning to flow into housing 112 , fl ap valve 150 seals opening 113 to prevent material from entering housing 112 . Alternatively, flap valve 150 may be formed from a hydrophilic material if the pore size of the hydrophilic m aterial is sized to block the passage of blood components. When the distal end 102 of needle 100 is properly positioned within the patient's vein, ie,

blood

The transparent housing 112 allows the medical practitioner to visualize blood flow through th e needle 100 as air flows through the needle 100 and air is vented and blood enters the reser voir 112a through the opening 110. make it possible. This allows the medical practitioner to c onfirm that the distal end 102 of the needle 100 has been properly positioned within the patie nt's vein for drawing blood. This provides a significant benefit to medical practitioners attempt ing to draw blood from patients, especially those who have limited experience with drawing bl ood from patients with phlebotomy needles.

[0023]

FIG. 3 illustrates an alternative embodiment of the vented phlebotomy needle of the present disclosure with a flashback chamber generally indicated as 200. As shown in FIG. Needle 200 i s substantially similar to needle 100, except as described below. Needle 200 includes distal en d 202 , proximal end 204 and central portion 206 . Distal end 202 has a sharpened end 202a configured to pierce patient tissue, and proximal end 204 has a sharpened end 202a configure

d to pierce a stopper of a blood collection tube (see FIG. 1A). It has a tapered end 204a. Cent ral portion 206 includes an opening or hole 210 and an engagement member 212a. Material 2 14 is positioned over hole 210 . Material 214 may be a hydrophilic material that wicks blood in to the material so that blood flow through needle 200 can be readily discerned by medical per sonnel. To facilitate venting of needle 200, material 214 may be a hydrophilic material that is permeable to air but impermeable to liquids, such as blood. In one embodiment, the hydrophil ic material can be of the type that changes color when in contact with blood. The material ma y be in the form of collar 250 (Fig. 3) or plug 252 (Fig. 4). Additionally, the material may be p ositioned within a transparent housing or hub 212, or alternatively positioned adjacent openin g 210 without any housing. In an alternative embodiment, the material is a hydrophobic mate rial that is air permeable but blood impermeable. It is noted that ventilation openings 226 ma y be provided in housing 212 to facilitate ventilation of the housing. A vent can be in the form of an opening in housing 212 that allows air to flow out of housing 212 as blood enters.

[0024]

In an alternative embodiment, further illustrated in FIGS. 3 and 3A, material 214 may be for med of an expandable material that allows air to pass through vent openings 226 before cont acting the expandable material with blood. enable Material 214 may expand upon contact with blood, closing vent opening 226 . Although only hydrophilic and hydrophobic materials have been disclosed herein, other materials that facilitate the passage of air while preventing the p assage of blood and provide an indication of blood flow are disclosed in the present disclosure .

phlebotomy needles. The material may have other configurations not disclosed herein. For exa mple, the material may define a pad that covers the opening.

FIGS.

6 and 7 illustrate another embodiment of the phlebotomy needle of the present disclosure wi th a flashback chamber, generally indicated as device 398. FIG. Phlebotomy needle 398 includ es needle 400 and stepped housing 408 . Needle 400 includes distal end 402 , proximal end 4 04 and central portion 406 . Distal end 402 has a pointed end 402a configured to penetrate ti ssue of a patient, and proximal end 404 is adapted to pierce a stopper (not shown) of a blood collection tube (not shown). It has a configured pointed end 404a.

The

stepped housing 408 has a distal portion 408a and a larger diameter proximal portion 408b. A stepped housing 408 is supported at the central portion 406 . Distal portion 408a defines a t hroughbore 412 sized to receive central portion 406 of the needle. Distal portion 408a is seale d and secured to needle 400 using adhesive 410, for example. Alternatively, other known tech niques such as crimping, clamping, screws, welding, etc. may be used to secure needle 400 to housing 408 . Proximal portion 408b is a transparent or translucent material.

formed to facilitate visualization within proximal portion 408 b of housing 408 . Proximal porti on 408 b also defines a through hole 414 that communicates with through hole 412 but has a

larger diameter than through hole 412 . Proximal portion 408 b defines an annular recess 416 between portion 408 b and proximal end 404 of needle 400 . Recess 416 is sized to receive hy drophilic material 418 and inner fluted member 420 . An inner fluted member 420 is positione d around proximal end 404 of needle 400 and defines a plurality of channels 422 in communic ation with hydrophilic material 418 . A ventilation opening 409 is provided through housing 40 8 .

[0028]

An elastomeric shield 428 is positioned over the proximal end 404 of the needle 400 . As dis cussed above, elastomeric shield 428 may be resilient, sealing proximal end 404 of needle 40 0 when proximal end 404 of needle 400 is not connected to a blood collection tube (not show n). function to Elastomeric shield 428 includes a closed proximal end 428a and an open distal end 428b. Open distal end 428 b includes an annular flange 430 positioned adjacent material 418 within recess 416 of housing 408 . A proximal portion 408b of the housing 408 includes a n inwardly extending annular rib 432 that engages a flange 430 of an elastomeric shield 428 a nd a distal end 428b of the shield 428. within recess 416 of housing 408 . A channel 436 is de fined between elastomeric shield 428 and proximal end 404 of needle 400 , as indicated by ar row 434 . Channel 436 directs blood from proximal end 404 of needle 400 into fluted channel 422 of fluted member 420 and into contact with hydrophilic material 418 . In use, when blood contacts material 418 , material 418 provides a visual indication of blood flow that is visible th rough proximal portion 408 b of housing 408 .

[0029]

defined with filter 116 (FIGS. 2A-2B), defined with filter 252 (FIGS. 4-4A), or defined with fil ter 39 (FIG. 5), or defined with check valve 150 (FIG. 5). FIG. 2C) Vent opening 113, as well as openings 226 (FIGS. 3-3A) and opening 409 (FIG. 6) can all be described as passive vent o penings, which are positioned within the needle cannula. Allows gases with pressures greater than atmospheric pressure to automatically leak into the atmosphere. These passive ventilatio n openings do not require any action by the user of the device according to the invention.

[0030]

It is understood that various modifications may be made to the embodiments disclosed herei n. Therefore, the above should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision other modifications within the sc ope and spirit of the claims appended hereto.

drawing open —

[Fig. 1-1]

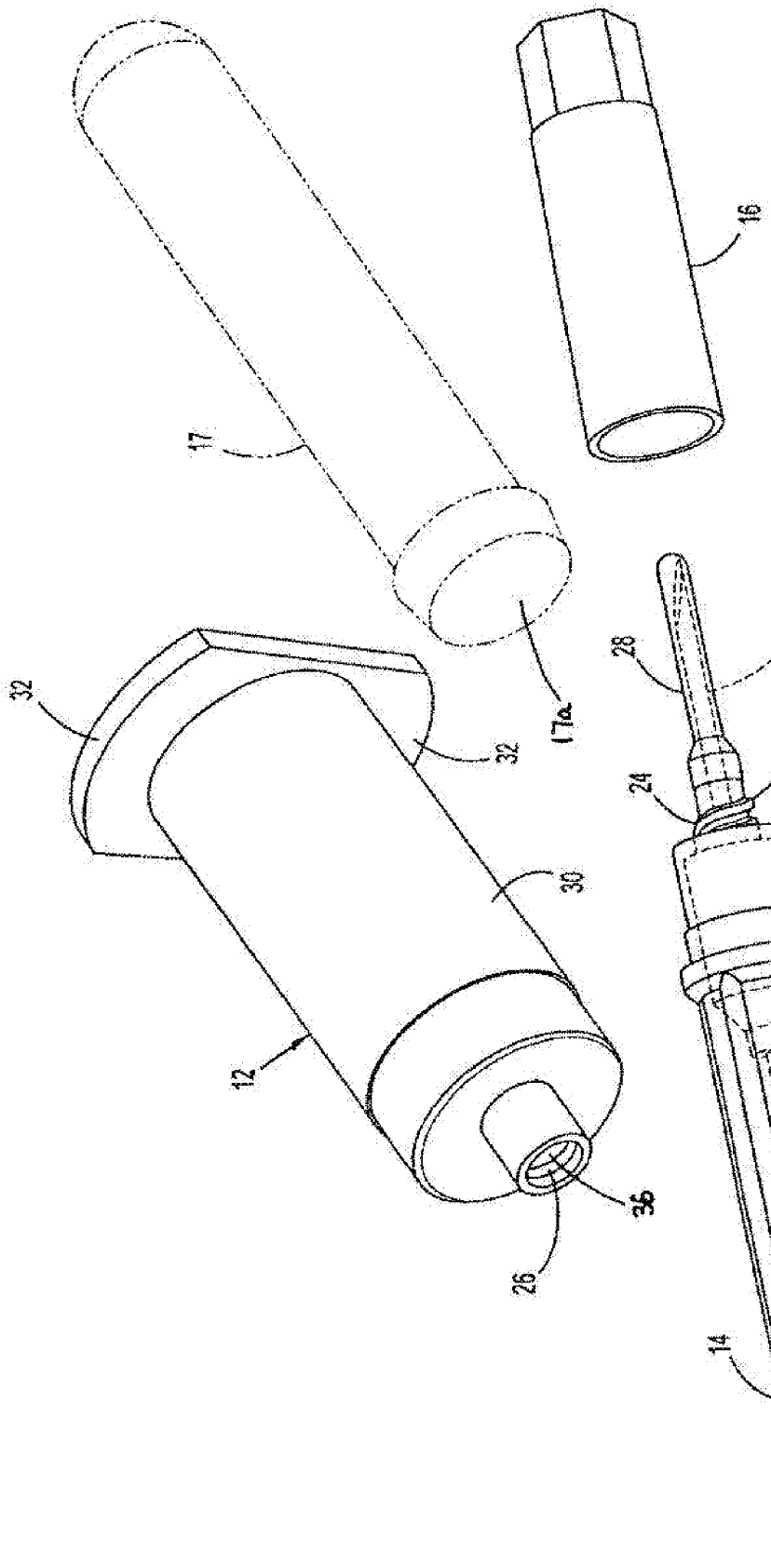


FIG. 1

[Figure 1-2]

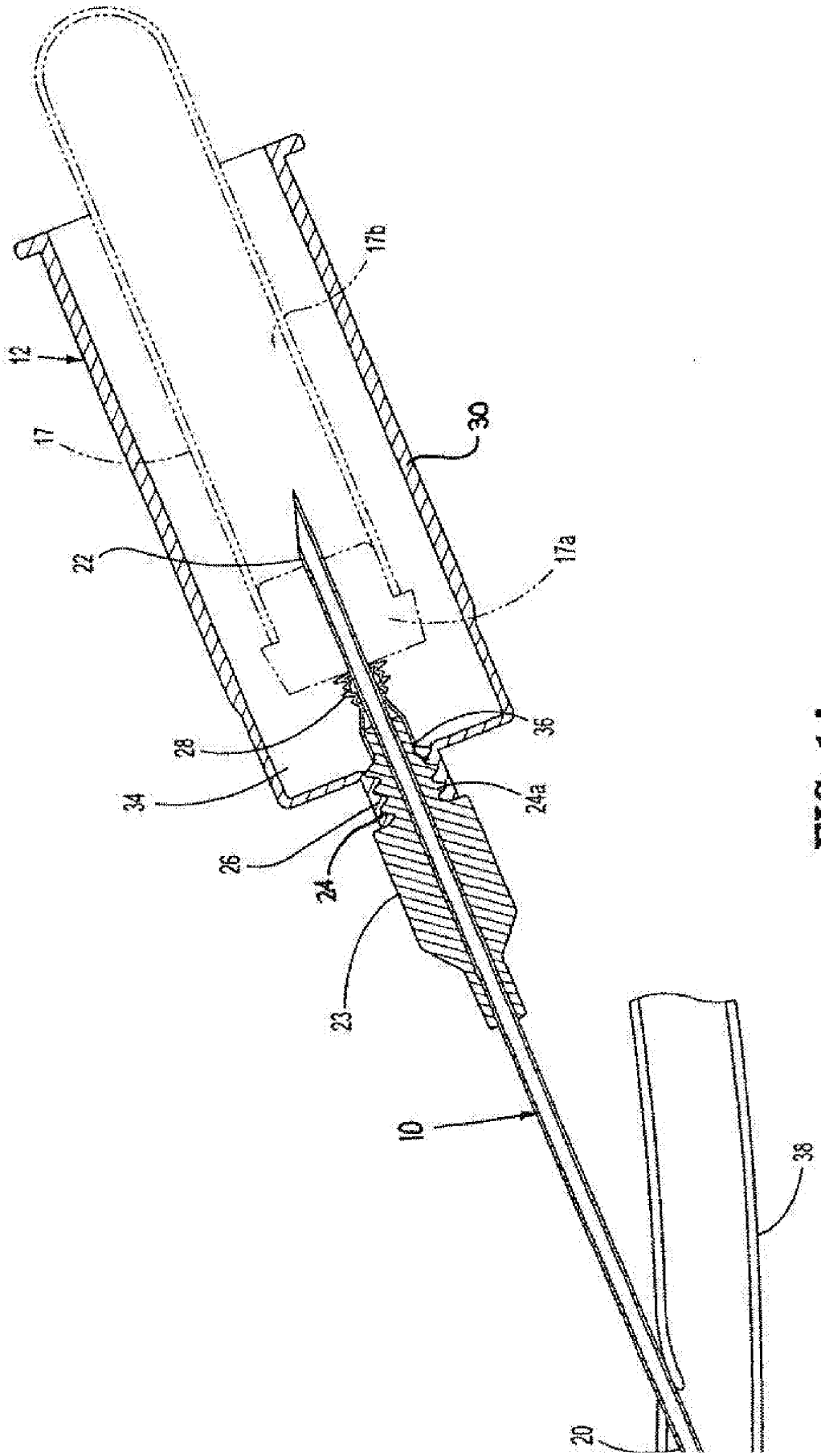
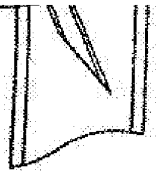


FIG. 1A

[Figure 2-1]



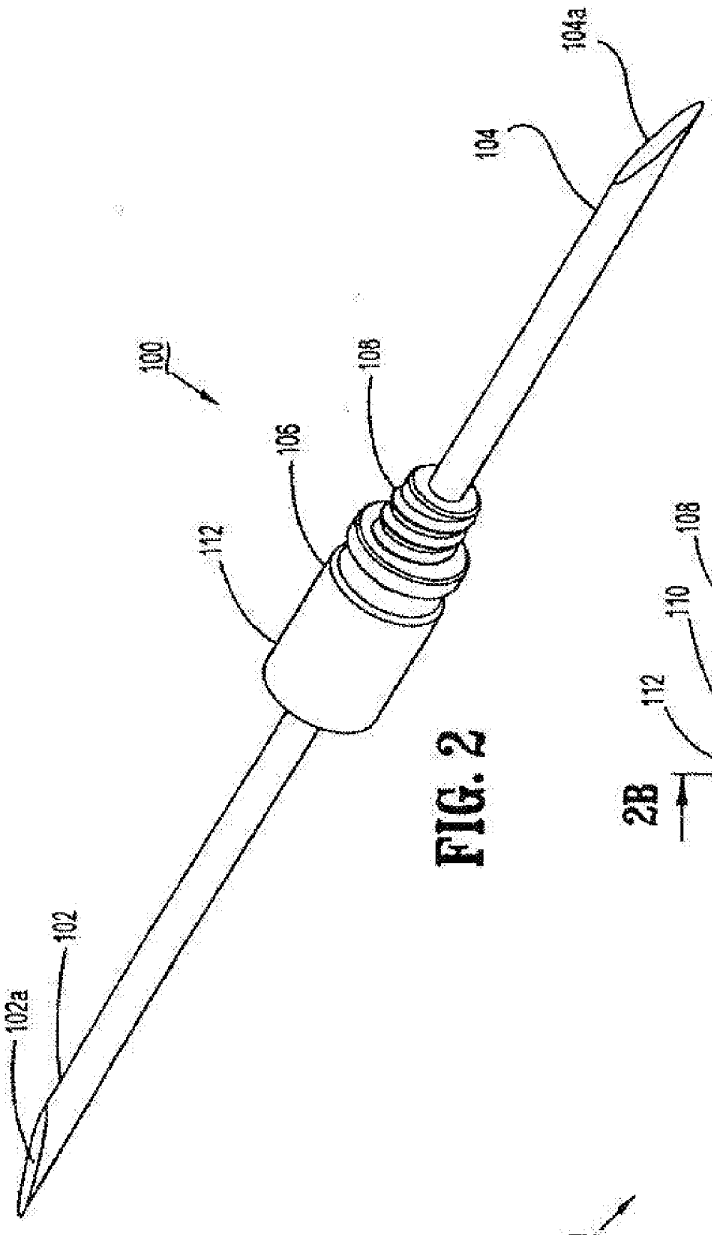


FIG. 2

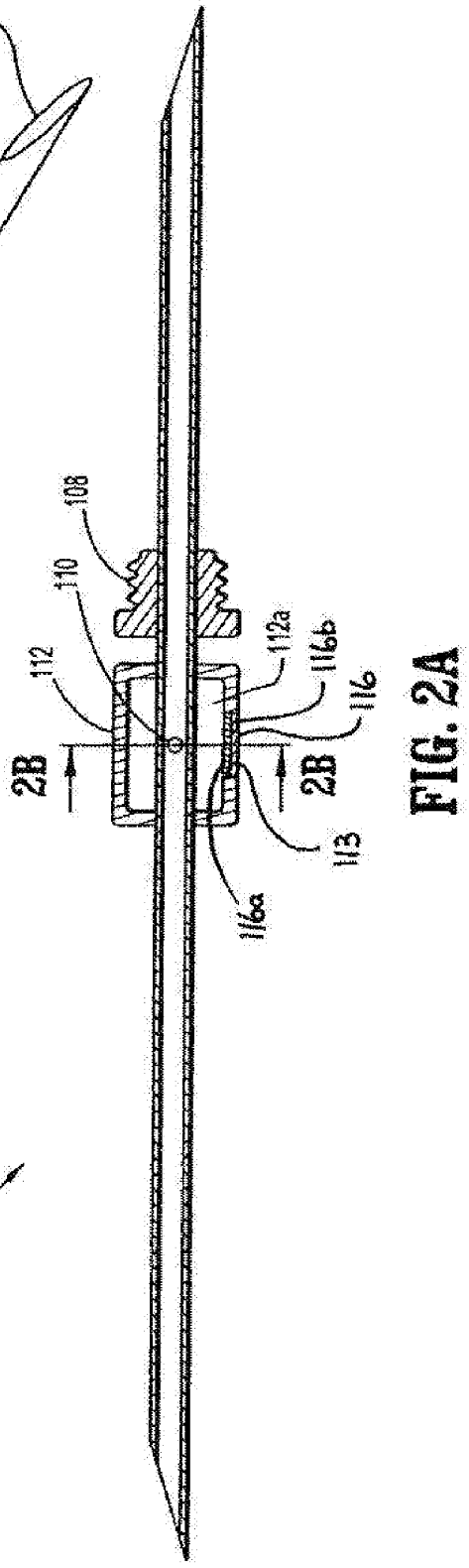


FIG. 2A

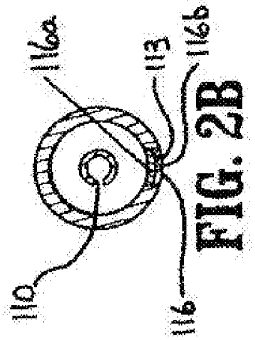


FIG. 2B

[Figure 2-2]

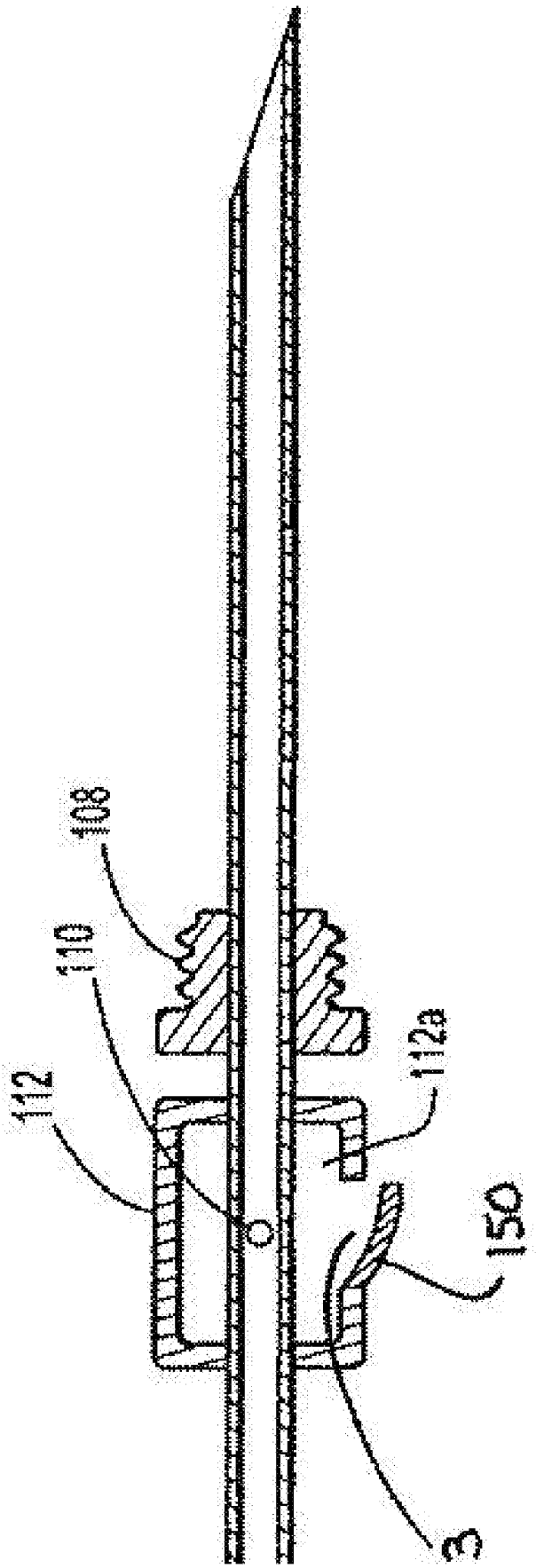
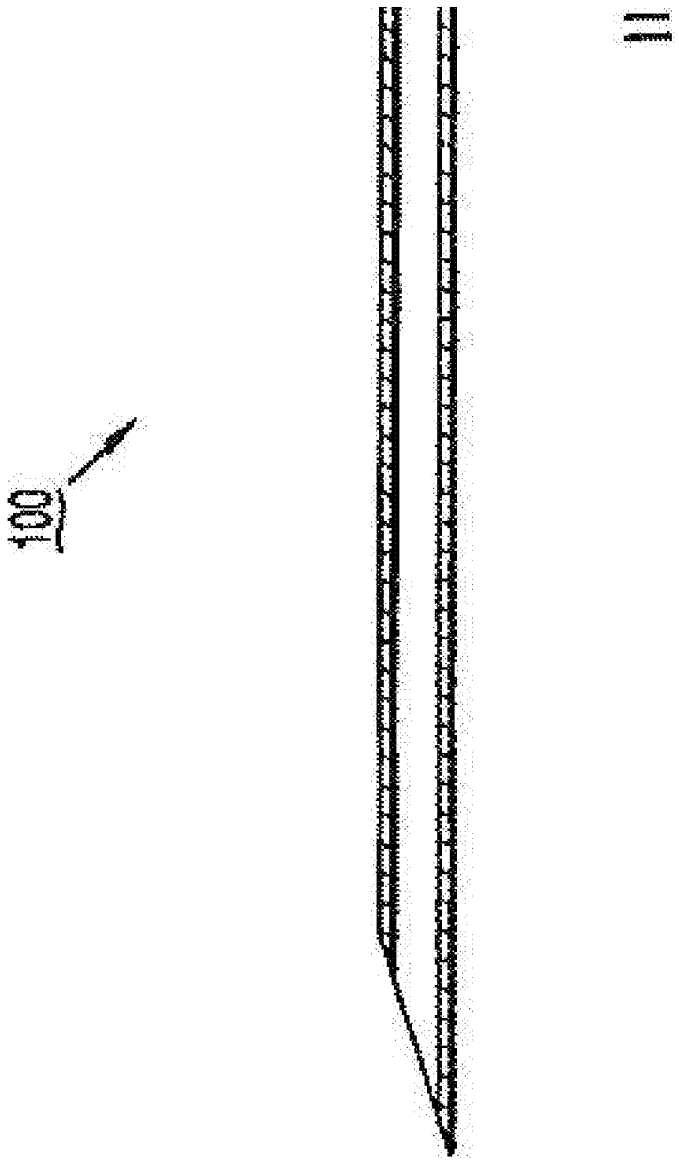


FIG. 2C

[Figure 3]



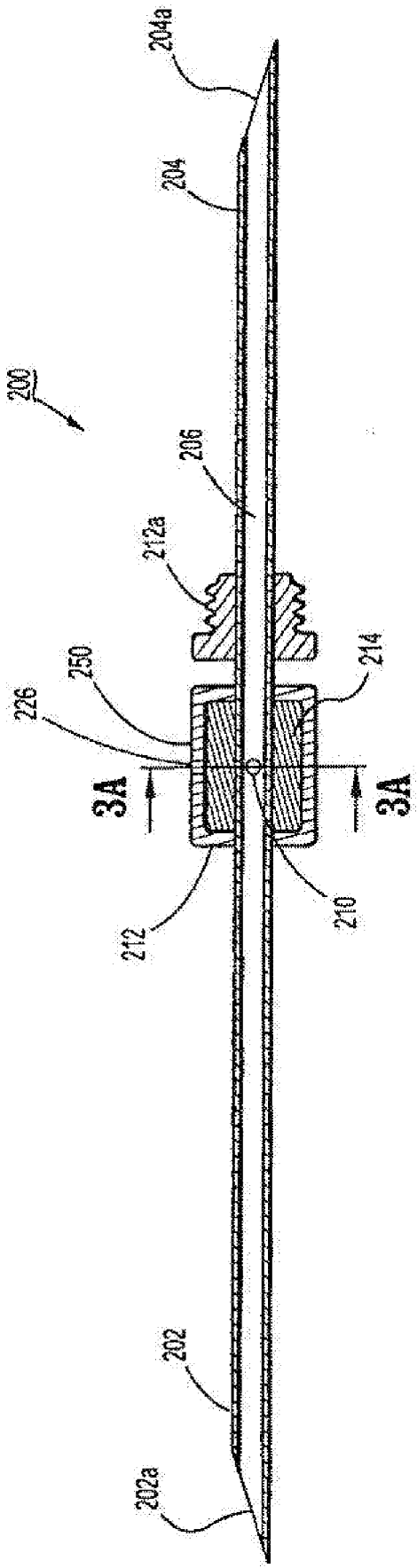

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204a
204
206
212a
214
250
226
3A
3A
212
210
202
202a

FIG. 3

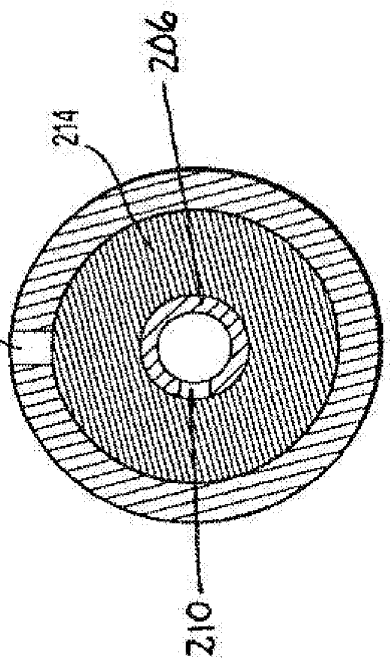

206
214
226
210

FIG. 3A

[Figure 4]

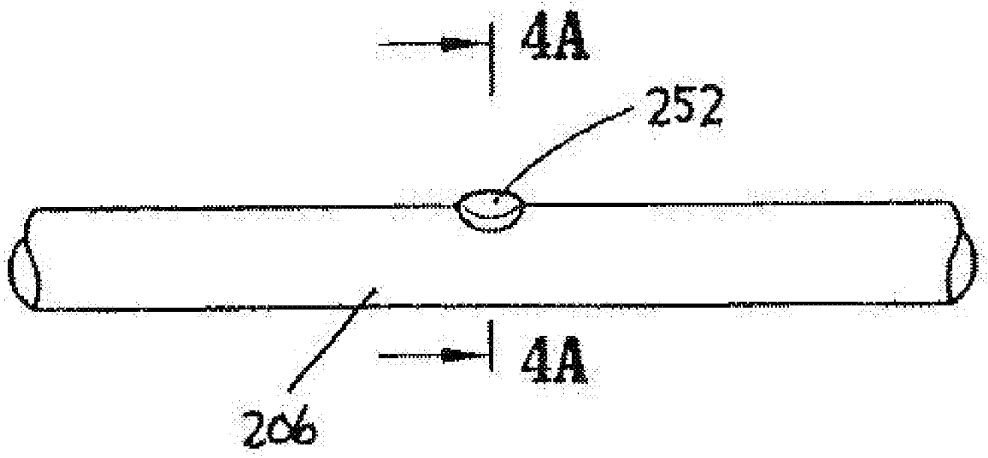


FIG. 4

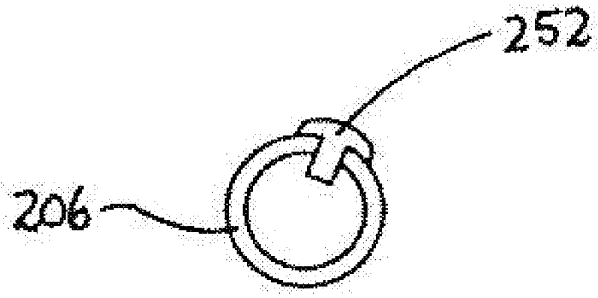


FIG. 4A

[Figure 5]

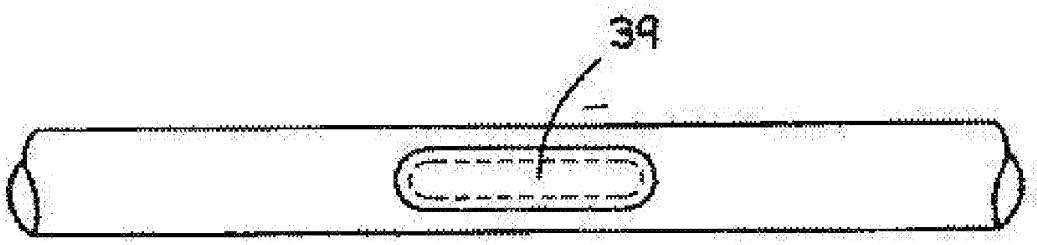


FIG. 5

[Fig. 6]

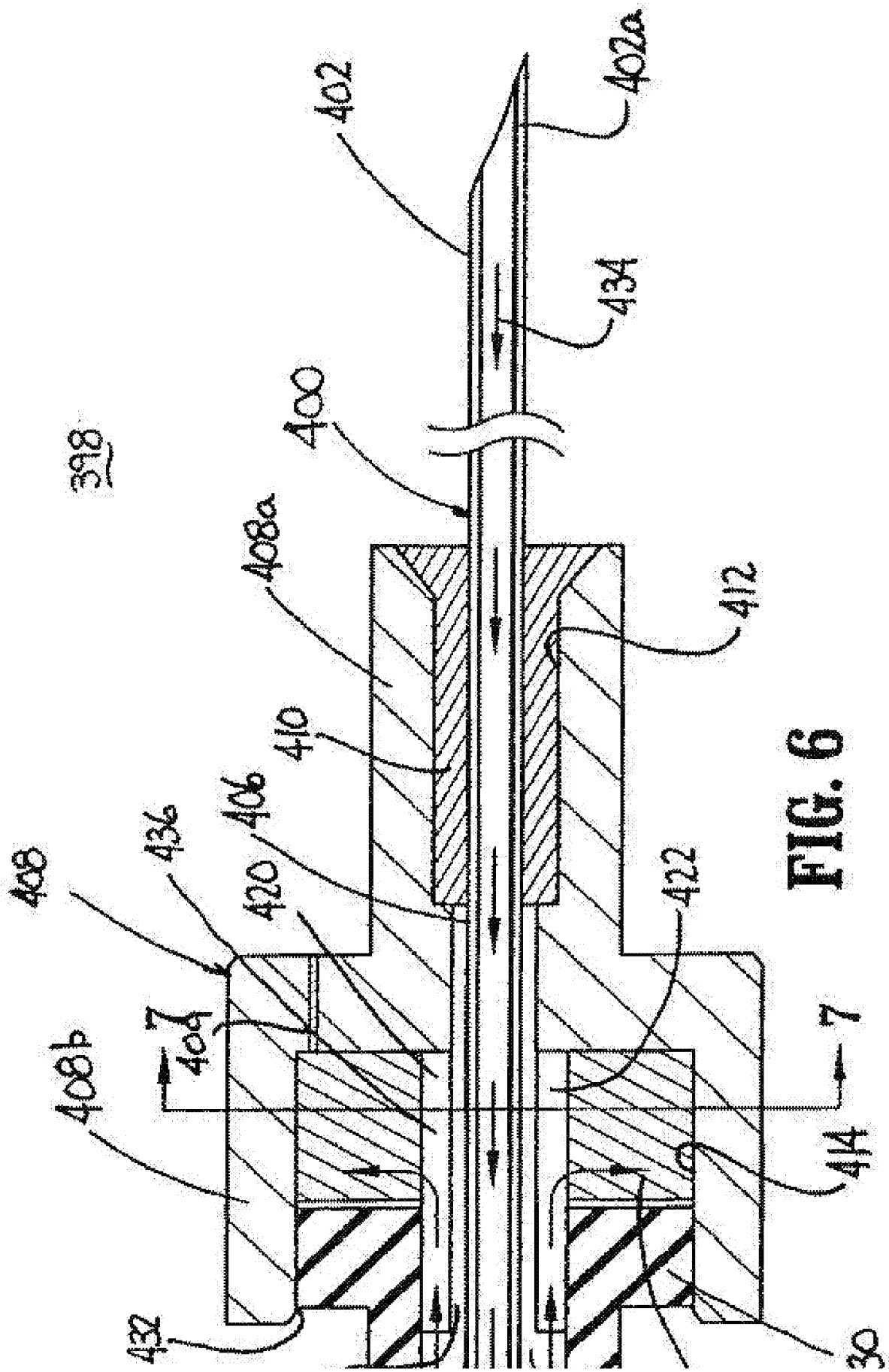

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402a
434
400
398
408a
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7
404
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408b
414
432
30

FIG. 6

[Fig. 7]

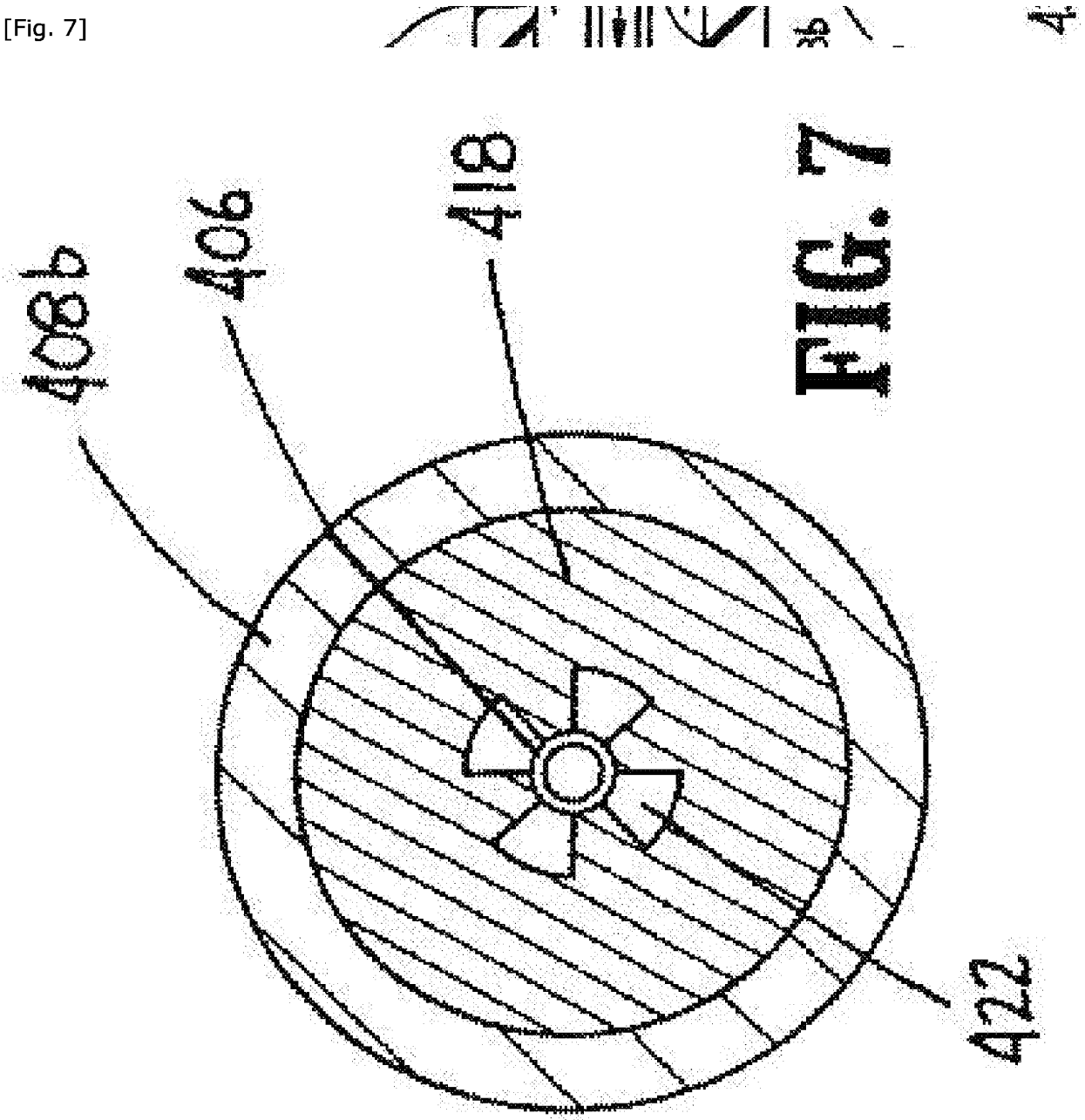


FIG. 7

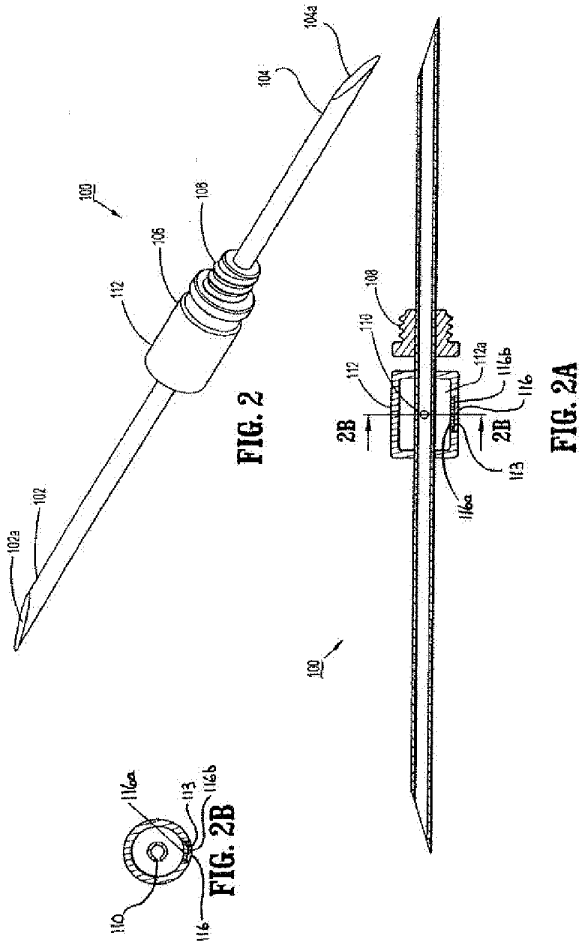
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Magnify and Rotate



Representative drawing

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VENTED PHLEBOTOMY NEEDLE WITH FLASHBACK CHAMBER

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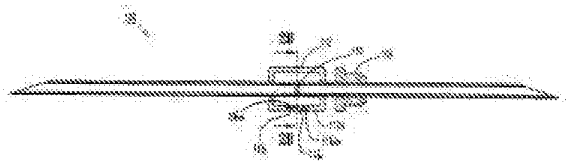
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Abstract of JP2013240628 (A)



PROBLEM TO BE SOLVED: To provide a less expensive, less complex phlebotomy needle which facilitates visualization of flashback.SOLUTION: A central portion 106 of a needle 100 includes a hole or opening 110 which communicates with a flow channel defined by the needle 100 and a transparent housing 112 is positioned about the opening 110 to facilitate visualization of blood flow through the needle 100. A material which allows passage of air and provides an indication of blood flow through the needle 100 is positioned over the opening 110. The material is in the form of a plug or, alternately, in the form of a patch or collar. The phlebotomy needle includes the needle 100 and the housing 112 having a passive vent and a viewing region for visualizing blood flow in the housing 112.

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A61B	5/153	(2006.01)	A61B	5/14	300F	

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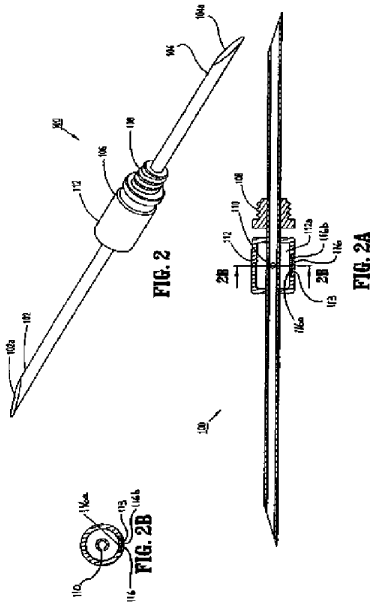
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最終頁に続く

(54)【発明の名称】フラッシュバックチャンバを備えた通気型瀉血針

(57)【要約】　（修正有）
【課題】フラッシュバックの可視化を容易にするより安価な、より簡単な瀉血針の提供。
【解決手段】針１００の中央部分１０６は穴または開口部１１０を含み、該穴または開口部１１０は、針１００によって画定された流路と連通し、透明の筐体１１２が、開口部１１０の周りに位置決めされ、針１００を通る血流の可視化を容易にする。空気の通過を可能にし、針１００を通る血流の表示を提供する材料が、開口部１１０を覆い位置決めされる。材料は、プラグの形であるか、または代替として、パッチまたはカラーの形である。瀉血針は、針１００と、受動通気孔を有する筐体１１２と、筐体１１２の血流を可視化するための観察領域とを含む。
【選択図】図２－１



【特許請求の範囲】
【請求項１】
瀉血針であって：
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分とを有し、該遠位の針部分と該近位の針部分が流体チャンネルを画定する、針；
該針上に支持される筐体であって、受動通気孔を含み、該筐体が該筐体中に血液を観察するための観察領域を画定する、筐体；および
該近位の針部分の周りに位置決めされるエラストマーのシールドであって、該エラストマーのシールドおよび該近位の針部分が該筐体中への流体の流路を画定する、エラストマーのシールド、を備える、瀉血針。
【請求項２】
前記筐体内に位置決めされる縦溝のある部材をさらに含み、該縦溝のある部材が複数の流体チャンネルを画定する、請求項１に記載の瀉血針。
【請求項３】
前記縦溝のある部材が、前記エラストマーのシールドを超えて遠位方向に延びる、請求項２に記載の瀉血針。
【請求項４】
前記縦溝のある部材の流体チャンネルが血液の通過を可能にするように構成されている、請求項２に記載の瀉血針。
【請求項５】
前記筐体内に支持される親水性材料をさらに含む、請求項２に記載の瀉血針。
【請求項６】
前記流路が、血液を、前記針の近位端から前記縦溝のある部材の流体チャンネル中に、および前記親水性材料との接触に向ける、請求項５に記載の瀉血針。
【請求項７】
前記縦溝のある部材の一部分が、前記親水性材料によって取り囲まれる、請求項５に記載の瀉血針。
【請求項８】
前記縦溝のある部材の近位端が前記エラストマーのシールドによって取り囲まれ、そして該縦溝のある部材の遠位端が前記親水性材料によって取り囲まれる、請求項５に記載の瀉血針。
【請求項９】
前記筐体の近位部分が、内方に延びる環状のリブを含む、請求項５に記載の瀉血針。
【請求項１０】
前記エラストマーのシールドが環状のフランジを含む開いた遠位端を有し、前記筐体の環状のリブが該フランジを係合し、該エラストマーのシールドの遠位端を該筐体内に保持する、請求項９に記載の瀉血針。
【請求項１１】
前記エラストマーのシールドのフランジが、前記親水性材料に隣接して位置決めされる、請求項１０に記載の瀉血針。
【請求項１２】
前記エラストマーシールドの遠位端が前記筐体中に受容され、そして該エラストマーシールドの近位端が該筐体から近位方向に延びる、請求項１に記載の瀉血針。
【発明の詳細な説明】
【技術分野】
【０００１】
（１．技術分野）
本開示は、フラッシュバックの可視化を容易にする構造を有する医療用針に関する。より詳細には、本開示は、フラッシュバックの可視化を容易にする構造を含む通気型瀉血針

に関する。
【背景技術】
【０００２】
（２．関連技術の背景）
患者から血液を抜き取る医療用デバイスは周知である。これらのデバイスは、標準的な針－注射器、蝶型針セット、および瀉血針を含む。通常、蝶型針セットは、尖った遠位端および針ハブに固定された近位端を有する中空の針を含む。針ハブの近位部分は、可撓性の配管に接続されている。針ハブは、配管と連通する流体導管を画定し、一対の可撓性の、半径方向に延びるウィングを含み、該ウィングは、医療従事者による蝶型針セットの把持を容易にする。一般に、可撓性の配管は、医療従事者が、針ハブに直近の配管を通る血流、すなわちフラッシュバックを可視化することを可能にする透明の材料で形成される。フラッシュバックの可視化は、針が患者の中に正しく挿入されたことを、医療従事者が確認することを可能にする。
【０００３】
一部の臨床医は、血液サンプルを採取するために、透明の針ハブを備えた皮下針－注射器を利用する。挿入の間、これらの臨床医たちは通常、針ハブの中のフラッシュバックを観察する。
【０００４】
一般に、瀉血針は、フラッシュバックを可視化するための構造を含んでいない。瀉血針にフラッシュバックを可視化するための構造がないことは、より経験のある医療従事者にとっては大きな欠点ではないが、瀉血針によって血液を抜き取る経験をほとんど有しない医療従事者にとっては、針が正しく患者の中に位置決めされたことを確認するいかなる手段もないことは、血液を抜き取るために必要な時間を増加させ得、患者の不快を増加させ得る。
【０００５】
上記の不利を克服する試みとして、Ｎｏｒｒｉｓらへの特許文献１は、瀉血針を開示し、該瀉血針は、採血管に取り付け可能であり、外側針、内側針、およびそれらの間にバルブ（ｂｕｌｂ）を含む。バルブは、透明であり、外側針が正しく患者の静脈内に位置決めされたとき、医療従事者が血液を可視化することを可能にする。バルブは、針内から空気を通気するために医療従事者によって押し下げられ得るボタンも含む。針内の空気は、血液が針を通って流れることを妨げ、通気されなければならない。
【先行技術文献】
【特許文献】
【０００６】
【特許文献１】米国特許第５，４５０，８５６号明細書
【発明の概要】
【発明が解決しようとする課題】
【０００７】
Ｎｏｒｒｉｓの瀉血針は、フラッシュバックの可視化を容易にするが、フラッシュバックの可視化を容易にするより安価な、より簡単な瀉血針が望まれる。
【課題を解決するための手段】
【０００８】
本開示は瀉血針に関し、該瀉血針は、組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、および開口部を画定する中央の針部分とを含む。遠位の針部分、近位の針部分および中央の針部分は、開口部と連通する流体チャンネルを画定する。材料が、開口部に隣接して位置決めされる。材料は、空気が開口部を通って流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものである。一実施形態において、材料は、開口部に隣接する血流、すなわちフラッシュバックの可視表示を提供する。
【０００９】

一実施形態において、材料は疎水性材料を含む。代替の実施形態において、材料は親水性毛管作用材料を含む。さらに別の実施形態において、材料は疎水性のプラグを含む。あるいは、材料は開口部の周りに位置決めされたカラー部を画定し得る。

【００１０】

一実施形態において、開口部は円形である。あるいは、開口部は様々な構成、例えば長方形またはスロット形状であることが想定されている。

【００１１】

一実施形態において、透明の筐体が開口部の周りに位置決めされ、フラッシュバックの可視化を容易にする。筐体はまた、材料を包含するように位置決めされ得、針から空気を通気するための通気孔を含み得る。

【００１２】

一実施形態において、瀉血針は、針ホルダーと係合するように構成された係合構造を含む。

【００１３】

一実施形態において、空気が開口部を通って流体チャンネルの中に入ることを阻止するために、逆止弁が提供される。さらに別の実施形態において、瀉血針は、針ホルダーを含む。

例えば、本発明は以下の項目を提供する。

（項目１）

瀉血針であって、

組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、

採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、

開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、

該開口部に隣接して位置決めされた材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、材料と

を備えている、瀉血針。

（項目２）

上記材料は疎水性材料を含む、項目１に記載の瀉血針。

（項目３）

上記材料は親水性毛管作用材料を含む、項目１に記載の瀉血針。

（項目４）

上記材料は、上記開口部の方に向かう親水性材料の内側層と、疎水性材料の外側層とを含む、項目１に記載の瀉血針。

（項目５）

上記開口部は円形である、項目１に記載の瀉血針。

（項目６）

上記開口部は細長いスロットを画定する、項目１に記載の瀉血針。

（項目７）

上記開口部の周りに位置決めされた透明の筐体をさらに含む、項目１に記載の瀉血針。

（項目８）

上記瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造をさらに含む、項目１に記載の瀉血針。

（項目９）

上記材料は、上記開口部を覆い上記針の周りに位置決めされたカラー部を画定する、項目１に記載の瀉血針。

（項目１０）

上記カラー部の材料の周りに位置決めされた透明の筐体をさらに含む、項目９に記載の瀉血針。

（項目１１）
空気が、上記開口部を通って上記流体チャンネルの中に入ることを阻止するための逆止弁をさらに含む、項目１に記載の瀉血針。
（項目１２）
針ホルダーをさらに含む、項目１に記載の瀉血針。
（項目１３）
上記材料は、上記開口部を通る血流の可視表示を提供する、項目１に記載の瀉血針。
（項目１４）
瀉血針であって、
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、
採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、
開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、
該開口部に隣接して位置決めされた疎水性材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、疎水性材料と、
該開口部の周りに位置決めされた透明の筐体と、
該瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造と
を備えている、瀉血針。
（項目１５）
上記針ホルダーをさらに含む、項目１４に記載の瀉血針。
（項目１６）
瀉血針であって、
組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、
採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分と、
開口部を画定する中央の針部分であって、該遠位の針部分、該近位の針部分および該中央の針部分は、該開口部と連通する流体チャンネルを画定する、中央の針部分と、
該開口部に隣接して位置決めされた親水性毛管作用材料であって、空気が該開口部を通って該流体チャンネルを出ることを可能にし、一方、血液の通過を防止するタイプのものであり、血流の可視表示をさらに可能にする、親水性毛管作用材料と、
該開口部の周りに位置決めされた透明の筐体と、
該瀉血針で支持された係合構造であって、針ホルダーと係合するように構成された、係合構造と
を備えている、瀉血針。
（項目１７）
上記針ホルダーをさらに含む、項目１６に記載の瀉血針。
（項目１８）
瀉血針であって、該瀉血針は、
針であって、組織を貫通するように構成された尖った遠位端を有する遠位の針部分と、採血管のストッパを貫通するように構成された尖った近位端を有する近位の針部分とを含み、該遠位の針部分および該近位の針部分は、流体チャンネルを画定する、針と、
該針で支持された筐体であって、受動通気孔を含み、該筐体の血液を可視化するための観察領域を画定する、筐体と
を備えている、瀉血針。
（項目１９）
上記近位の針部分の周りに位置決めされたエラストマーのシールドをさらに含み、該エラストマーのシールドおよび該近位の針部分が、上記筐体の中への流体の流路を画定する、項目１８に記載の瀉血針。
（項目２０）

上記筐体内に位置決めされた縦溝のある部材をさらに含み、該縦溝のある部材は、複数の流体チャンネルを画定する、項目１８および項目１９のうちのいずれか一項に記載の瀉血針。

（項目２１）

上記筐体内に支持された親水性材料をさらに含む、項目１８～項目２０のうちのいずれか一項に記載の瀉血針。

（項目２２）

上記針は、上記筐体の中への開口部を画定する中央部分を有する、項目１８～項目２１のうちのいずれか一項に記載の瀉血針。

【図面の簡単な説明】

【００１４】

フラッシュバックチャンバを備えた本開示の通気型瀉血針の実施形態が、図面を参照して本明細書に開示される。

【図１－１】図１は、針ホルダー、保護針カバーおよび幻影で示された採血管を備えた「従来技術」の瀉血針の斜視図であり、部品は分離されている。

【図１－２】図１Ａは、組み立てられた「従来技術」の瀉血針、針ホルダー、および幻影で示された採血管の側面断面図であり、瀉血針の遠位部分は静脈内に位置決めされている。

【図２－１】図２は、本開示の瀉血針の一実施形態の側面斜視図である。図２Ａは、図２で示された瀉血針の断面図である。図２Ｂは、図２Ａの切断線２Ｂ－２Ｂに沿った断面図である。

【図２－２】図２Ｃは、本開示の瀉血針の別の実施形態の側面断面図である。

【図３】図３は、本開示の瀉血針の代替の実施形態の側面断面図である。図３Ａは、図３の切断線３Ａ－３Ａに沿った断面図である。

【図４】図４は、本開示の瀉血針の別の実施形態の側面斜視切取り図である。図４Ａは、図４の切断線４Ａ－４Ａに沿った断面図である。

【図５】図５は、本開示の瀉血針の別の実施形態の側面斜視切取り図である。

【図６】図６は、本開示の瀉血針の別の実施形態の側面断面図である。

【図７】図７は、図６の切断線７－７に沿った断面図である。

【発明を実施するための形態】

【００１５】

（実施形態の詳細な記述）

フラッシュバックチャンバを備えた本開示の通気型瀉血針の実施形態がここで、図面を参照して詳細に記述され、該図面においては、同様の参照番号は、幾つかの図面の各々において同一のまたは対応する要素を示す。

【００１６】

図１は、公知の瀉血針１０、針ホルダー１２、ならびに針カバー１４および１６を示す。採血管１７が幻影で示されている。瀉血針１０は、遠位の針部分２０と、近位の針部分２２と、係合部分２４を備えた中間の針ハブ２３とを含む。係合部分２４は、瀉血針１０を針ホルダー１２に接続することを容易にするように提供される。一実施形態において、係合部分は、雄継手２４ａを含み、雄継手２４ａは、雌継手または係合部材２６と係合するように構成され、係合部材２６は、針ホルダー１２の遠位端に提供される。あるいは、ねじ、スナップ型コネクタ、その他を含む他の係合構造が使用され得る。下にさらに詳細に記述されるように、エラストマーのシールド２８が近位の針部分２２を覆い位置決めされ、近位の針部分２２をシールする。

【００１７】

針ホルダー１２は、実質的に円筒状の本体３０を含み、実質的に円筒状の本体３０は、係合部材２６を含む遠位端および一対のフランジ部材３２を含む近位端を有する。フランジ部材３２は、医療従事者による採血管１７の把持および挿入を容易にする。円筒状の本体３０は、採血管１７を受け入れるための空洞３４（図１Ａ）を画定する。通常、採血管

１７は、貫通可能ストッパ１７ａによってシールされ、低圧の空洞１７ｂ（図１Ａ）を画定する。ホルダー１２の遠位端は、係合部材２６を通る開口部３６を画定し、開口部３６は、近位の針部分２２を受け入れる大きさとされる。

【００１８】

図１Ａに示されるように、使用に際して、針１０は、係合部分２４および係合部材２６を介して針ホルダー１２の遠位端に固定される。針１０が針ホルダー１２に固定されると、近位の針部分２２は、針ホルダー１２の本体３０の空洞３４内に位置決めされ、エラストマーのシールド２８は、近位の針部分２２を覆い位置決めされる。次に、貫通可能ストッパ１７ａを含む採血管１７（幻影で示される）が、空洞３４内に位置決めされる。採血管１７が空洞３４の中に挿入されると、近位の針部分２２が、ストッパ１７ａと係合し、シールド２８を貫通する。近位の針部分２２が、ストッパ４０を貫通し、採血管１７の空洞１７ｂに入るように、シールド２８は下向きに圧縮（図１Ａ）される。遠位の針部分２０が患者の静脈３８に正しく位置決めされ、採血管１７が空洞３４内に位置決めされると、血液が、針１０を通って採血管１７の中に流入するように、通常、採血管１７は、真空に維持される。採血管１７が針ホルダー１２から取り外されると、弾力的なエラストマーのシールド２８は、その元の構成に戻り、近位の針部分２２を被覆し、近位の針部分２２をシールする。

【００１９】

図２および図２Ａは、概して１００として示されるフラッシュバックチャンバを備えた本開示の瀉血針の一実施形態を示す。針１００は、遠位端１０２と、近位端１０４と、中央部分１０６とを含む。遠位端１０２は、患者の組織を貫通するように構成された尖った端１０２ａを有し、近位端１０４は、採血管１７（図１Ａを参照）のストッパ１７ａを貫通するように構成された尖った端１０４ａを有する。中央部分１０６は、上に論議されたように、係合部材１０８を含み、係合部材１０８は針ホルダー（図１）と係合するように構成される。中央部分１０６はまた、開口部または穴１１０と、開口部１１０を画定する部分の中央部分１０６の周りに位置決めされた半透明または透明の筐体１１２とを含む。開口部１１０は円形として示されているが、他の構成、例えば長方形、正方形、楕円形、細長いスロット３９（図５）、その他が想定されている。透明の筐体１１２は、血液レザバ１１２ａを画定する。通気開口部１１３は好ましくは、透明の筐体１１２に形成される。通気開口部１１３が針１００の通気を容易にし、針１００を通る血流を可能にする。下に論議されるように、筐体１１２の通気開口部１１３は、空気の通過は許すが、例えば血液のような液体の通過は許さない材料によって被覆され得る。

【００２０】

図２Ａおよび図２Ｂを参照して、通気開口部１１３は、フィルタ１１６で被覆され得る。フィルタ１１６は好ましくは、親水性材料の内側層１１６ａと、疎水性材料の外側層１１６ｂとを含む。好ましくは、層１１６ａおよび層１１６ｂのうちの少なくとも１つは、０．４５ミクロンを下回る孔サイズを有する。かかる孔サイズは、空気の通過は可能にするが、バクテリアが筐体１１２の中に入ることを防止する。

【００２１】

図２Ｃを参照して、代替の実施形態において、フィルタ１１６は、例えばフラップ弁１５０のような疎水性逆止弁によって置き換えられ得る。図示のように、フラップ弁１５０は、筐体１１２の中に血液が流入し始めると、筐体１１２から外向きに曲がり、通気開口部１１３を露出させ、筐体１１２を通気するように構成される。逆止弁が開いたとき、血液が通気開口部１１３から出ることを防止するために、疎水性シート１５２が開口部１１３を覆い位置決めされる。血液が筐体１１２の中に流入し始めるのに先立って、フラップ弁１５０は開口部１１３をシールし、物質が筐体１１２の中に入ることを防止する。あるいは、フラップ弁１５０は、親水性材料の孔サイズが血液成分の通過を遮るサイズである場合は、該親水性材料から形成され得る。

【００２２】

針１００の遠位端１０２が患者の静脈内に正しく位置決めされたとき、すなわち、血液

が針１００を通って流れ、空気が通気されて、血液が開口部１１０を通ってレザバ１１２ａの中に入るとき、透明の筐体１１２は、医療実施者が針１００を通る血流を可視化することを可能にする。これによって、医療実施者は、針１００の遠位端１０２が、血液を抜き取るために患者の静脈内に正しく位置決めされたことを確認することができる。これは、患者から血液を抜き取ろうと試みる医療実施者に対して、特に瀉血針によって患者から血液を抜き取ることについて限られた経験しか有しないような実施者に対して大きな利益を提供する。

【００２３】

図３は、概して２００として示されるフラッシュバックチャンバを備えた本開示の通気型瀉血針の代替の実施形態を示す。針２００は、下に記述されるとおりを除いて、針１００と実質的に同様である。針２００は、遠位端２０２と、近位端２０４と、中央部分２０６とを含む。遠位端２０２は、患者の組織を貫通するように構成された尖った端２０２ａを有し、近位端２０４は、採血管（図１Ａを参照）のストッパを貫通するように構成された尖った端２０４ａを有する。中央部分２０６は、開口部または穴２１０と係合部材２１２ａとを含む。材料２１４は、穴２１０を覆い位置決めされている。医療従事者が針２００を通る血流を容易に識別し得るように、材料２１４は、材料の中に血液を毛管作用で吸い込む親水性の材料であり得る。針２００の通気を容易にするために、材料２１４は、空気に対しては透過性があるが、例えば血液のように液体に対しては透過性がない親水性材料であり得る。一実施形態において、親水性材料は、血液と接触したとき、色が変わるタイプのものであり得る。材料は、カラー２５０（図３）またはプラグ２５２（図４）の形であり得る。さらに、材料は、透明の筐体もしくはハブ２１２内に位置決めされ得るか、または代替的に、いかなる筐体もなく開口部２１０に隣接して位置決めされ得る。代替の実施形態において、材料は、空気は通すが血液は通さない疎水性の材料である。通気開口部２２６は筐体２１２に提供され得、筐体の通気を容易にし得ることに留意される。通気孔は、筐体２１２における開口部の形であり得、該開口部は、血液が入ると筐体２１２から空気が流れ出ることを可能にする。

【００２４】

図３および図３Ａでさらに示される代替の実施形態において、材料２１４は、膨張可能な材料で形成され得、該膨張可能な材料が血液と接触する前に、空気が通気開口部２２６を通ることを可能にする。材料２１４は、血液と接触すると膨張し得、通気開口部２２６を閉じ得る。

【００２５】

本明細書において、親水性材料および疎水性材料のみが開示されたが、血液の通過を防止しながら空気の通過を容易にし、血流の表示を提供する他の材料が、本開示の瀉血針に対して使用され得る。材料は、本明細書に開示されていない他の構成を有し得る。例えば、材料は、開口部を被覆するパッドを画定し得る。

【００２６】

図６および図７は、概してデバイス３９８として示されるフラッシュバックチャンバを備えた本開示の瀉血針の別の実施形態を示す。瀉血針３９８は、針４００と段付き筐体４０８とを含む。針４００は、遠位端４０２と、近位端４０４と、中央部分４０６とを含む。遠位端４０２は、患者の組織を貫通するように構成された尖った端４０２ａを有し、近位端４０４は、採血管（図示されず）のストッパ（図示されず）を貫通するように構成された尖った端４０４ａを有する。

【００２７】

段付き筐体４０８は、遠位部分４０８ａおよびより大きな直径の近位部分４０８ｂを有する。段付き筐体４０８は、中央部分４０６で支持されている。遠位部分４０８ａは、針の中央部分４０６を受け入れる大きさとされた通し穴４１２を画定する。遠位部分４０８ａは、例えば接着剤４１０を使用して、針４００にシールされ、固定される。あるいは、他の公知の技術、例えばクリンプ加工、クランプ、ねじ、溶接その他が使用され得、針４００を筐体４０８に固定し得る。近位部分４０８ｂは、透明の材料または半透明の材料で

形成され、筐体４０８の近位部分４０８ｂ内の可視化を容易にする。近位部分４０８ｂはまた、通し穴４１４を画定し、通し穴４１４は通し穴４１２と連通するが、通し穴４１２よりも直径が大きい。近位部分４０８ｂは、部分４０８ｂと針４００の近位端４０４との間に環状のリセス４１６を画定する。リセス４１６は、親水性材料４１８および内側の縦溝のある部材４２０を受け入れるような大きさとされる。内側の縦溝のある部材４２０が、針４００の近位端４０４の周りに位置決めされ、親水性材料４１８と連通する複数のチャンネル４２２を画定する。通気開口部４０９は、筐体４０８を通して提供される。

【００２８】

エラストマーのシールド４２８は、針４００の近位端４０４を覆い位置決めされる。上に論議されたように、エラストマーのシールド４２８は弾力的であり得、針４００の近位端４０４が採血管（図示されず）に接続されていないとき、針４００の近位端４０４をシールするように機能する。エラストマーのシールド４２８は、閉じた近位端４２８ａと開いた遠位端４２８ｂとを含む。開いた遠位端４２８ｂは環状のフランジ４３０を含み、環状のフランジ４３０は、筐体４０８のリセス４１６内で材料４１８に隣接して位置決めされる。筐体４０８の近位部分４０８ｂは、内向きに延びる環状のリブ４３２を含み、内向きに延びる環状のリブ４３２は、エラストマーのシールド４２８のフランジ４３０と係合し、シールド４２８の遠位端４２８ｂを筐体４０８のリセス４１６内に保持するように位置決めされる。矢印４３４によって示されるように、流路４３６は、エラストマーのシールド４２８と針４００の近位端４０４との間に画定される。流路４３６は、針４００の近位端４０４から縦溝のある部材４２０の縦溝のあるチャンネル４２２の中に血液を導き、親水性材料４１８と接触させる。使用に際して、血液が材料４１８と接触すると、材料４１８は、筐体４０８の近位部分４０８ｂを通して目視可能となる血流の可視表示を提供する。

【００２９】

フィルタ１１６と共に画定された（図２Ａ～図２Ｂ）、フィルタ２５２と共に画定された（図４～図４Ａ）、もしくはフィルタ３９と共に画定された（図５）、または逆止弁１５０と共に画定された（図２Ｃ）通気開口部１１３、ならびに開口部２２６（図３～図３Ａ）および開口部４０９（図６）はすべて、受動通気開口部として記述され得、該受動通気開口部は、針カニューレ内において大気圧よりも大きな圧力の気体が大気中に自動的に漏れることを可能にする。これらの受動通気開口部は、本発明によるデバイスのユーザによるいかなる行動も必要としない。

【００３０】

本明細書に開示された実施形態には、様々な変更がなされ得ることは理解される。したがって、上述は、限定するものとして解釈されるべきではなく、好ましい実施形態の単なる例示として解釈されるべきである。当業者は、本明細書に添付された請求項の範囲および精神内で他の変更に想到する。

【図１－１】

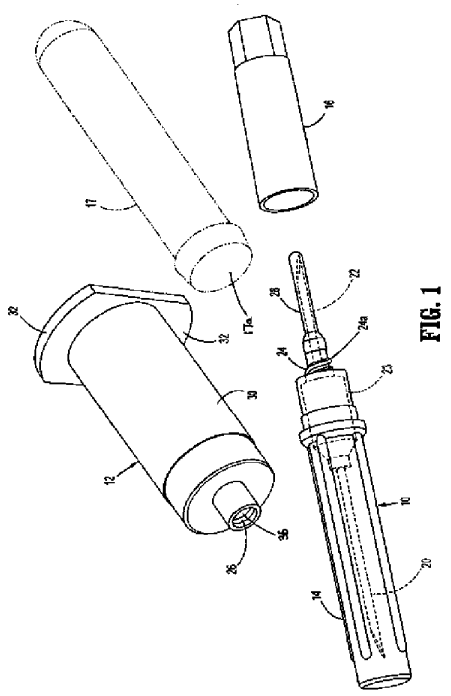


FIG. 1

【図１－２】

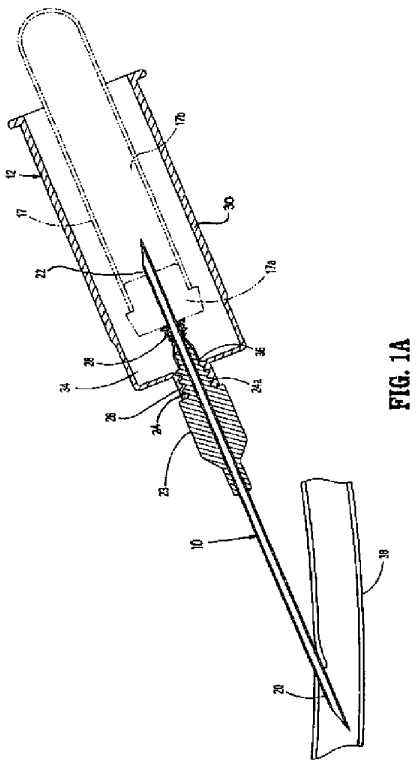


FIG. 1A

【図２－１】

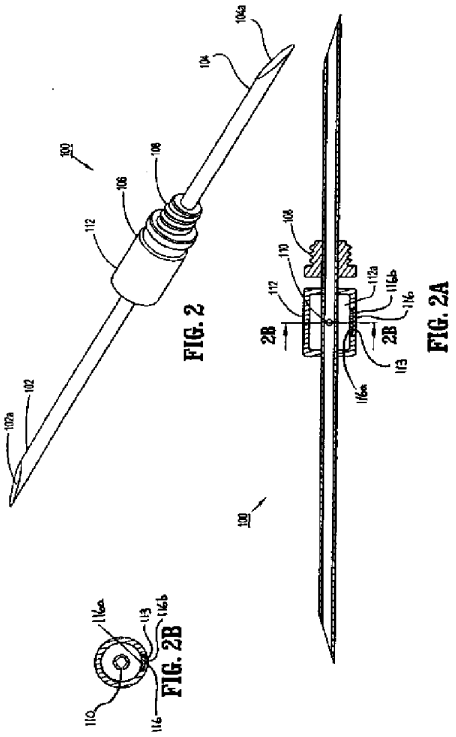


FIG. 2

FIG. 2A

FIG. 2B

【図２－２】

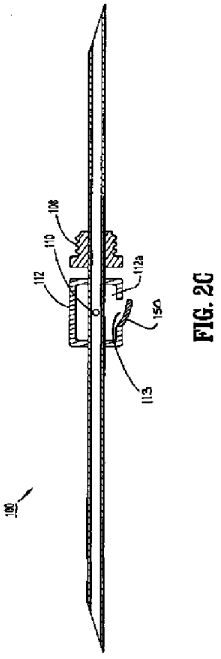


FIG. 2C

【図３】

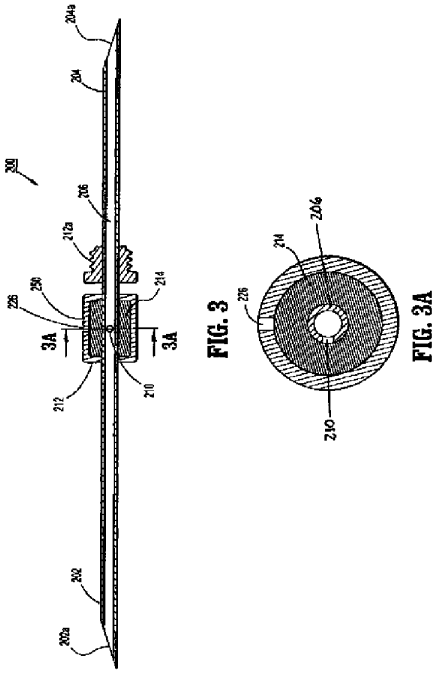


FIG. 3

FIG. 3A

【図４】

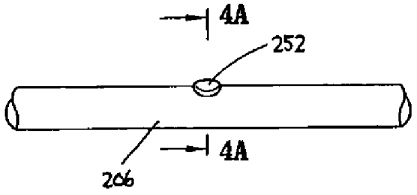


FIG. 4

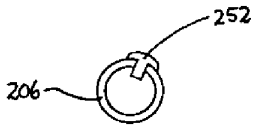


FIG. 4A

【図５】

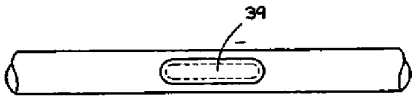


FIG. 5

【図６】

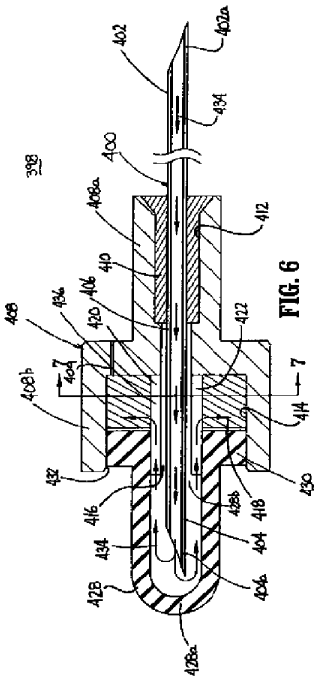


FIG. 6

【図７】

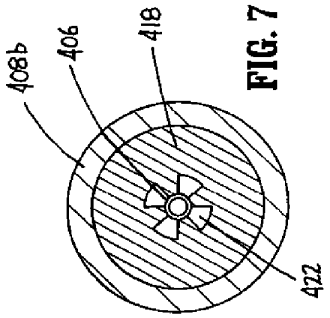


FIG. 7

フロントページの続き

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2013240628000001.pdf

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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)

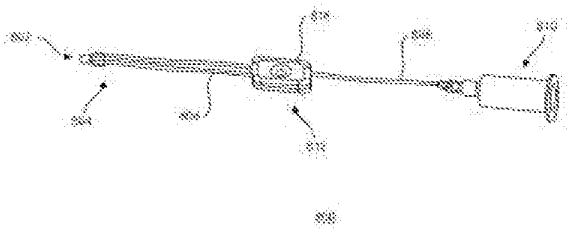
Classification: **- international:** ***A61B5/15; A61B5/153; A61B5/154; A61B5/157***
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150221 (US); A61B5/150251 (EP, US); A61B5/150274 (EP, US); A61B5/150351 (US); A61B5/150755 (US); A61B5/150786 (US); A61B5/150946 (US); A61B5/150992 (EP, US); A61B5/1535 (EP, US); A61B5/1545 (EP, US);** A61B5/150389 (EP, US); A61B5/150488 (EP, US); A61B5/157 (EP, US)

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Abstract of WO2018125929 (A1)



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

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(54) Title: BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

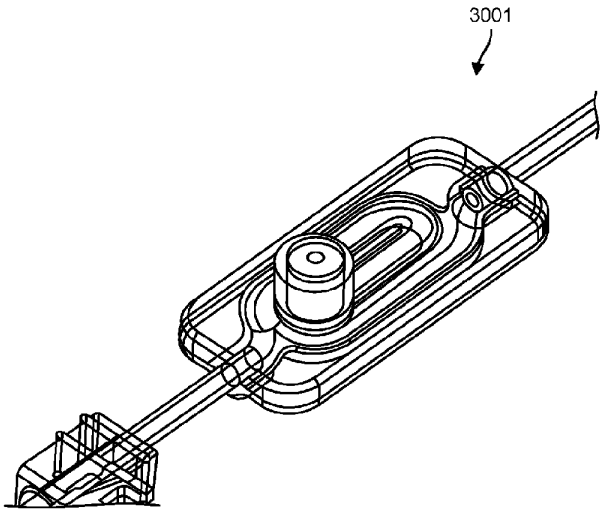


FIG. 30B

(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 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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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

BACKGROUND

[0001] 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.

[0002] 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.

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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.

[0007] 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.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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

[0012] 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.

[0013] 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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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.

[0018] 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.

[0019] 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.

[0020] The blood sequestration device, in one aspect can include an inlet port, an outlet port, a sequestration chamber connected with the inlet port via a junction, the sequestration chamber having a vent that includes an air permeable blood barrier, the vent being defined by an outer wall that at least partially circumscribes the air permeable blood barrier and includes one or more air vents, the vent further includes a cap that at least partially covers the wall and a one-way seal abutting the air permeable blood barrier that inhibits air from entering the sequestration chamber, and a sampling channel having a proximal end connected with the inlet port via the junction, and a distal end connected with the outlet port. In certain related aspects, the sequestration chamber, the sampling channel and the junction are sized and configured such that a first portion of blood flows into the sequestration chamber toward the air permeable blood barrier for sequestration therein, and a second portion of blood bypasses the sequestration chamber and the first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

[0021] In another aspect, the sampling channel and the junction is sized and configured such that a first portion of blood flows into and fills the sequestration chamber to displace air therein through the vent, and such that a second portion of blood bypasses the sequestration chamber and the first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

[0022] The blood sequestration and sampling system sequestration device, in certain aspects can include a blood sampling pathway having a patient needle on a proximal end and a sample collection device on a distal end; and a blood sequestration device attached on the blood sampling pathway between the proximal end and distal end of the blood sampling pathway. The blood sequestration device in one aspect can include an inlet port coupled with the blood sampling pathway toward the patient needle, an outlet port coupled with the blood sampling pathway toward the sample collection device, a sequestration chamber connected with the inlet port via a junction, which chamber has a

vent that includes an air permeable blood barrier, the vent being defined by an outer wall that at least partially circumscribes the air permeable blood barrier and includes one or more air vents, the vent further including a cap that at least partially covers the wall and a one-way seal abutting the air permeable blood barrier that inhibits air from entering the sequestration chamber; and a sampling channel having a proximal end connected with the inlet port via the junction, and a distal end connected with the outlet port. In a certain related aspect, the sequestration chamber, the sampling channel and the junction can be sized and configured such that a first portion of blood flows into the sequestration chamber toward the air permeable blood barrier for sequestration therein, and a second portion of blood bypasses the sequestration chamber and the first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

[0023] 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.

[0024] 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

[0025] These and other aspects will now be described in detail with reference to the following drawings.

[0026] FIG. 1 illustrates a blood sample optimization system.

[0027] FIG. 2 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0028] FIG. 3 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0029] FIG. 4 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0030] FIG. 5 illustrates a blood sample optimization system in accordance with another alternative implementation.

[0031] FIG. 6 illustrates a blood sample optimization system in accordance with an alternative implementation.

[0032] FIG. 7 is a flowchart of a method for optimizing a quality of a blood culture.

[0033] FIGS. 8A – 8E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with some implementations.

[0034] FIG. 9 illustrates a pathway splitter for use in a blood sequestrations system.

[0035] FIGS. 10A – 10D illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with alternative implementations.

[0036] FIGS. 11A – 11E illustrate a blood sequestration system for non-contaminated blood sampling, in accordance with other alternative implementations.

[0037] FIGS. 12A-12D illustrate a blood sample optimization system including a blood sequestration device in accordance with yet other alternative implementations.

[0038] FIGS. 13A-13D illustrate a blood sample optimization system 1300 in accordance with yet another alternative implementations.

[0039] 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.

[0040] FIGS. 15A-15G illustrate a blood sequestration device and method of using the same, in accordance with yet another implementation.

[0041] FIGS. 16A-16D illustrate a blood sequestration device in accordance with yet another implementation.

[0042] FIGS. 17A – 17E illustrate a bottom member of a housing for a blood sequestration device.

[0043] FIGS. 18A – 18F illustrate a top member of a housing for a blood sequestration device.

[0044] FIGS. 19A and 19B illustrate a blood sequestration device having a top member mated with a bottom member.

[0045] FIG. 20 shows a blood sample optimization system including a blood sequestration device.

[0046] FIG. 21 illustrates a non-vented blood sequestration device using a wicking material chamber.

[0047] FIGS. 22A and 22B illustrate a material makeup of a filter for sequestering blood in a sequestration chamber of a blood sequestration device.

[0048] FIGS. 23A – 23E illustrate another implementation of a blood sequestration device that uses a vacuum force from a blood collection device.

[0049] FIGS. 24A – 24D illustrate another implementation of a blood optimization system and blood sequestration device.

[0050] FIGS. 25A – 25D illustrate another implementation of a blood optimization system and blood sequestration device.

[0051] FIGS. 26A – 26E illustrate another implementation of a blood optimization system and blood sequestration device.

[0052] FIGS. 27A – 27D illustrate another implementation of a blood optimization system and blood sequestration device.

[0053] FIGS. 28A – 28F illustrate another implementation of a blood optimization system and blood sequestration device.

[0054] FIGS. 29A – 29C illustrate another implementation of a blood optimization system and blood sequestration device.

[0055] FIGS. 30A – 30G illustrate another implementation of a blood optimization system and blood sequestration device.

[0056] Like reference symbols in the various drawings indicate like elements.

DETAILED DESCRIPTION

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[00100] 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.

[00101] 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.

[00102] 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.

[00103] 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.

[00104] 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.

[00105] 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.

[00106] 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.

[00107] 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.

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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 inlet 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.

[00112] 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.

[00113] In some instances, as shown in FIG. 15H, an inlet port 1532 can include a male luer connector for connecting to a removable patient needle, and an outlet port 11534 can include a female luer connector for connecting with a syringe. This implementation of the inlet port and outlet port can be used with any device described herein, for avoiding a propensity of a Vacutainer-type device collapsing a patient's vein. In this implementation, a clinician can use the syringe in a modulated fashion to obtain a blood sample. In operation, the syringe is attached to the outlet port 1004, and the needle is attached to the inlet port 1002. A venipuncture is performed with the needle, and without the clinician pulling on the syringe. An initial aliquot of blood fills a sequestration chamber, and then the syringe can be used to draw a sample of blood through the collection channel, bypassing the sequestered blood in the sequestration chamber.

[00114] 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 inlet port, and outlet 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.

[00115] 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.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] 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.

[00124] 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.

[00125] 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 member 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.

[00126] 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 outlet 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.

[00127] 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 inlet 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.

[00128] 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.

[00129] 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.

[00130] 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.

[00131] 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.

[00132] 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.

[00133] 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.

[00134] 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.

[00135] 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.

[00136] 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 2308 before the initial aliquot of blood is sequestered in the sequestration chamber 2306. For instance, valve 2308 can also be formed as a flap, door or closable window or barrier within the sampling channel 2308.

[00137] FIGS. 23C – 23E illustrate an alternative implementation of the blood sequestration device 2300', in which a sequestration chamber 2320 branches off from a main collection channel 2322 between an inlet port 2316 to connect with a patient needle and an outlet port 2318 to connect with a blood sample collection device, such as a Vacutainer, a syringe, or the like. The sequestration chamber 2320 includes an air-permeable, blood impermeable blood barrier 2324, such as a hydrophobic plug of material, or a filter formed of one or more layers, for example. A valve 2324 closes off

and opens the collection channel 2322, and the device 2300' can be used similarly as described above.

[00138] FIG. 24A – 24D illustrate a blood sample optimization system 2400 that includes a patient needle 2402 for vascular access to a patient's bloodstream, a blood sample collection device 2404 to facilitate the collecting of one or more blood samples for blood testing or blood cultures, and a conduit 2406 providing a fluid connection between the patient needle 2402 and the blood sample collection device 2404. In some implementations, the blood sample collection device 2404 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 2402.

[00139] The blood sample optimization system 2400 further includes a blood sequestration device 2408, located at any point on the conduit 2406 between the patient needle 2402 and the blood sample collection device 2404. The location of the blood sequestration device 2408 can be based on a length of the conduit between the blood sequestration device 2408 and the patient needle 2402, and the associated volume that length provides.

[00140] The blood sequestration device 2408 includes an inlet port 2412 for being connected to the conduit 2406 toward the patient needle 2402, and an outlet port 2414 for being connected to the conduit 2406 toward the blood sample collection device 2404, and a housing 2416. The housing 2416 can be any shape, although it is shown in FIGS. 24A – D as being substantially cylindrical, and includes the inlet port 2412 and outlet port 2414, which can be located anywhere on the housing although shown as being located on opposite ends of the housing 2416.

[00141] The blood sequestration device 2408 further includes a blood sequestration chamber 2418 connected with the inlet port 2412. The blood sequestration chamber 2418 is defined by an inner chamber housing 2419 that is movable from a first position to receive and sequester a first aliquot of blood, to a second position to expose one or more apertures 2424 at a proximal end of the inner chamber housing 2419 to allow blood to bypass and/or flow around the inner chamber housing 2419 and through a blood sample channel 2422 defined by the outer surface of the inner chamber housing 2419 and the

inner surface of the housing 2416. The blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418.

[00142] In operation, the inner chamber housing 2419 is in the first position toward the inlet port 2412, such that the one or more apertures 2424 are closed, and the blood sequestration chamber 2418 is in a direct path from the patient needle. Upon venipuncture of a patient, and drawing of blood by way of a syringe or Vacutainer, or other blood collection device 2404, the initial aliquot of blood flows into the blood sequestration chamber 2418. As the initial aliquot of blood flows into the blood sequestration chamber, it displaces air therein and eventually the blood contacts the blood barrier 2420, forcing the inner chamber housing to the second position. The inner chamber housing 2419 and/or housing 2416 can include a locking mechanism of one or more small tabs, grooves, detents, bumps, ridges, or the like, to maintain the inner chamber housing 2419 in the first position until the blood sequestration chamber 2418 is filled, providing force to overcome the locking mechanism to enable movement of the inner chamber housing 2419 to the second position. Once in the second position, the initial aliquot of blood is sequestered in the blood sequestration chamber 2418 and the one or more apertures 2424 are opened to create a pathway from the inlet port 2412 to the blood sampling channel 2422, bypassing and/or flowing around the blood sequestration chamber 2418.

[00143] As described above, the housing 2416 and/or inner chamber housing 2419 can be formed as cylindrical and concentric, but can be any shape, such as squared, rectangular, elliptical, oval, or other cross-sectional shape. The outer surface of the distal end of the inner chamber housing 2419 can have one or more outwardly projecting tangs 2421with gaps therebetween. The tangs 2421 contact the inner surface of the housing 2416 to help define the blood sampling channel 2422 therebetween, and to help stop the inner chamber housing 2419 in the second position. The gaps between the tangs 2421 enable blood to flow through the blood sampling channel 2422 and to the outlet port 2414. When the inner chamber housing 2419 is in the second position and the blood sequestration chamber 2418 is filled with the first aliquot of blood, further blood samples will automatically flow through the inlet port 2412, through the one or more apertures 2424, through the blood sampling channel 2422, through the gaps between the tangs 2421, and ultimately through the outlet port 2414 to be collected by a blood sampling device 2404.

[00144] FIGS. 25A – D show a blood optimization system 2500 and blood sequestration device 2502, formed substantially as described in FIGS. 15, 16, 17, 18 and 19, but being formed to inhibit a user or other object from touching or blocking an air venting mechanism from a blood sequestration chamber 2520. Air initially in the blood sequestration chamber 2520 is displaced by an initial aliquot of blood upon venipuncture, where a patient's blood pressure overcomes the ambient air pressure in the blood sequestration chamber 2520. The air venting mechanism includes an air permeable blood barrier 2506, such as a porous material or set of materials that allows air to escape but blocks blood from leaving the blood sequestration chamber 2520.

[00145] The air venting mechanism includes an inner wall 2516 that at least partially circumscribes or surrounds the air permeable blood barrier 2506, and an outer wall 2504 spaced apart from the inner wall 2516. The outer wall 2504 can have one or more air vents 2514 formed therein. The outer wall 2504 extends higher upward than the inner wall 2516, such that a lid 2510, such as a cap, plug, cover, etc., can be attached to the outer wall 2504 and be displaced by a small distance from the top of the inner wall 2516. A seal 2508 in the form of a silicone wafer, or other elastomeric material, fits within the outer wall 2504 to cover the air permeable blood barrier 2506 and abut the top of the inner wall 2516. The seal 2508 covers and seals the air permeable blood barrier 2506 and inhibits air from entering the blood sequestration chamber 2520 through the air permeable blood barrier 2506. A fulcrum 2512 on an underside of the lid 2510 allows the seal 2508 to flexibly disconnect from the top of the inner wall 2516 when pushed by air displaced from the blood sequestration chamber 2520, to allow air to vent from the air permeable blood barrier 2506 and through the one or more air vents 2514 in the outer wall 2504.

[00146] FIG. 26A – E illustrate a blood sample optimization system 2600 that includes a patient needle 2602 for vascular access to a patient's bloodstream, a blood sample collection device 2604 to facilitate the collecting of one or more blood samples for blood testing or blood cultures, and a conduit 2606 providing a fluid connection between the patient needle 2602 and the blood sample collection device 2604. The conduit 2606 can include flexible tubing. In preferred implementations, the blood sample collection device 2604 includes a protective shield 2605 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 2602.

[00147] The blood sample optimization system 2600 further includes a blood sequestration device 2608, located at any point on the conduit 2606 between the patient needle 2602 and the blood sample collection device 2604. The location of the blood sequestration device 2608 can be based on a length of the conduit between the blood sequestration device 2608 and the patient needle 2602, and the associated volume that length provides.

[00148] The blood sequestration device 2608 includes an inlet port 2612 for being connected to the conduit 2606 toward the patient needle 2602, and an outlet port 2614 for being connected to the conduit 2606 toward the blood sample collection device 2604. The blood sequestration device 2608 includes an outer housing 2616 and an inner housing 2617, both having a cylindrical form, and being connected concentrically. The outer housing 2616 includes an outer wall 2618 and an inner conduit 2620 that defines a blood sampling channel 2622 to convey blood through the conduit 2606 to the blood sampling device 2604. The inner housing 2617 fits snugly between the inner conduit 2620 and the outer wall 2618 of the outer housing, and is rotatable in relation to the outer housing 2616. The fit between the outer housing 2616 and the inner housing 2617 can be a friction fit that maintains the housings in a particular position. The inner housing 2617 defines a blood sequestration chamber 2624, preferably a helical or corkscrew channel around the outer surface of inner conduit 2620 of the outer housing 2616, and which terminates at an air vent 2628 having an air permeable blood barrier, as shown in FIG. 26E.

[00149] The blood sequestration chamber 2624 is connected with the blood sampling channel 2622 via diversion junction 2624 formed in the inner conduit 2620, when the blood sequestration device in a first state, illustrated in FIG. 26C. The protective shield 2606 on the collection needle 2604 provides a block for air or blood, enabling a diversion of an initial aliquot of blood into the blood sequestration chamber 2624 as the patient's blood pressure overcomes the ambient air pressure in the blood sequestration channel 2624 to displace air therefrom through air vent 2628.

[00150] When the inner housing 2617 is rotated relative to the outer housing 2616, or vice versa, to a second state, as illustrated in FIG. 26D, the blood sequestration chamber 2624 is shut off from diversion junction 2624, enabling a direct path from the patient needle through the conduit 2606 to the collection needle 2604, via blood sampling channel 2622. The outer housing 2616 and/or inner housing 2617 can include ridges or grooves formed within a portion of their surfaces, to facilitate relative rotation from the first state to the second state.

[00151] FIGS. 27A – D illustrate a blood optimization system 2700 and blood sequestration device 2702, formed substantially as described with reference to at least FIGS. 15, 16, 17, 18, 19, and 25, but being formed to inhibit a user or other object from touching or blocking an air venting mechanism from a blood sequestration chamber 2720. Air initially in the blood sequestration chamber 2720 is displaced by an initial aliquot of blood upon venipuncture, where a patient's blood pressure overcomes the ambient air pressure in the blood sequestration chamber 2720. The air venting mechanism includes an air permeable blood barrier 2706, such as a porous material or set of materials that allows air to escape but blocks blood from leaving the blood sequestration chamber 2720.

[00152] The air venting mechanism includes an inner wall 2716 that at least partially circumscribes or surrounds the air permeable blood barrier 2706, and an outer wall 2704 spaced apart from the inner wall 2716. A cap 2722 is positioned on the air venting mechanism, preferably by having a lower cap wall 2728 that fits between the inner wall 2716 and the outer wall 2704 of the air venting mechanism, and frictionally abutting either the the inner wall 2716 or the outer wall 2704 or both. The cap 2722 further includes one or more vent holes 2724 or slits, apertures, openings, or the like, which extend through an upper surface of the cap 2722 around a downwardly extending plug 2726. The plug 2726 is sized and adapted to fit snugly within the space defined by inner wall 2716.

[00153] In a first position, as illustrated in FIG. 27C, the cap 2722 is extended from the air venting mechanism to allow air from the blood sequestration chamber 2720 to exit through the air permeable blood barrier 2706 and through the one or more vent holes 2724. Once the air from the blood sequestration chamber 2720 has been displaced, i.e., when the blood sequestration chamber 2720 is filled with the first aliquot of potentially tainted blood from the patient, then the cap 2722 can be pushed down on the air venting

mechanism in a second position as shown in FIG. 27D, so that the plug 2726 fits within the inner wall 2716 over the air permeable blood barrier 2706 to seal the air venting mechanism. In either the first position or the second position, the cap 2722 protects the air permeable blood barrier 2706 from outside air or from being touched by a user.

[00154] FIGS. 28A – F illustrate a blood optimization system 2800 and blood sequestration device 2802, formed substantially as described with reference to at least FIGS. 15, 16, 17, 18, 19, 25 and 26, but utilizing a multi-layered filter, and in some implementations, a filter with trapped reactive material, for an air permeable blood barrier. As shown in FIGS. 28C and D, an air permeable blood barrier 2803 includes a first layer 2804 of an air permeable but blood impermeable material, and a second layer 2806 that includes a reactive material, such as a hydrophobic material, for repelling blood while still allowing air to pass through both layers. As shown in FIGS. 28E and F, the air permeable blood barrier 2803 can include any number of layers, such as a third layer 2808 formed of the same air permeable but blood impermeable material as first layer 2804, while a second layer 2806 includes trapped or embedded blood reactive material.

[00155] FIGS. 29A – C illustrate a blood optimization system 2900 and blood sequestration device 2902, formed substantially as described with reference to at least FIGS. 15, 16, 17, 18, 19, 25 and 26, but in which a blood sequestration chamber 2904 is at least partially filled with a blood-absorptive material 2906. The blood-absorptive material 2906 can act as a wicking material to further draw in blood to be sequestered upon venipuncture of the patient, and prior to use of a blood drawing device such as a Vacutainer™ or a syringe, or the like.

[00156] FIGS. 30A – G illustrate a blood optimization system 3000 and blood sequestration device 3002, formed substantially as described with reference to at least FIGS. 15, 16, 17, 18, 19, 25 and 26. The blood sequestration device 3000 includes an inlet port 3002 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 3002 may also be connected with tubing or other conduit that is in turn connected with the patient needle. The inlet port 3002 defines an opening into the blood sequestration device 3000, 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.

[00157] The inlet port 3002 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 3002, such as by co-molding, gluing, laser weld, or thermally bonding the parts together. In this manner, the blood sequestration device 3000 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 3000 at the time of blood draw or sampling.

[00158] The blood sequestration device 3000 further includes an outlet port 3004, which defines an opening out of the blood sequestration device 3000 and to the blood sample collection device. The outlet port 3004 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 3000 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 3000 at the time of blood draw or sampling.

[00159] The blood sequestration device 3000 further includes a sampling channel 3006 between the inlet port 3002 and the outlet port 3004, and a sequestration chamber 3008 that is connected to and split off or diverted from the sampling channel 3006 at any point between the inlet port 3002 and the outlet port 3004. The sampling channel 3006 functions as a blood sampling pathway once a first aliquot of blood has been sequestered in the sequestration chamber 3008. The sampling channel 3006 can be any sized, shaped or configured channel, or conduit. In some implementations, the sampling channel 3006 has a substantially similar cross sectional area as the opening of the inlet port 3002. In other implementations, the sampling channel 3006 can gradually widen from the inlet port 3002 to the outlet port 3004. The sequestration chamber 3008 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 3006.

[00160] In some exemplary implementations, the diversion between the sampling channel 3006 and the sequestration chamber 3008 is by diverter junction 3007. Diverter junction 3007 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 3007 is configured such that the flow out of the inlet port 3002 is preferentially directed toward the sequestration chamber 3008. The sequestration chamber 3008 may also include or form a curve or ramp to direct the initial blood flow toward and into the sequestration chamber 3008.

[00161] The sequestration chamber 3008 is preferably maintained at atmospheric pressure, and includes a vent 3010 at or near a distal end of the sequestration chamber 3008. The vent 3010 may include an air permeable blood barrier 3012 as described above.

[00162] The blood sequestration device 3000 can include a housing 3001 that can be formed of multiple parts or a single, unitary part. In some implementations, and as illustrated FIG. 30F, the housing 3001 includes a top member 3020 and a bottom member 3022 that are mated together. The blood sequestration device 3000 can also include a gasket or other sealing member (not shown) so that when the top member 3020 is mechanically attached with the bottom member 3022, the interface between the two is sealed by the gasket or sealing member. The bottom member 3022 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 3006, the sequestration chamber 3008, and diverter junction 3007.

[00163] The sequestration chamber 3008 may have a larger cross section than the sampling channel 3006 so that the blood will preferentially move into the sequestration chamber first versus entering a smaller diameter on the sampling channel 3006.

[00164] In some implementations, the sampling channel 3006 and the sequestration chamber 3008 are formed by grooves, channels, locks or other pathways formed in housing 3001. The housing 3001 can be made of rubber, plastic, metal or any other suitable material. The housing 3001 can be formed of a clear or translucent material, or

of an opaque or non-translucent material. In other implementations, the housing 3001 can be mostly opaque or non-translucent, while the housing surface directly adjacent to the sampling channel 3006 and/or the sequestration chamber 3008 may be clear or translucent, giving a practitioner a visual cue or sign that the sequestration chamber 3008 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 3006. Other visual cues or signs of the sequestration can include, without limitation: the air permeable blood barrier 3012 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.

[00165] The air permeable blood barrier 3012 can be covered with, or surrounded by, a cap 3032. The cap 3032 can be sized and configured to inhibit a user from touching the air permeable blood barrier 3012 with their finger or other external implement, while still allowing air to exit the air permeable blood barrier 3012 as the air is displaced from the sequestration chamber 3008. The cap 3032 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.

[00166] The air venting mechanism includes a wall 3030 that at least partially circumscribes or surrounds the air permeable blood barrier 3012. The wall 3030 can have one or more air vents formed therein. The cap 3032 covers wall 3030 and can be snapped, glued, or otherwise attached in place. A seal 3017 in the form of a silicone wafer, or other elastomeric material, fits within the wall 3030 to cover the air permeable blood barrier 3012 and abut the top of the wall 3030. The seal 3017 covers and seals the air permeable blood barrier 3012 and inhibits air from entering the blood sequestration chamber 3008 through the air permeable blood barrier 3012. A fulcrum 3012 on an underside of the cap 3032 allows the seal 3008 to flexibly disconnect from the top of the inner wall 3016 when pushed by air displaced from the blood sequestration chamber 3008, to allow air to vent from the air permeable blood barrier 3012 and through the one or more air vents in the wall 3030 and/or cap 3032.

[00167] In use, the blood sequestration device 3000 includes a sampling channel 3006 and a sequestration chamber 3008. Both pathways are initially air-filled at atmospheric pressure, but the sampling channel 3006 is directed to an outlet port 3004 that will be initially sealed by a Vacutainer or other such sealed blood sampling device, and the sequestration chamber 3008 terminates at a vent 3010 to atmosphere that includes an air permeable blood barrier 3012.

[00168] 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 inlet port 3002 of blood sequestration device 3000. This initial volume of potentially contaminated blood will preferentially flow into the sequestration chamber 3008 by finding the path of least resistance. The patient's own blood pressure overcomes the atmospheric pressure in the vented sequestration chamber 3008 to displace air therein through the air permeable blood barrier 3012, but is not sufficient to overcome the air pressure that builds up in the sealed sampling channel 3006. In various exemplary embodiments, the sequestration chamber 3008 and sampling channel 3006 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.

[00169] Eventually, the sequestration chamber 3008 fills with blood that displaces air through the air permeable blood barrier 3012. Once the blood contacts the air permeable blood barrier, the blood interacts with the air permeable blood barrier 3012 material to completely or partially seal the vent 3010. A signal or indication may be provided that the practitioner can now utilize the Vacutainer or other blood sampling device.

[00170] Upon filling the blood sequestration pathway 3008 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 3006, possibly resulting in a small amount of blood moving past the diversion point into the sampling channel 3006, queuing up the uncontaminated blood to be drawn through the sampling channel 3006.

[00171] In yet another aspect, the blood sequestration chamber and/or blood sampling channel, or other component, of any of the implementations described herein,

can provide a visually discernable warning or result in a component adapted for operative fluid communication with the flash chamber of an introducer for an intravenous catheter into a blood vessel of a patient. The device and method provides a visually discernable alert when blood from the patient communicates with a test component reactive to communicated blood plasma, to visually change. The reaction with the blood or the plasma occurs depending on one or a plurality of reagents positioned therein configured to test for blood contents, substances or threshold high or low levels thereof, to visually change in appearance upon a result.

[00172] In yet other aspects, the blood sequestration chamber and/or blood sampling channel can be sized and adapted to provide a particular volumetric flow of blood, either during the sequestration process and/or the sampling process.

[00173] 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 via a junction, the sequestration chamber having a vent that includes an air permeable blood barrier, the vent being defined by an outer wall that at least partially circumscribes the air permeable blood barrier and includes one or more air vents, the vent further including a cap that at least partially covers the wall and a one-way seal abutting the air permeable blood barrier that inhibits air from entering the sequestration chamber; and

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

the sequestration chamber, the sampling channel and the junction being sized and configured such that a first portion of blood flows into the sequestration chamber toward the air permeable blood barrier for sequestration therein, and a second portion of blood bypasses the sequestration chamber and the first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

2. The blood sequestration device in accordance with claim 1, further comprising a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

3. The blood sequestration device in accordance with claim 1, wherein the vent further includes an inner wall within the outer wall and that contains the air permeable blood barrier.

4. The blood sequestration device in accordance with claim 1, wherein the one-way seal is positioned over the inner wall and within the outer wall of the vent.

5. The blood sequestration device in accordance with claim 4, wherein the cap includes an inner surface that faces the air permeable blood barrier, the

inner surface of the cap including a fulcrum against which the seal can flexibly unseal from the air permeable blood barrier to allow air to escape the sequestration chamber.

6. The blood sequestration device in accordance with claim 1, wherein the air permeable blood barrier includes a sealing material that seals the vent upon contact with blood.

7. The blood sequestration device in accordance with claim 1, wherein the air permeable blood barrier includes a filter having a first layer and a second layer, the second layer of the filter having a hydrophobic material to repel blood.

8. A blood sequestration and sampling system comprising;

a blood sampling pathway having a patient needle on a proximal end and a sample collection device on a distal end; and

a blood sequestration device attached on the blood sampling pathway between the proximal end and distal end of the blood sampling pathway, the blood sequestration device comprising:

an inlet port coupled with the blood sampling pathway toward the patient needle;

an outlet port coupled with the blood sampling pathway toward the sample collection device;

a sequestration chamber connected with the inlet port via a junction, the sequestration chamber having a vent that includes an air permeable blood barrier, the vent being defined by an outer wall that at least partially circumscribes the air permeable blood barrier and includes one or more air vents, the vent further including a cap that at least partially covers the wall and a one-way seal abutting the air permeable blood barrier that inhibits air from entering the sequestration chamber; and

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

the sequestration chamber, the sampling channel and the junction being sized and configured such that a first portion of blood flows into the sequestration chamber toward the air permeable blood barrier for sequestration therein, and a second portion of blood bypasses the sequestration chamber and the

first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

9. The blood sequestration system in accordance with claim 8, wherein the blood sequestration device further comprises a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

10. The blood sequestration system in accordance with claim 8, wherein the vent of the blood sequestration device further includes an inner wall within the outer wall and that contains the air permeable blood barrier.

11. The blood sequestration system in accordance with claim 8, wherein the one-way seal of the vent is positioned over the inner wall and within the outer wall of the vent.

12. The blood sequestration system in accordance with claim 11, wherein the cap includes an inner surface that faces the air permeable blood barrier, the inner surface of the cap including a fulcrum against which the seal can flexibly unseal from the air permeable blood barrier to allow air to escape the sequestration chamber.

13. The blood sequestration system in accordance with claim 8, wherein the air permeable blood barrier of the blood sequestration device includes a sealing material that seals the vent upon contact with blood.

14. The blood sequestration system in accordance with claim 8, wherein the air permeable blood barrier of the blood sequestration device includes a filter having a first layer and a second layer, the second layer of the filter having a hydrophobic material to repel blood.

15. A blood sequestration device comprising;

an inlet port;

an outlet port;

a sequestration chamber connected with the inlet port via a junction, the sequestration chamber having a vent that includes an air permeable blood barrier, the vent being defined by an outer wall that at least partially circumscribes the air permeable blood barrier and includes one or more air vents, the vent further including a cap that at least partially covers the wall and a one-way seal abutting the air permeable blood barrier that inhibits air from entering the sequestration chamber; and

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

the sequestration chamber, the sampling channel and the junction being sized and configured such that a first portion of blood flows into and fills the sequestration chamber to displace air therein through the vent, and such that a second portion of blood bypasses the sequestration chamber and the first portion of blood sequestered therein and is directed into the sampling channel toward the outlet port.

16. The blood sequestration device in accordance with claim 15, further comprising a housing that houses and defines the inlet port, the outlet port, the sequestration chamber, and the sampling channel.

17. The blood sequestration device in accordance with claim 15, wherein the vent further includes an inner wall within the outer wall and that contains the air permeable blood barrier.

18. The blood sequestration device in accordance with claim 15, wherein the one-way seal is positioned over the inner wall and within the outer wall of the vent.

19. The blood sequestration device in accordance with claim 18, wherein the cap includes an inner surface that faces the air permeable blood barrier, the inner surface of the cap including a fulcrum against which the seal can flexibly unseal from the air permeable blood barrier to allow air to escape the sequestration chamber.

20. The blood sequestration device in accordance with claim 15, wherein the air permeable blood barrier includes a sealing material that seals the vent upon contact with blood.

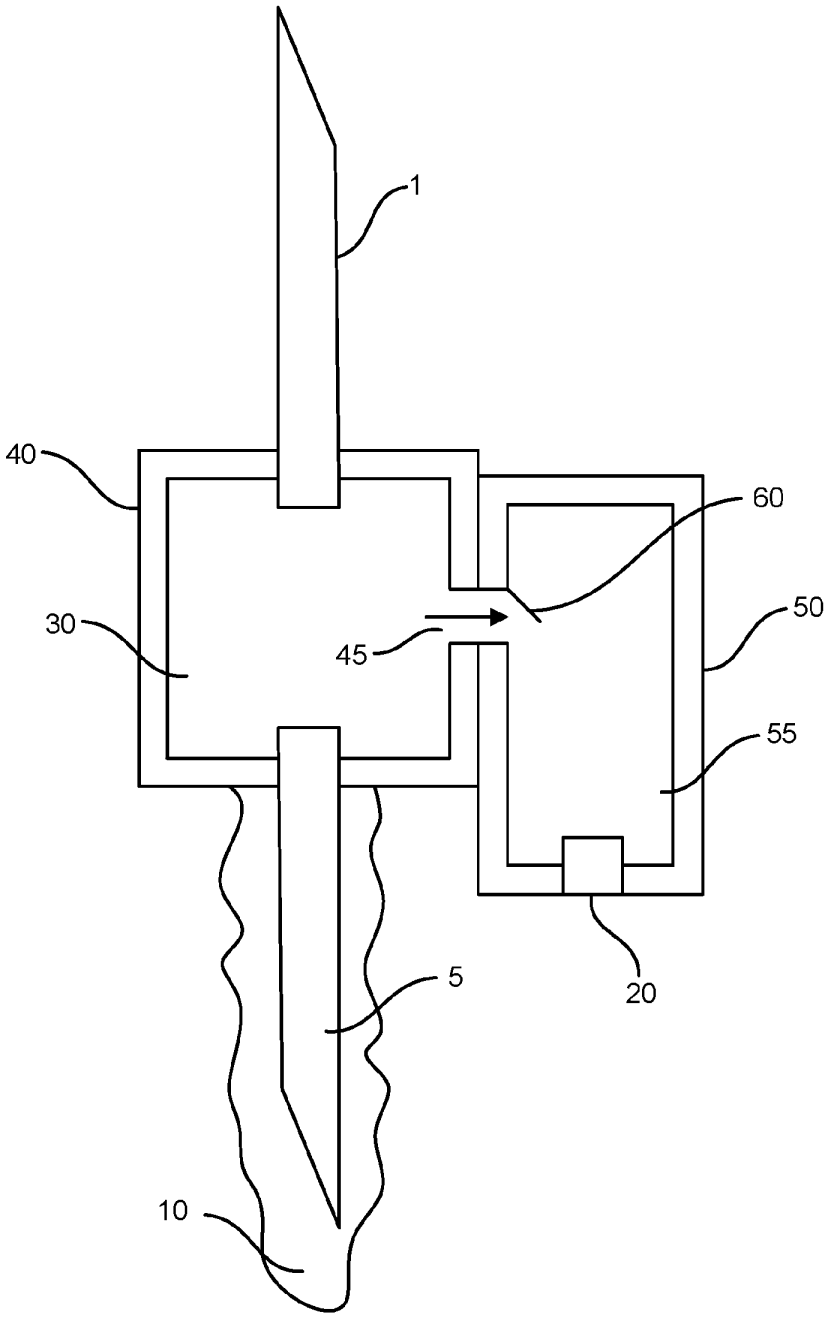


FIG. 1

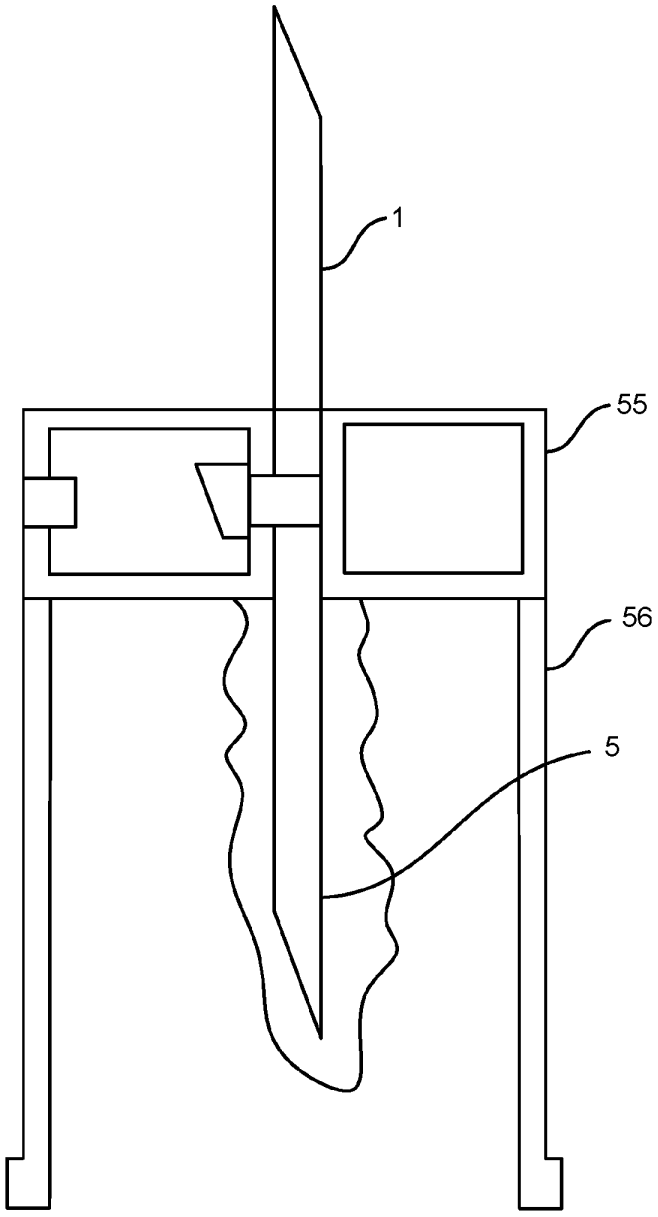


FIG. 2

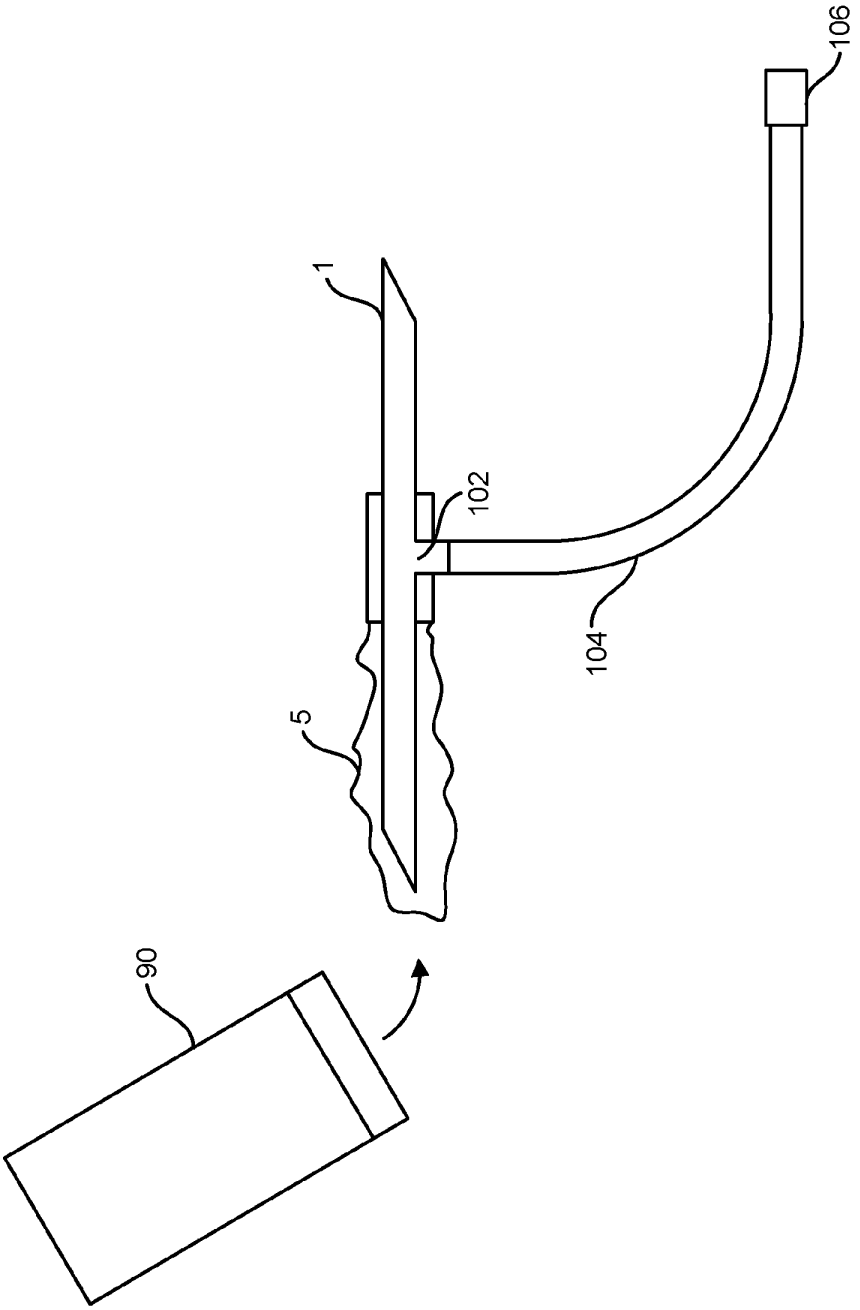


FIG. 3

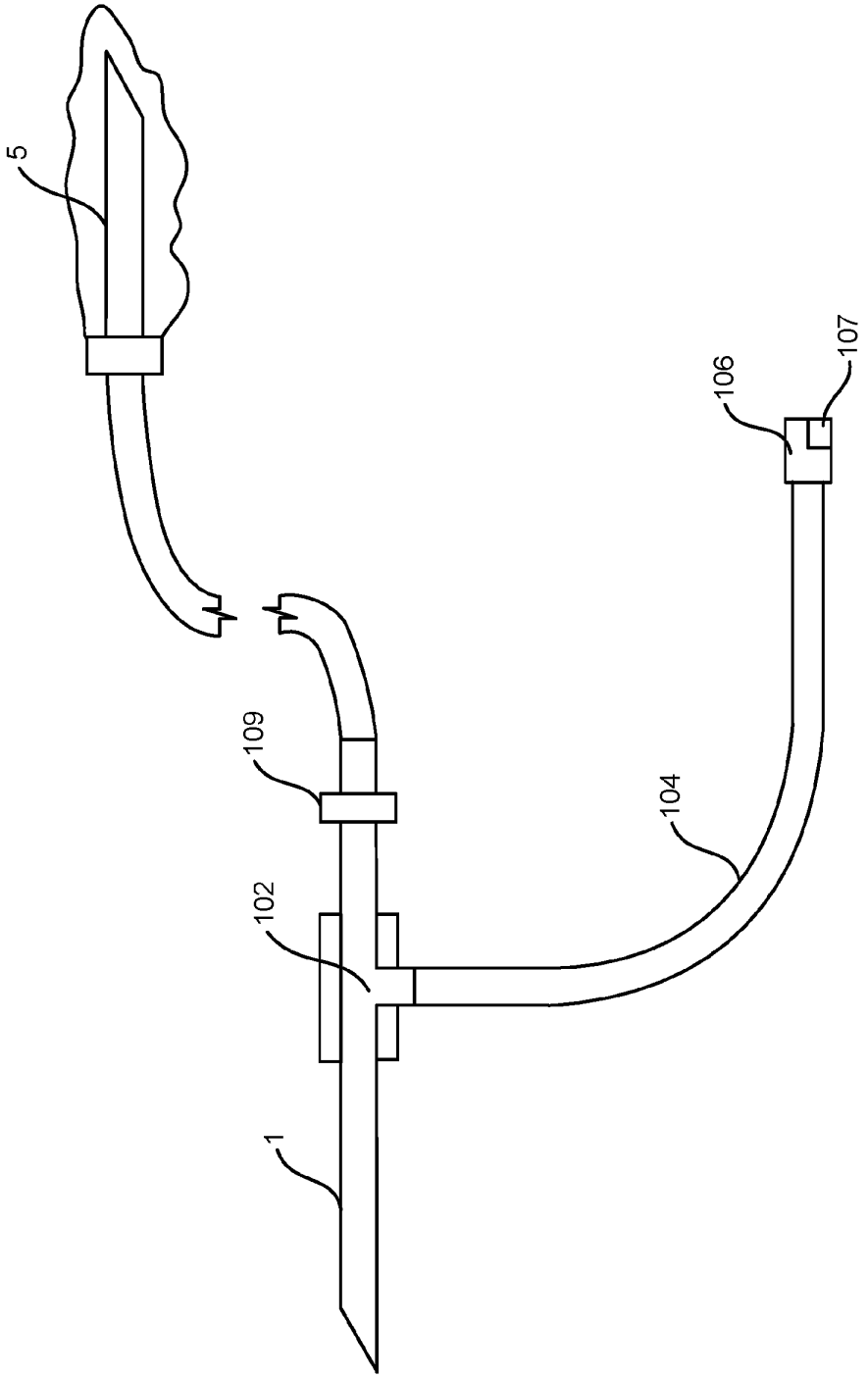


FIG. 4

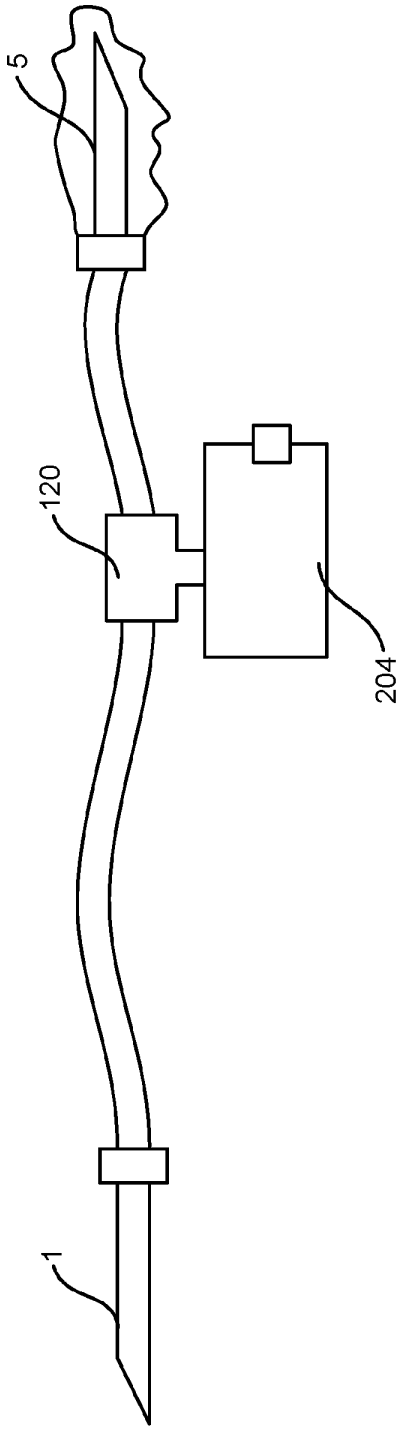


FIG. 5

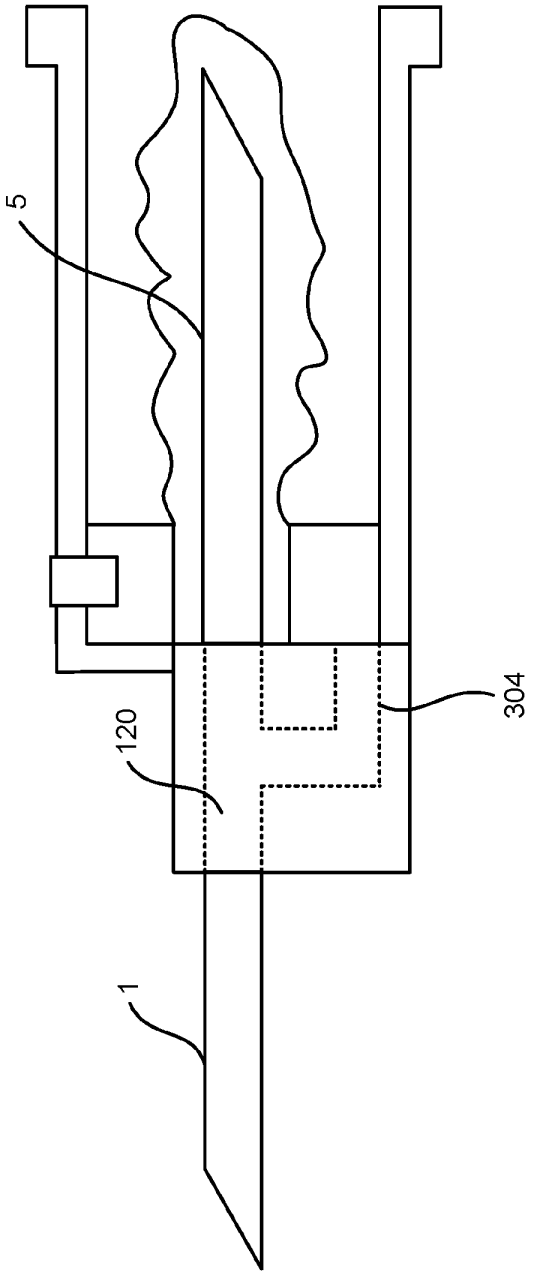


FIG. 6

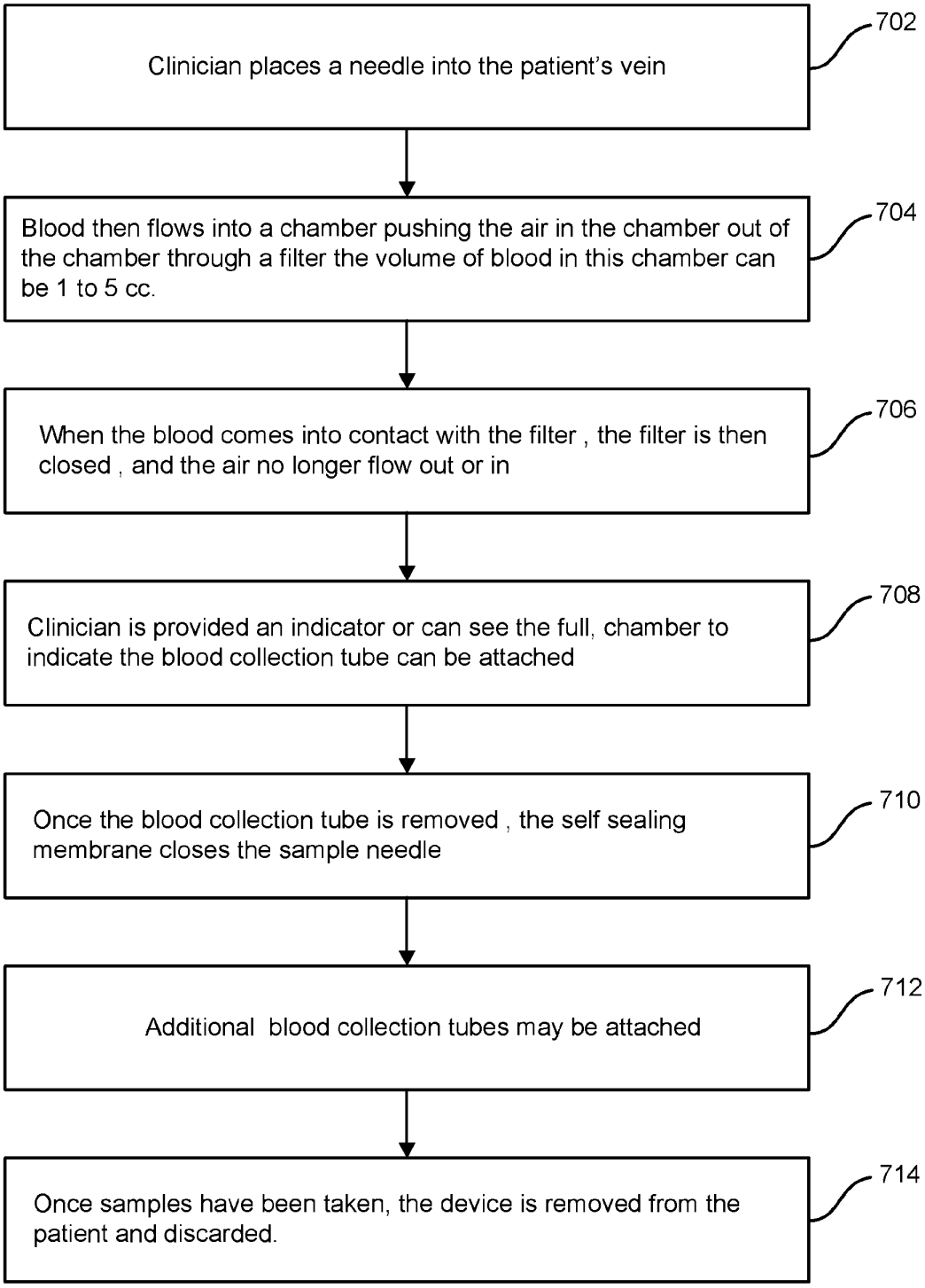

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air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

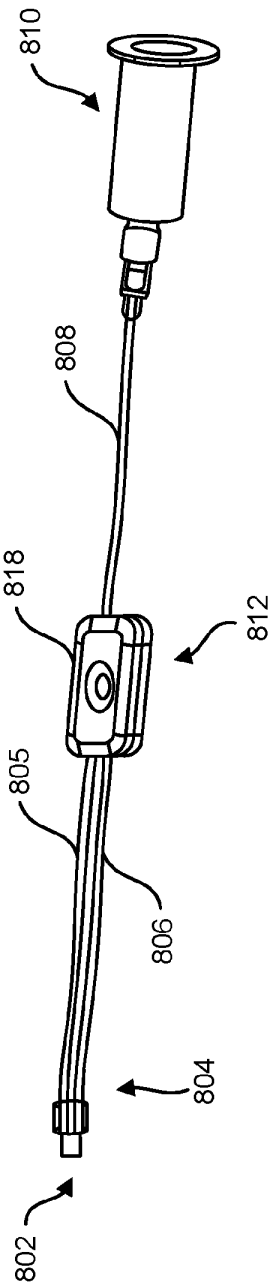


FIG. 8A

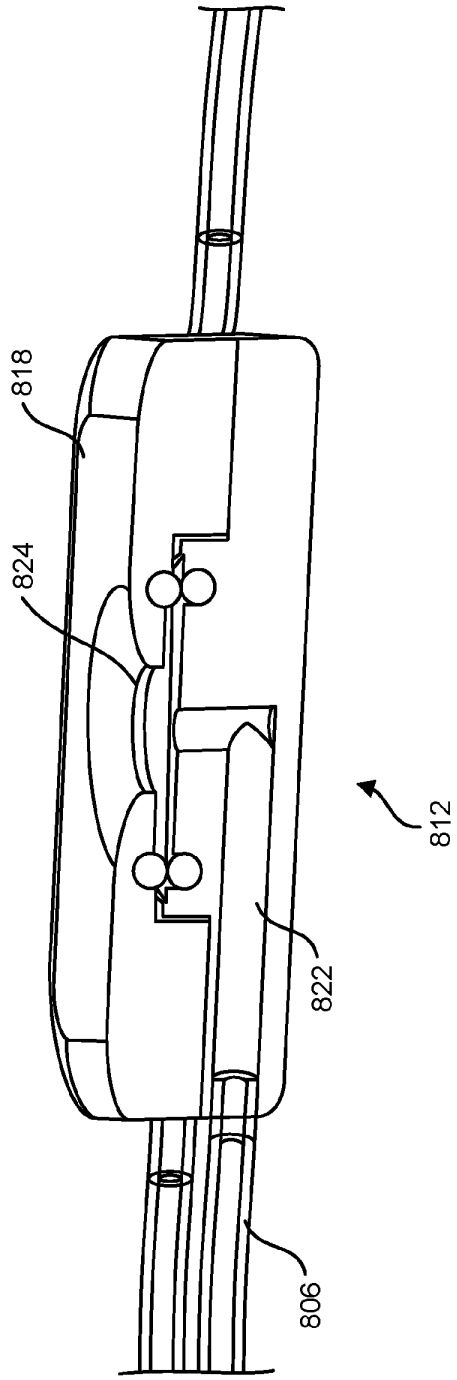


FIG. 8B

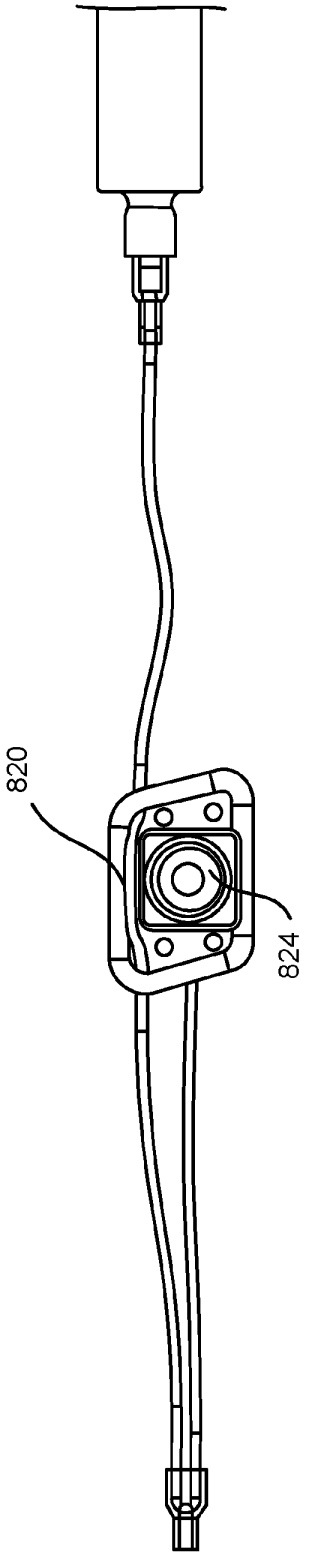


FIG. 8C

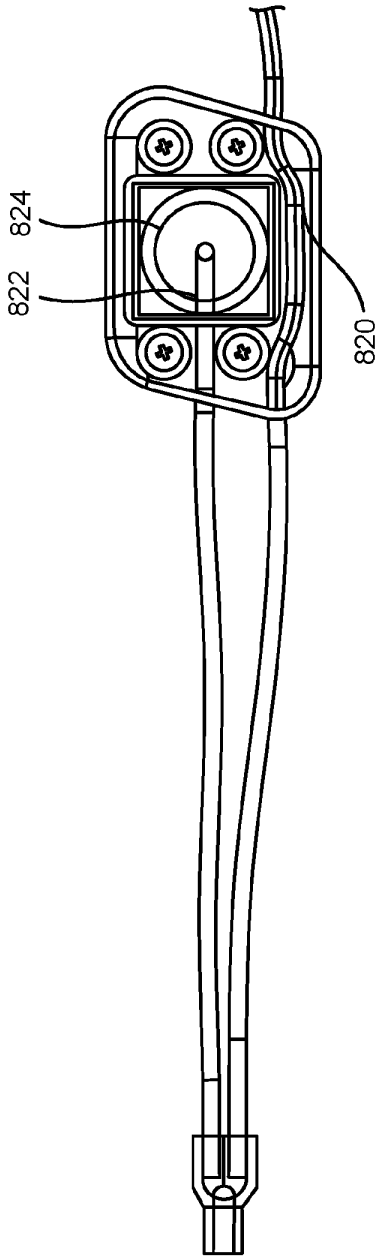


FIG. 8D

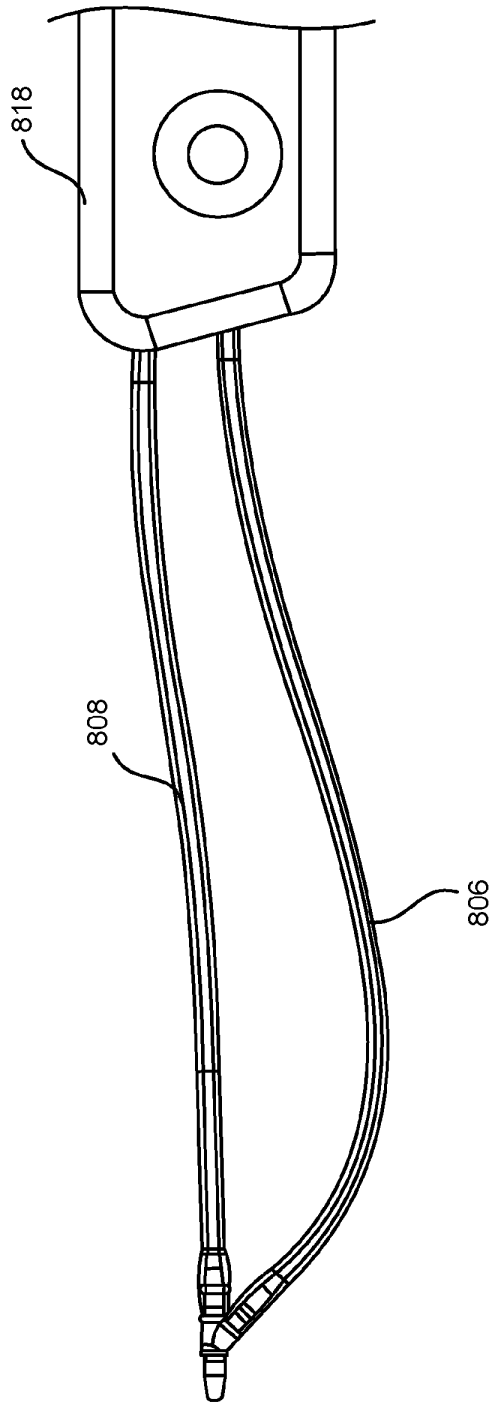


FIG. 8E

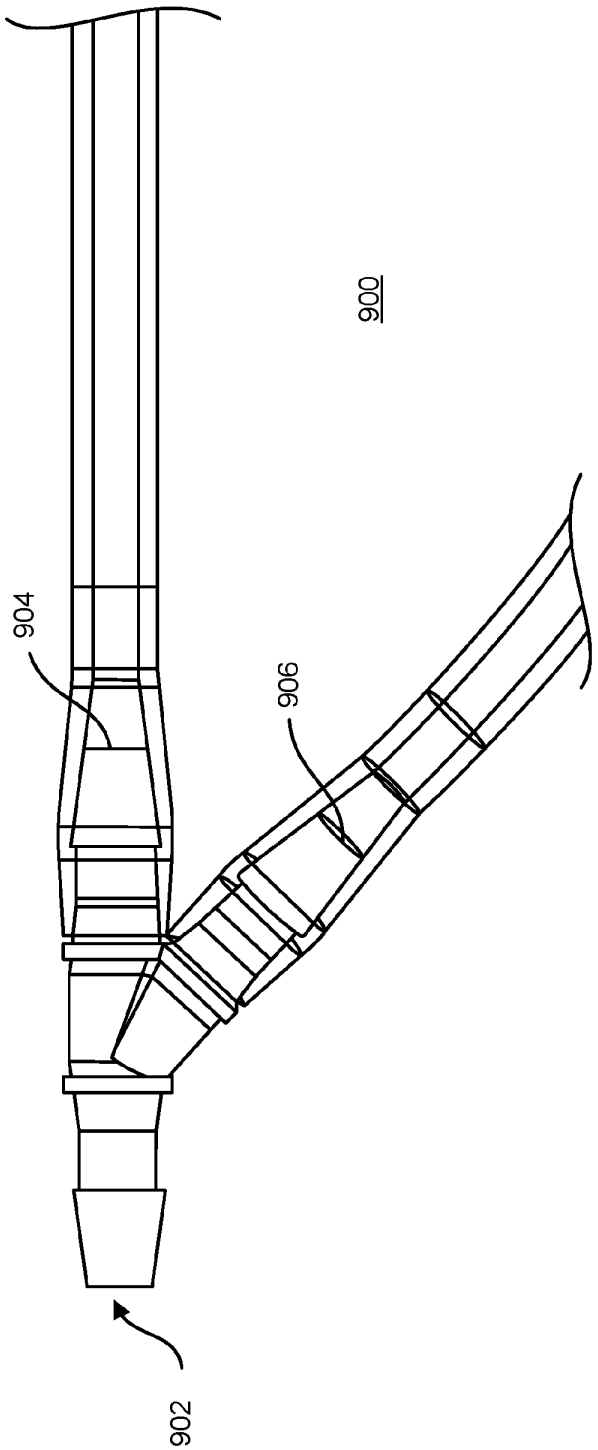


FIG. 9

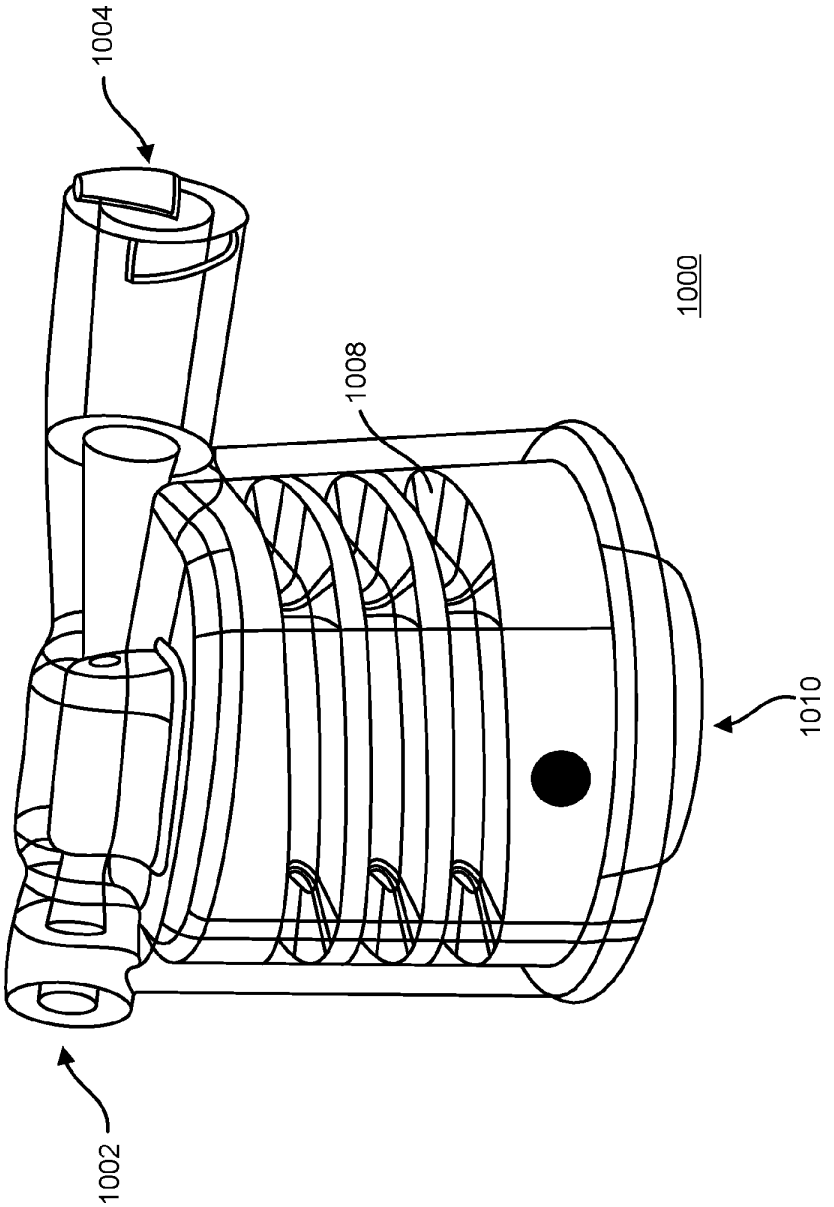


FIG. 10A

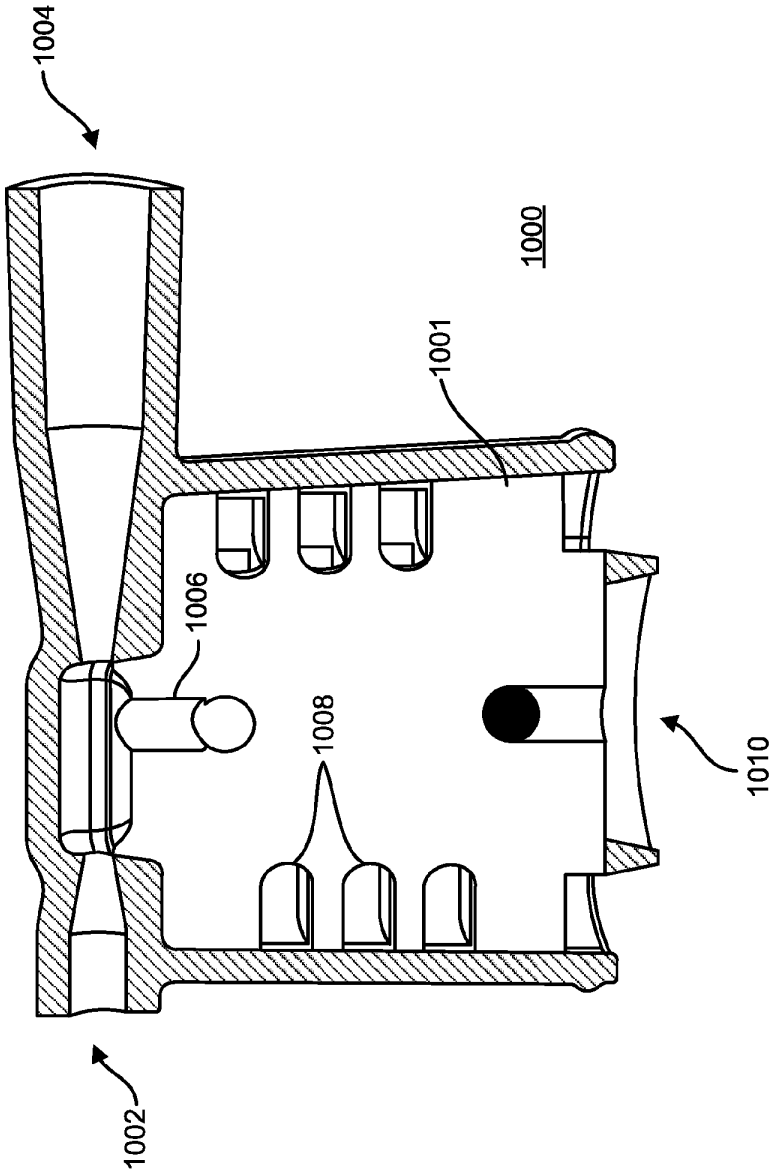


FIG. 10B

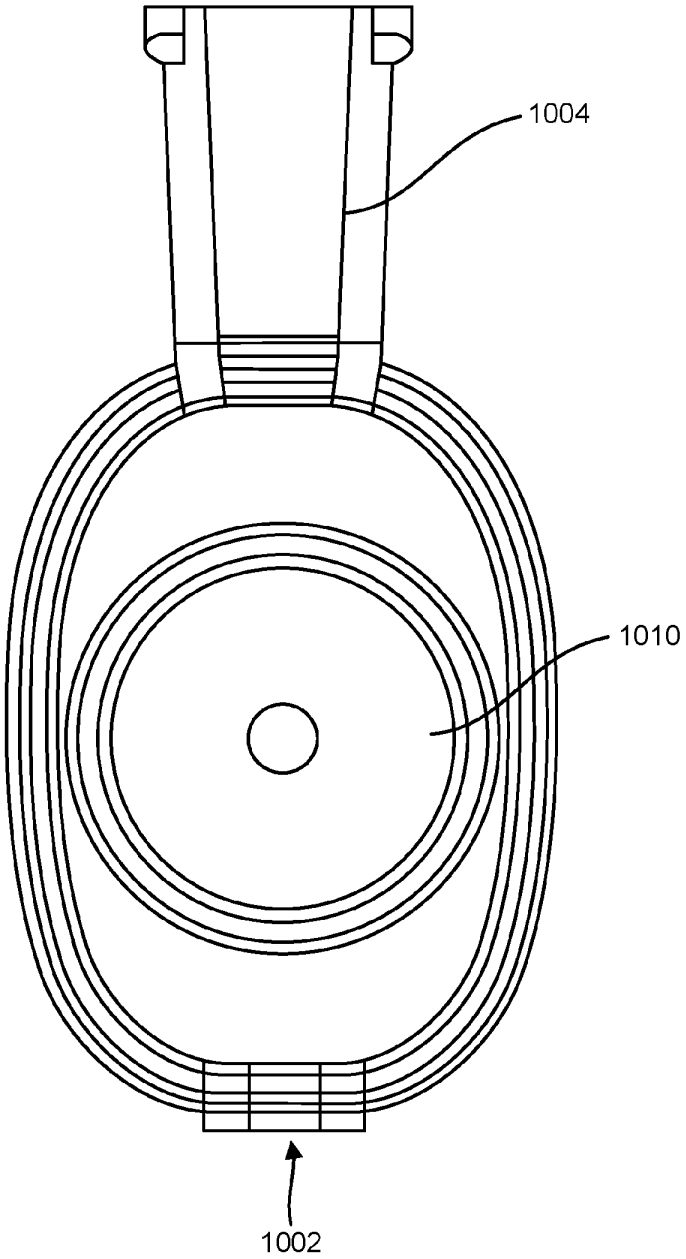


FIG. 10C

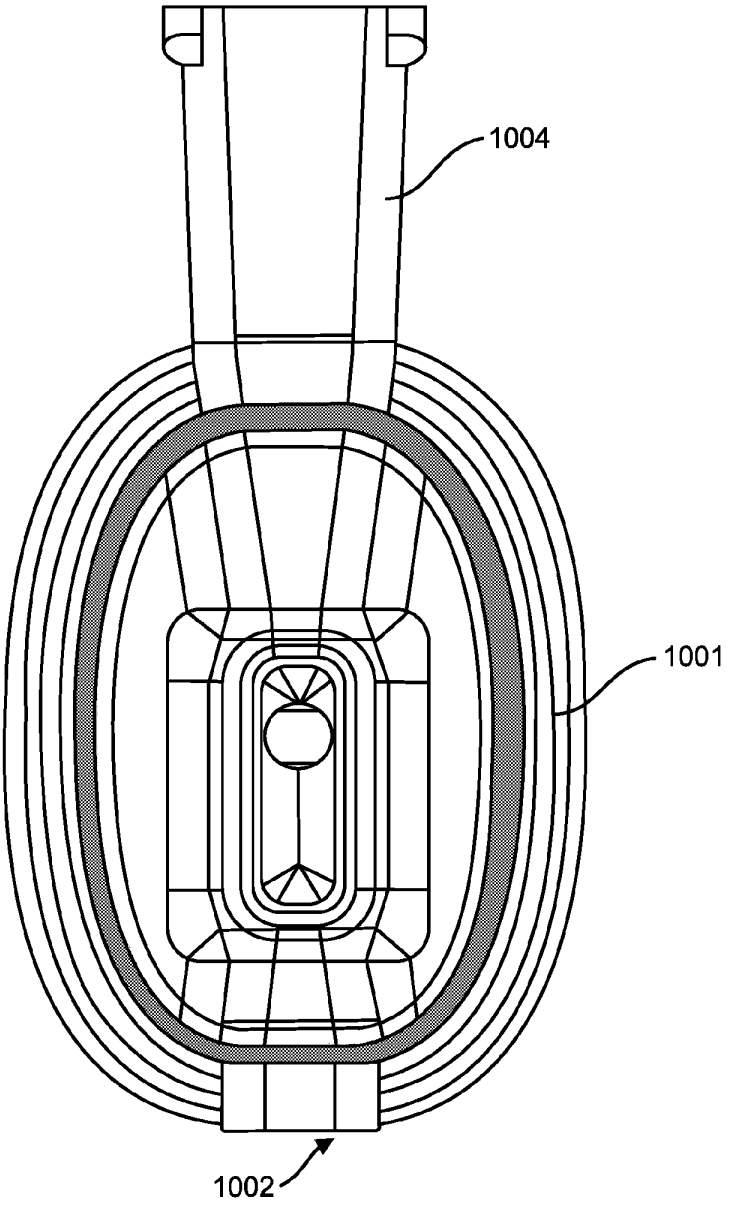


FIG. 10D

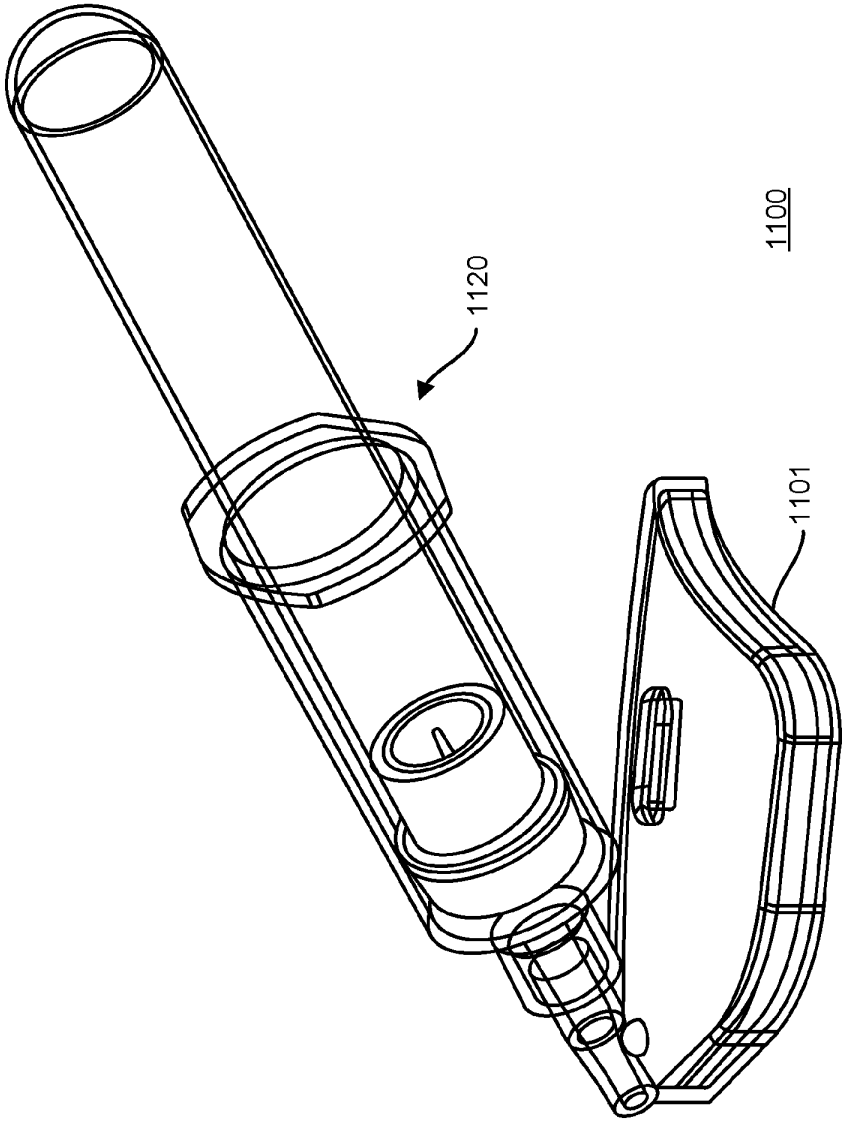


FIG. 11A

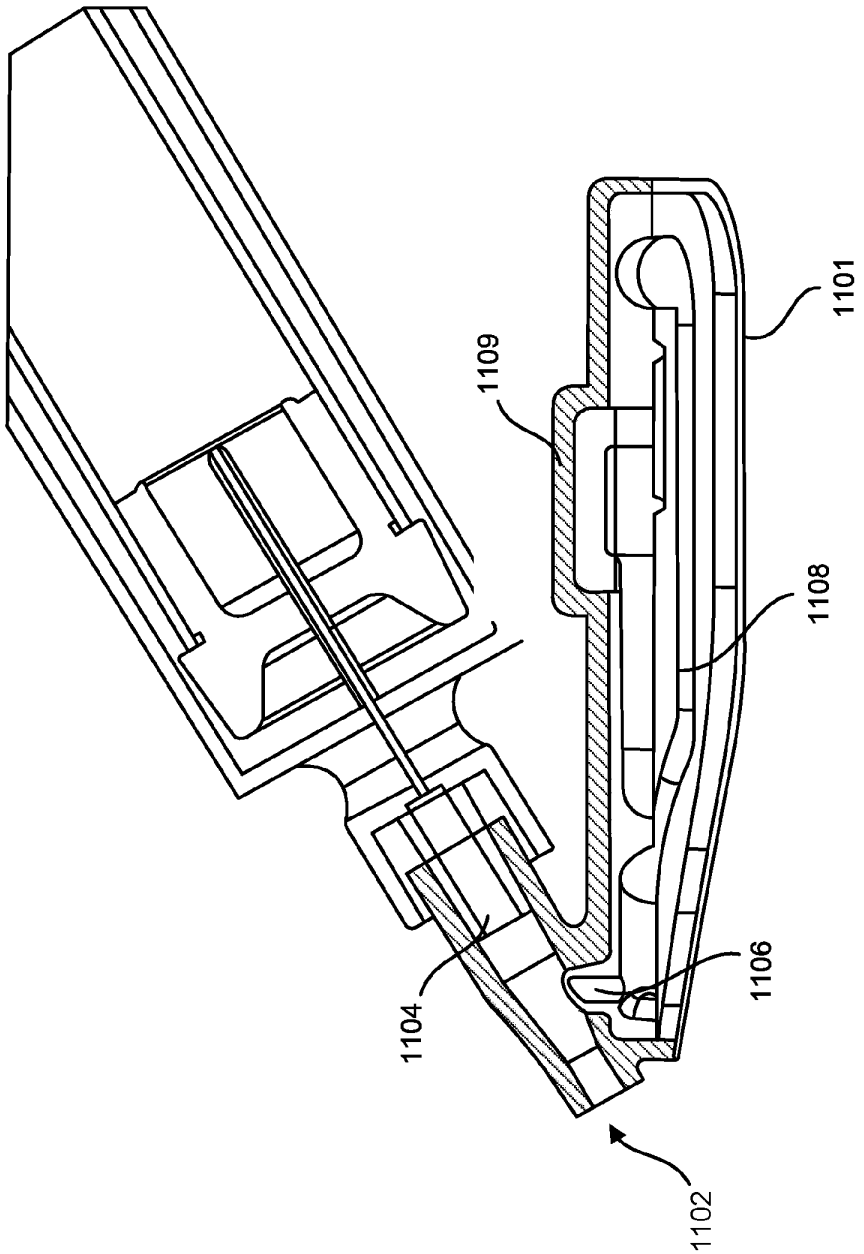


FIG. 11B

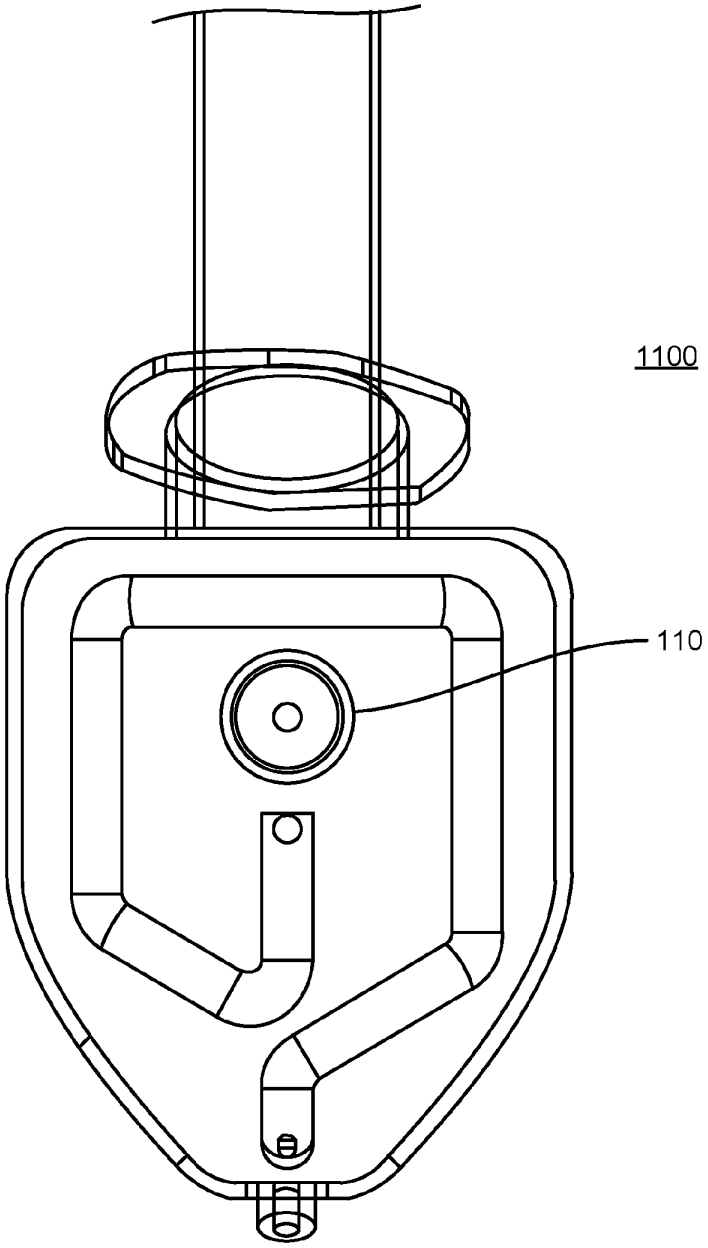


FIG. 11C

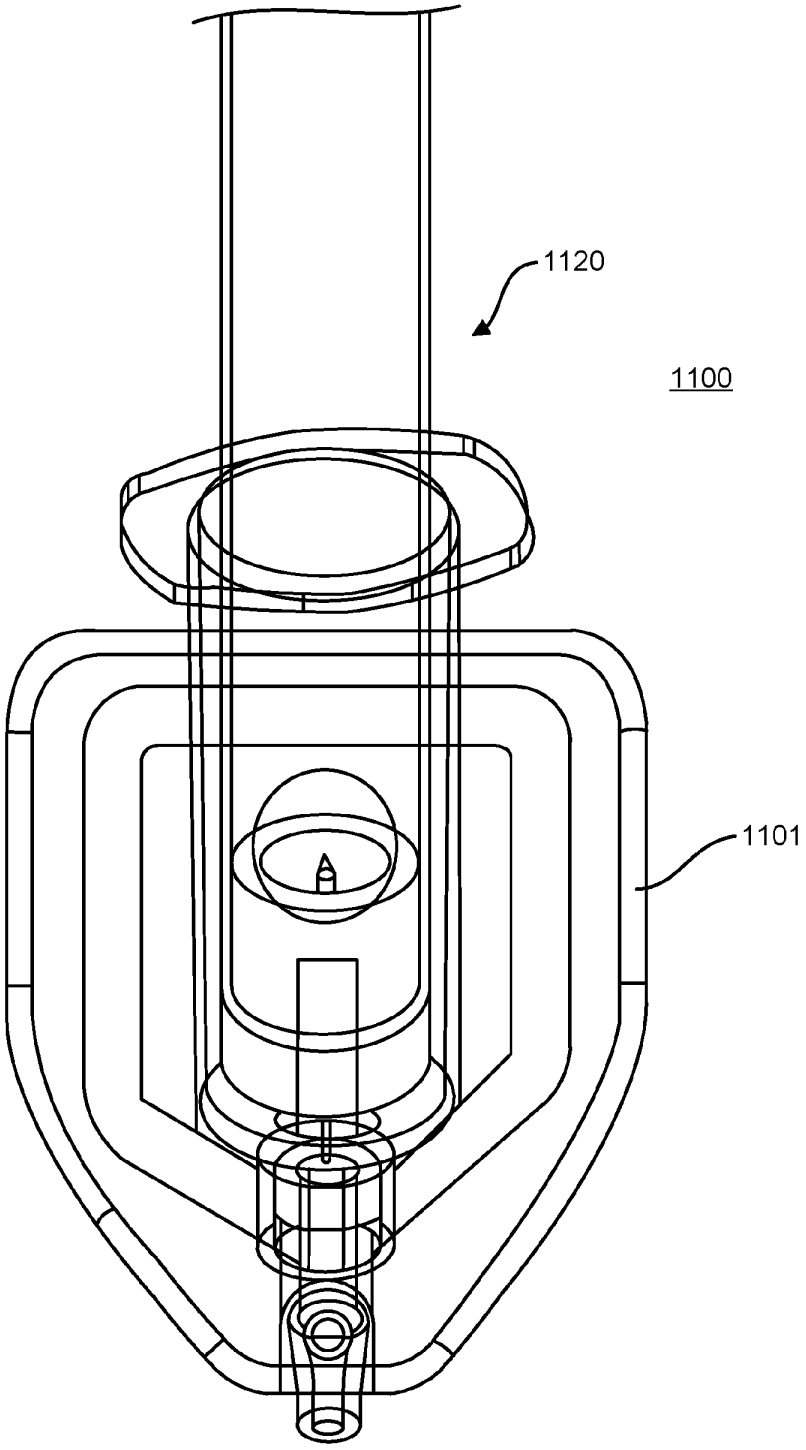


FIG. 11D

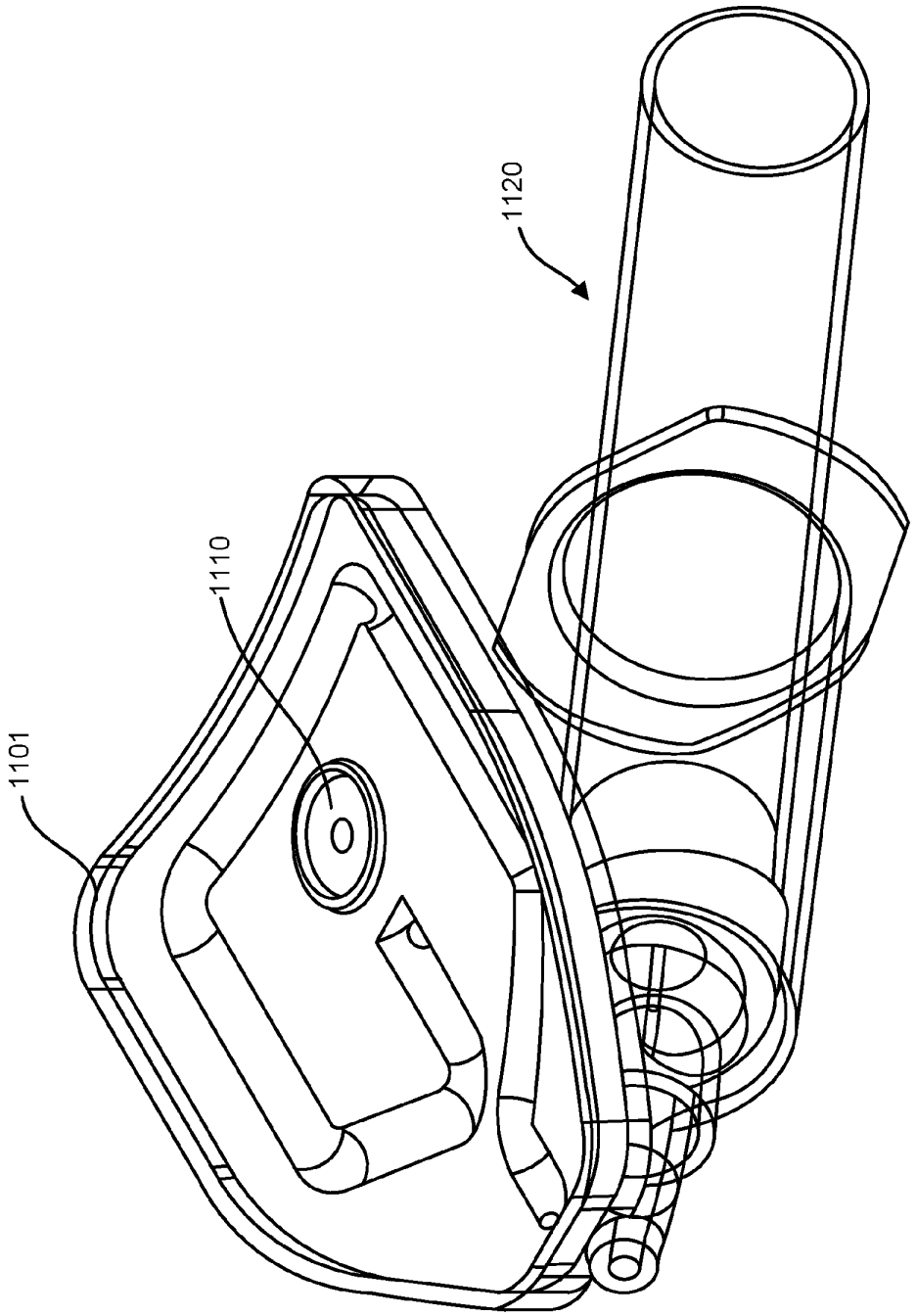


FIG. 11E

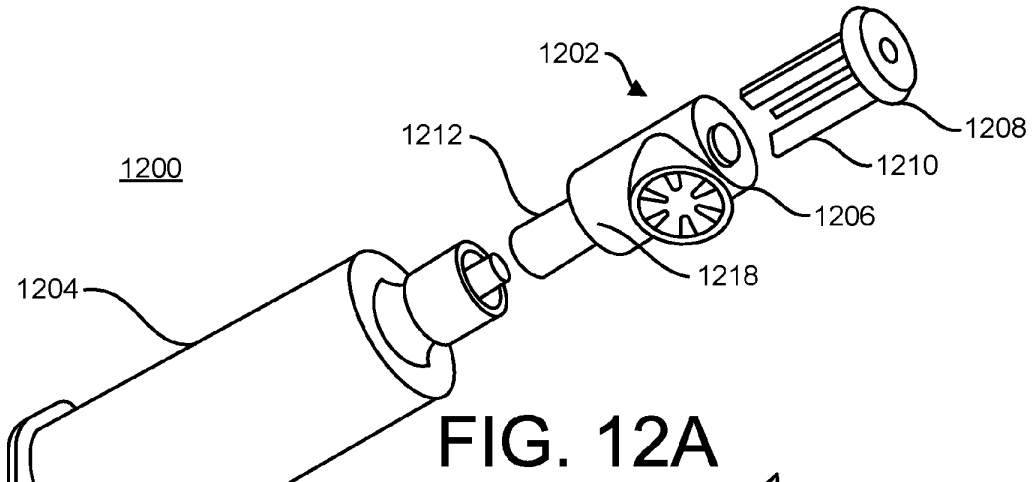


FIG. 12A

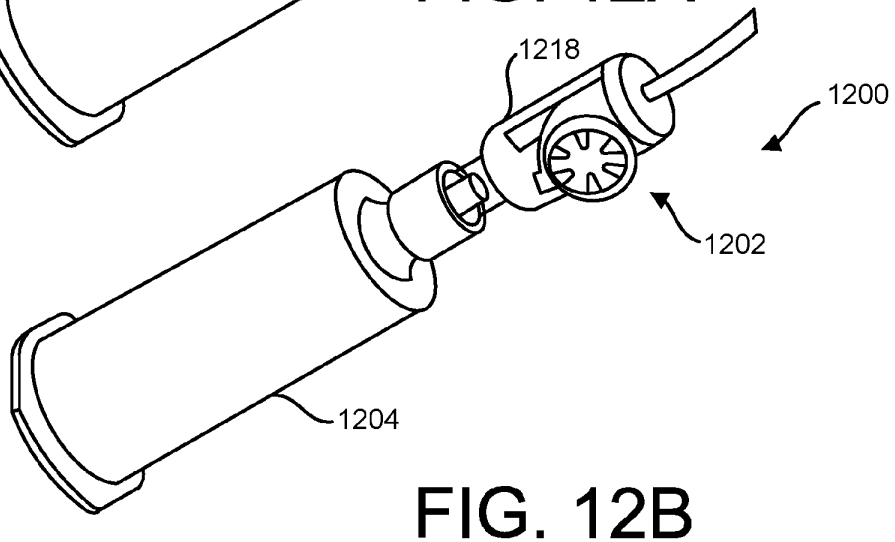


FIG. 12B

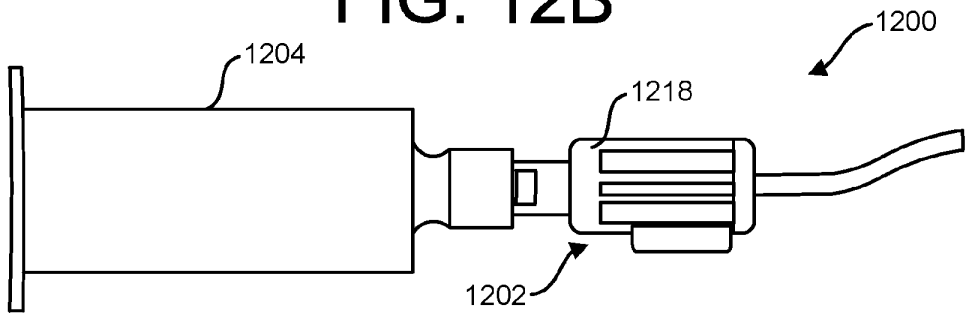


FIG. 12C

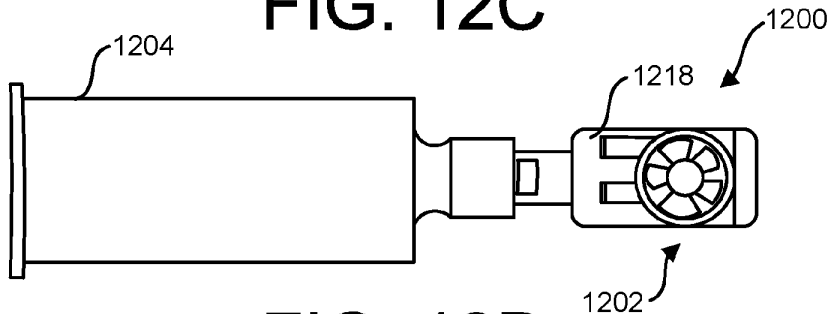


FIG. 12D

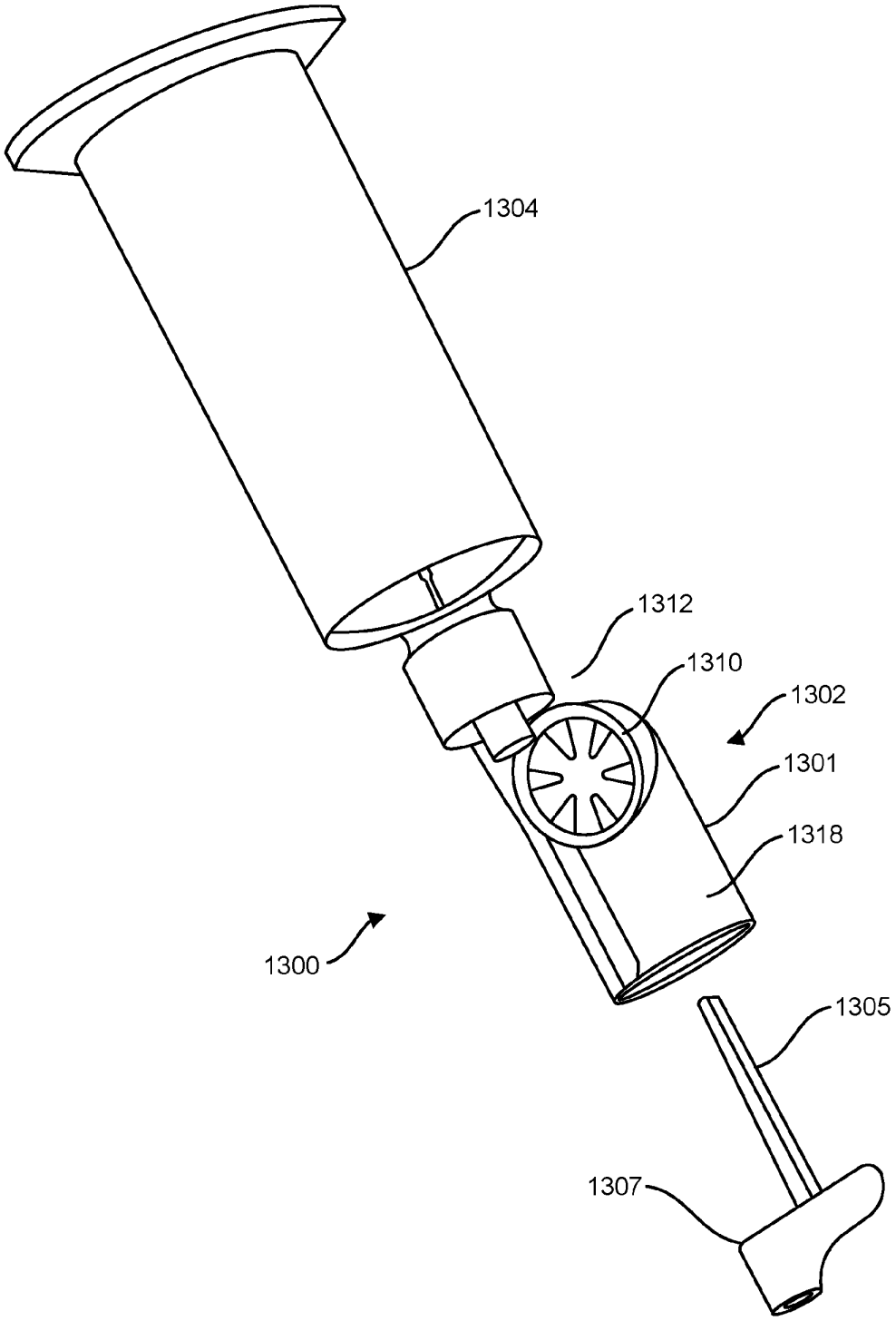


FIG. 13A

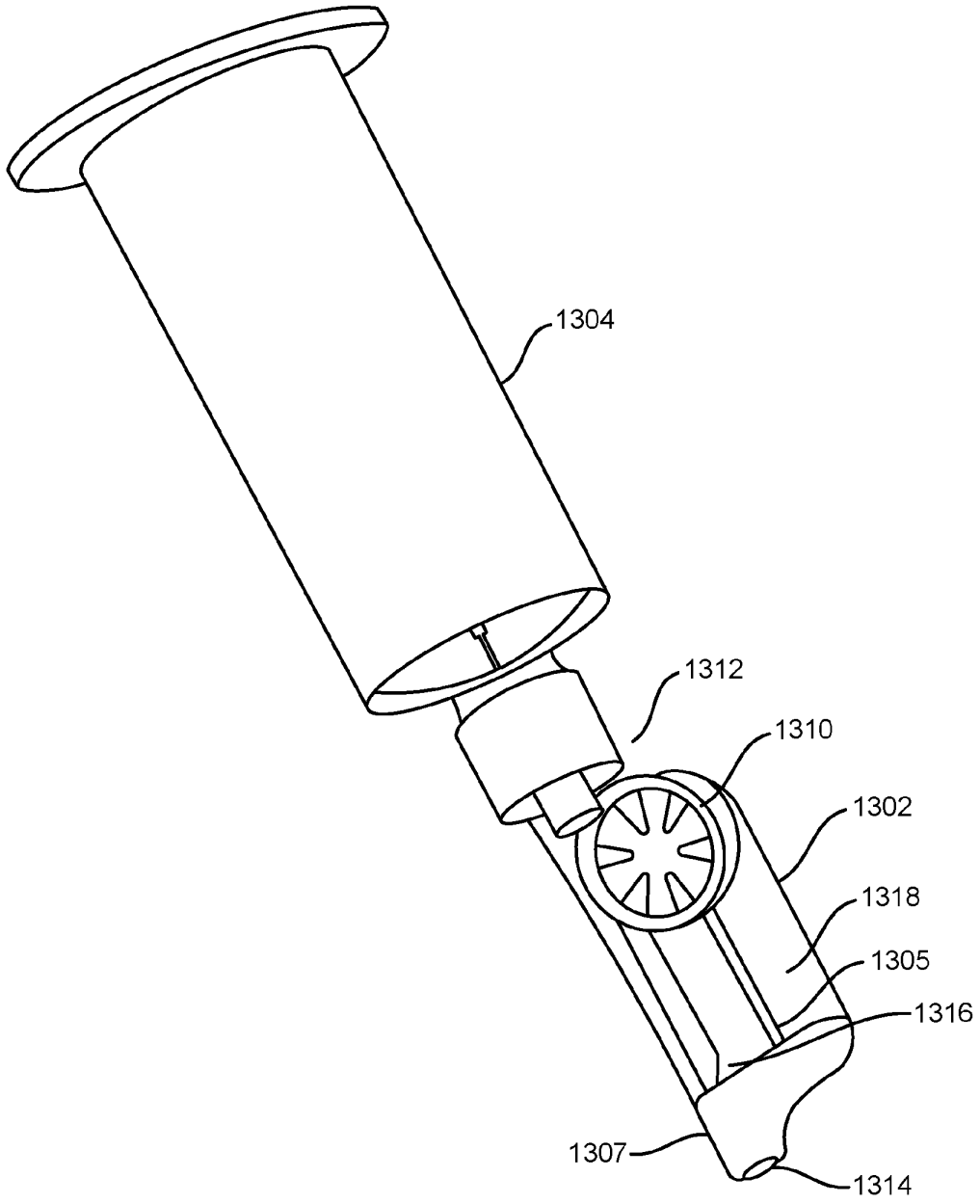


FIG. 13B

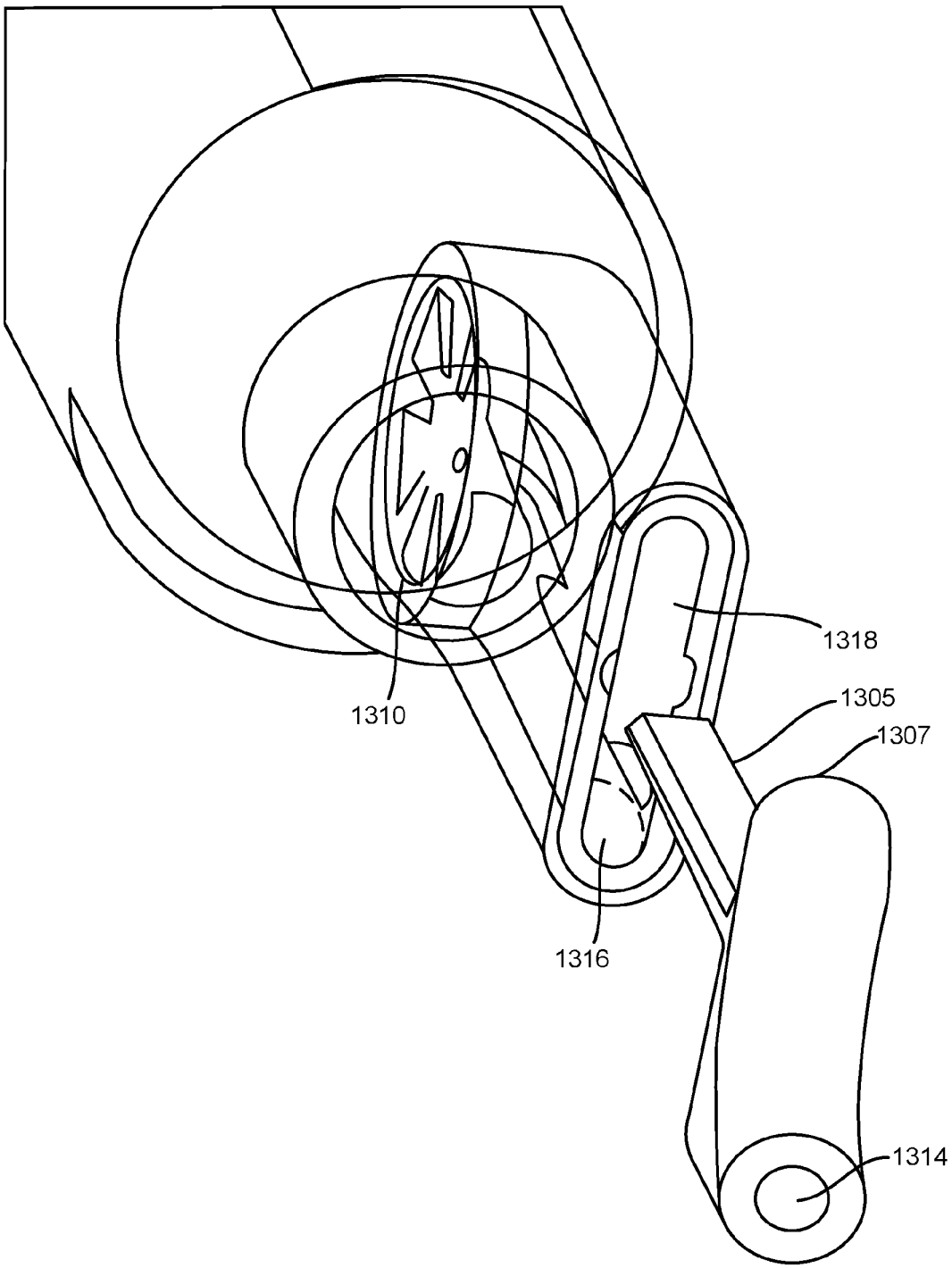


FIG. 13C

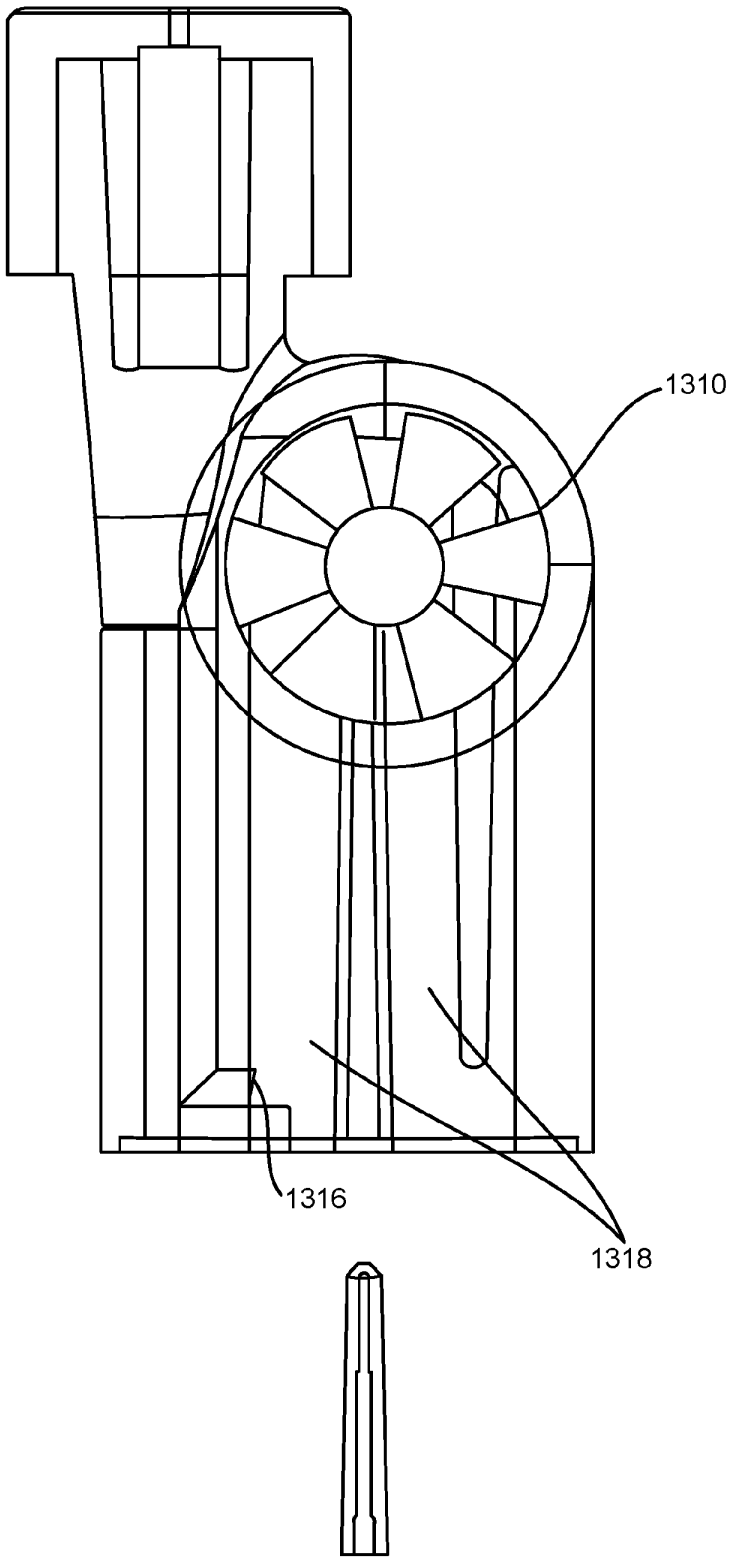


FIG. 13D

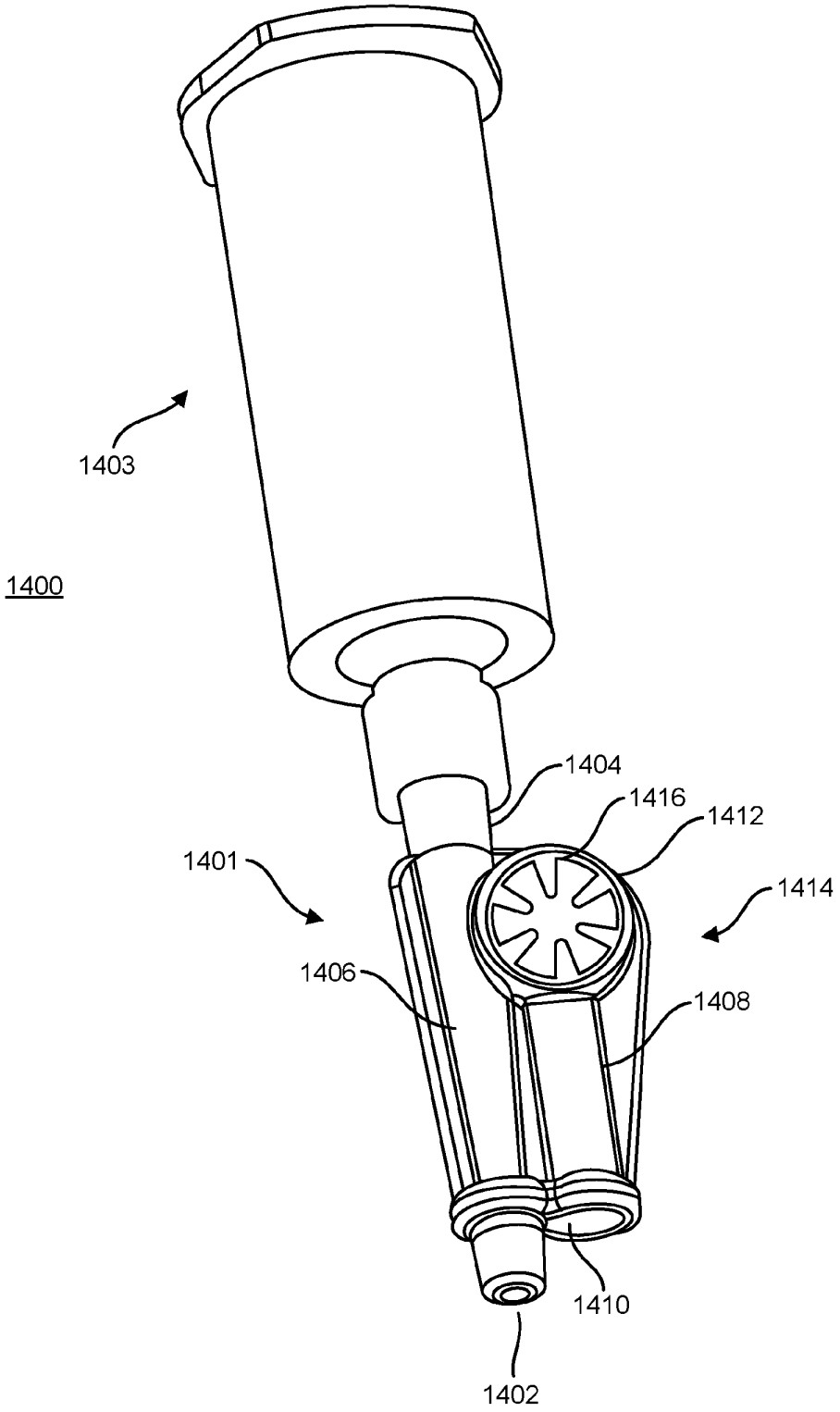


FIG. 14A

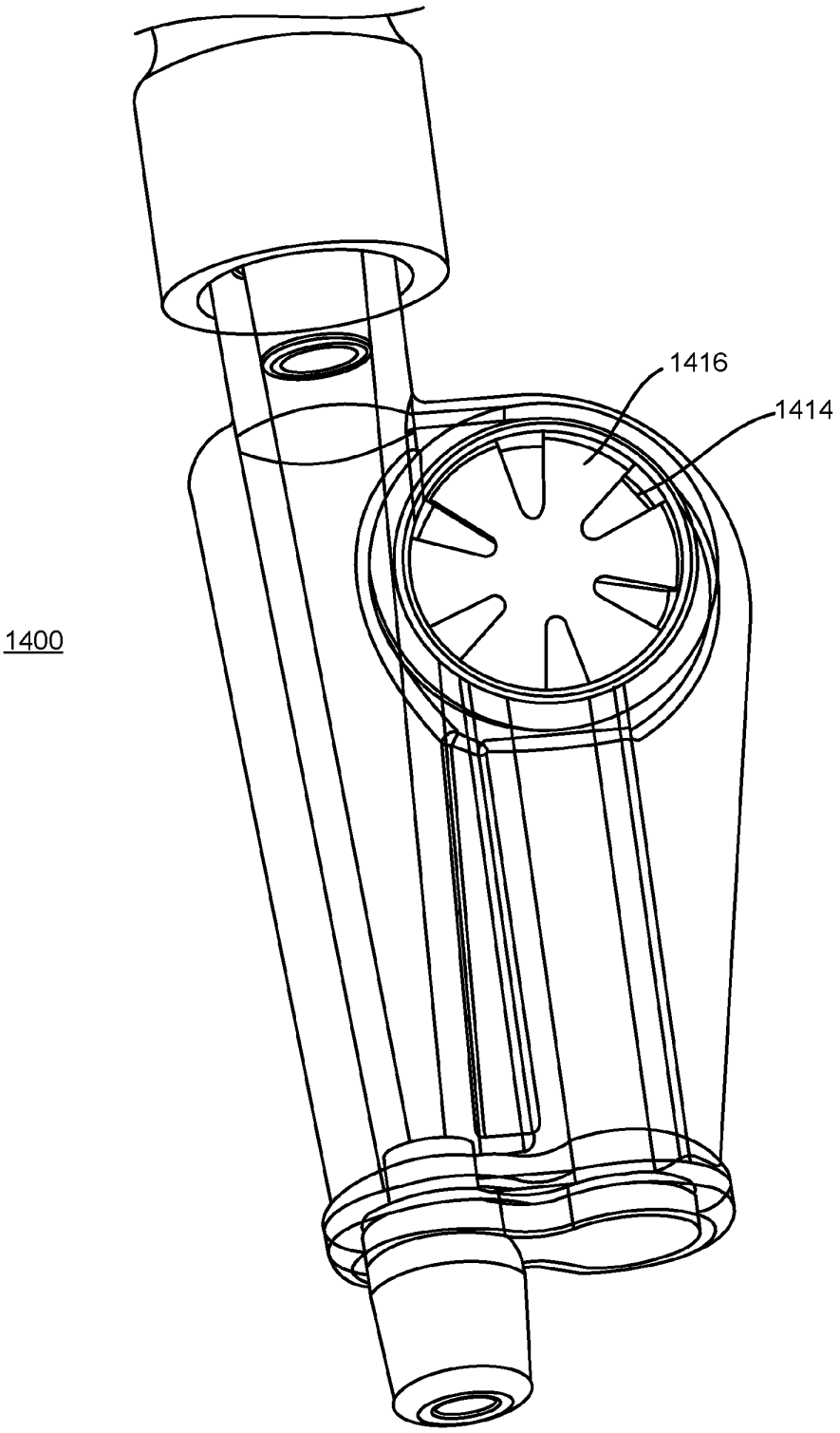


FIG. 14B

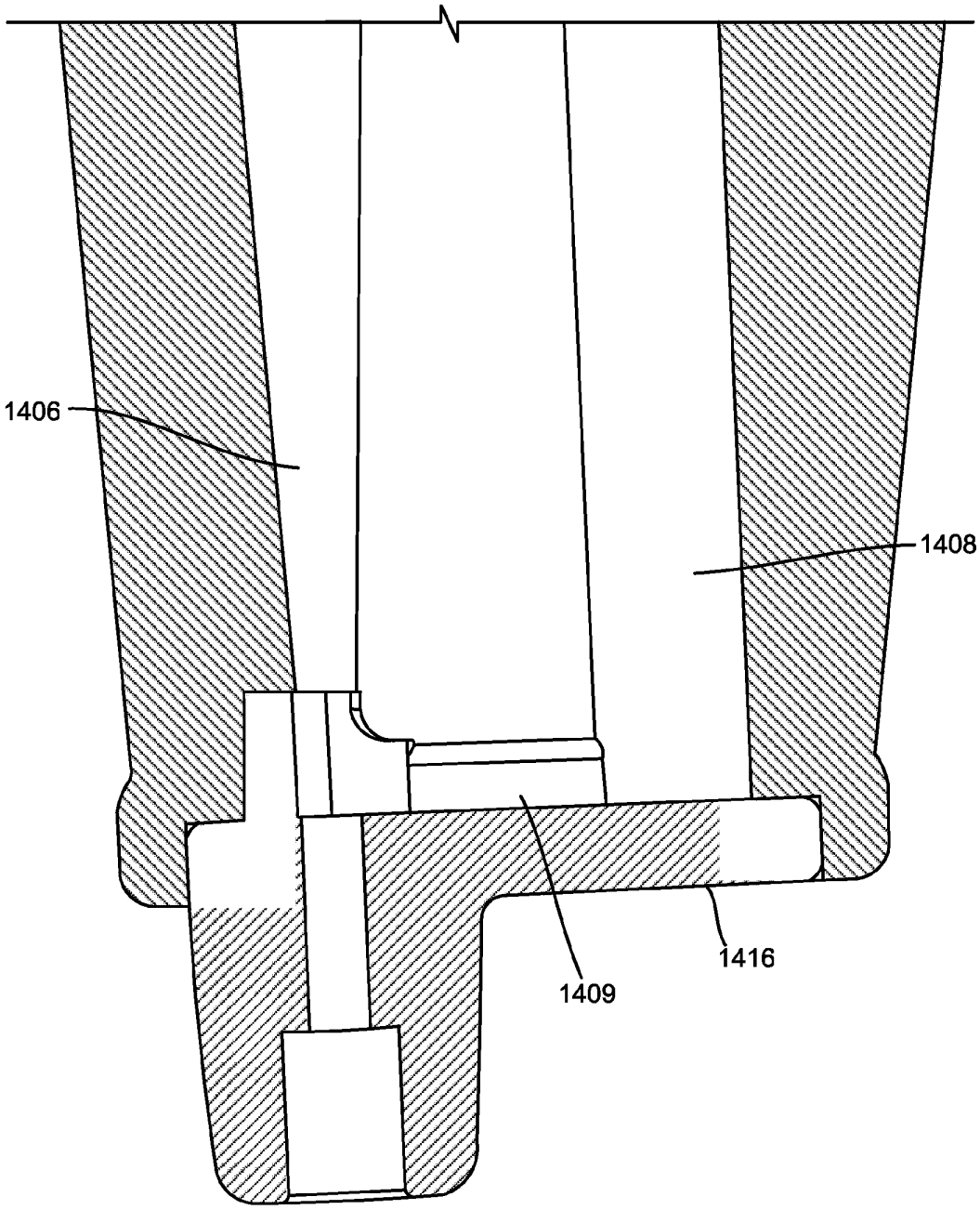


FIG. 14C

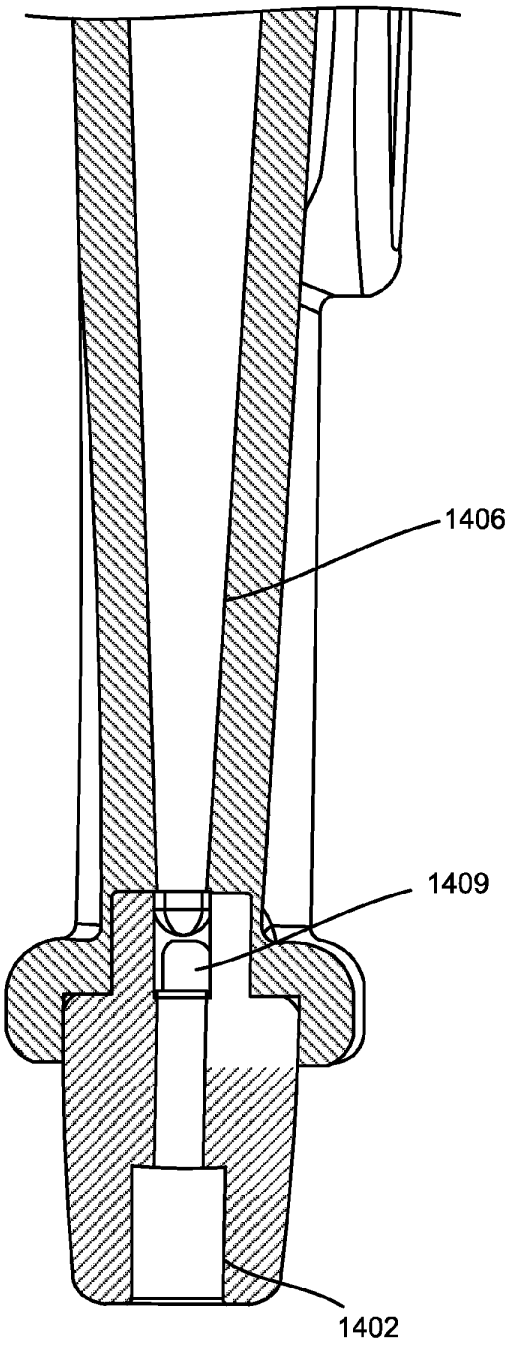


FIG. 14D

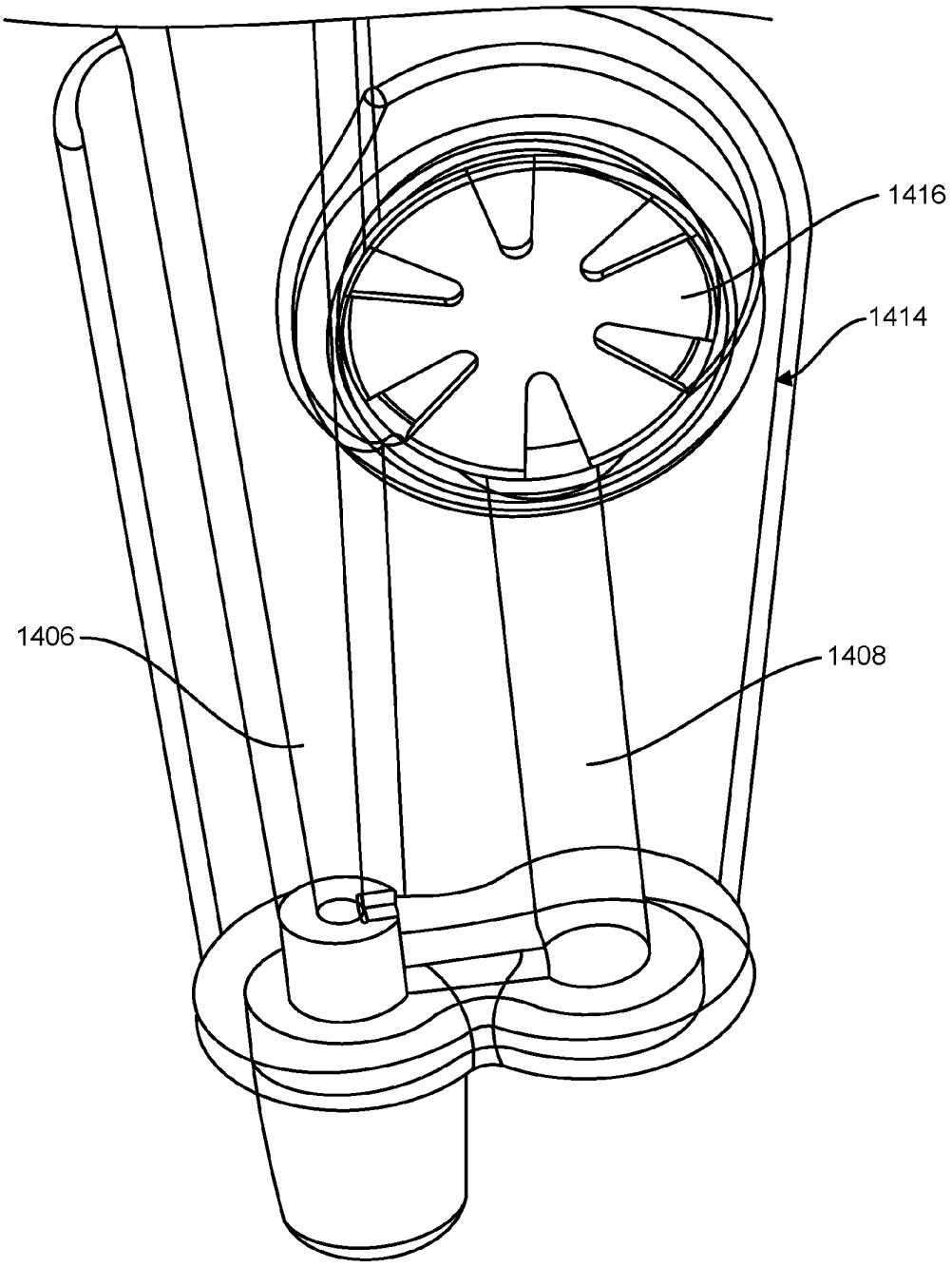


FIG. 14E

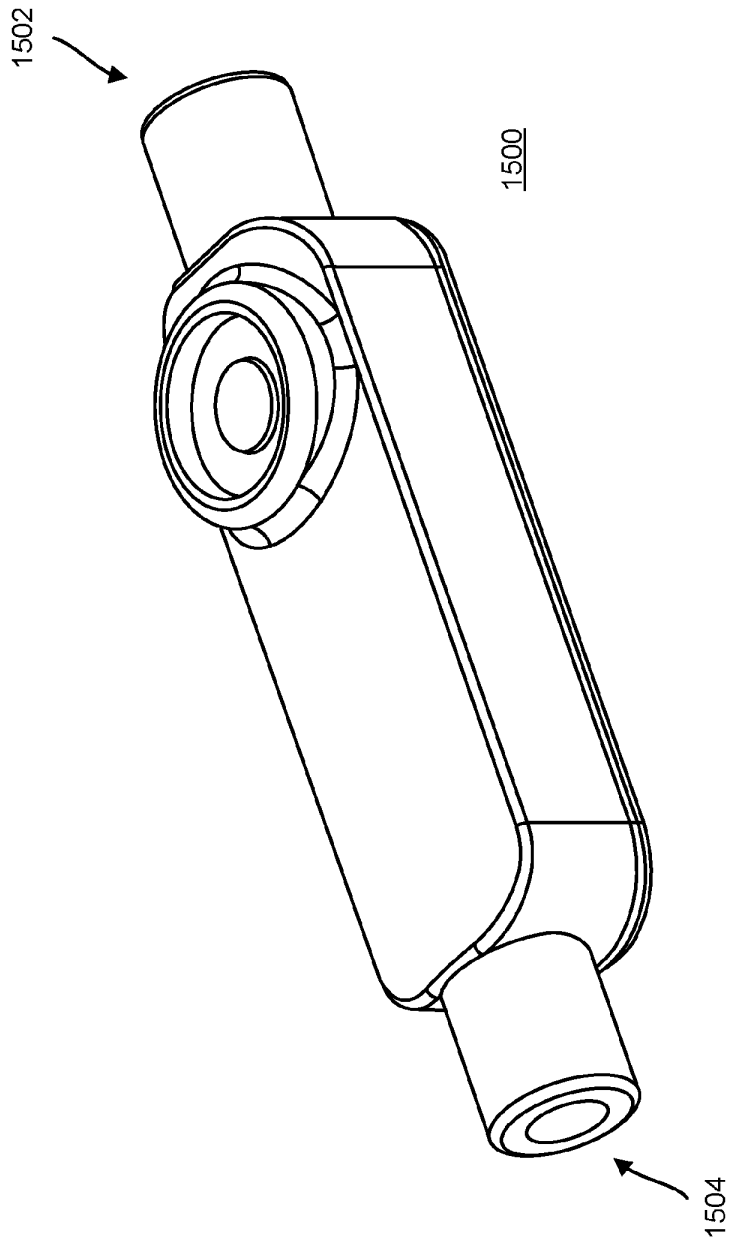


FIG. 15A

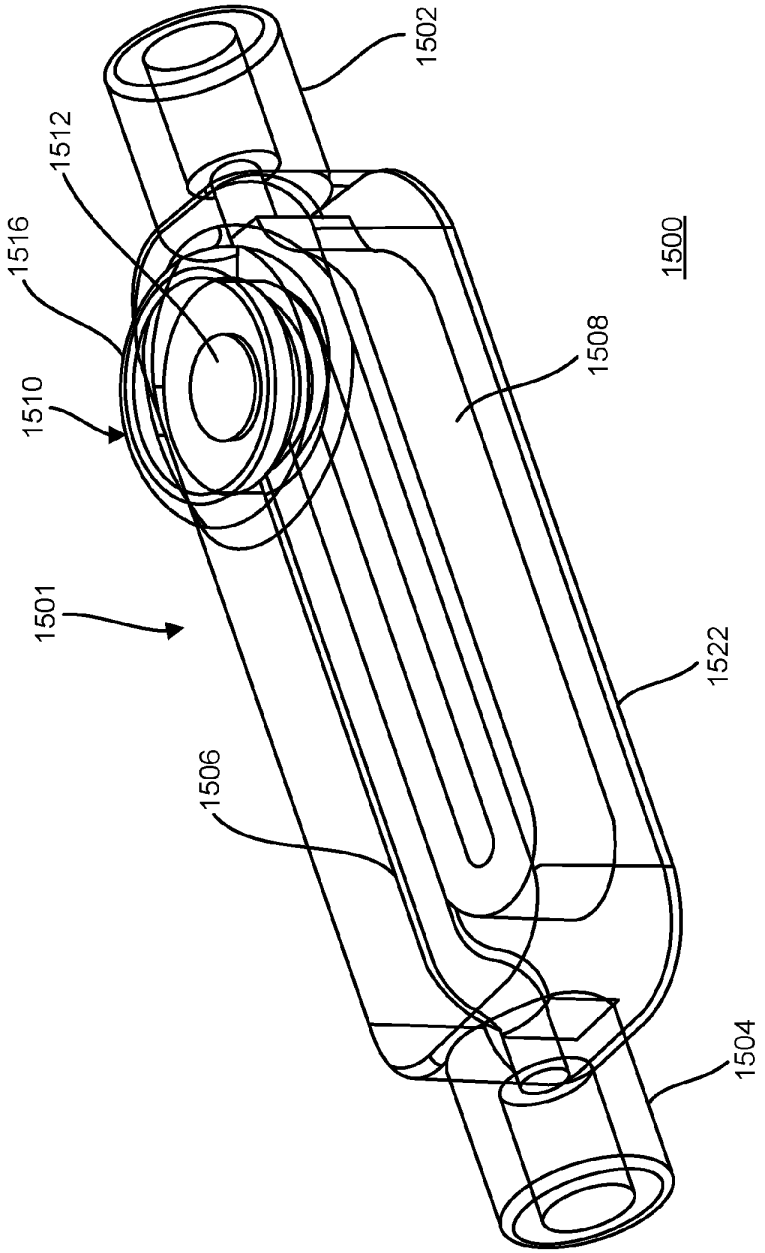


FIG. 15B

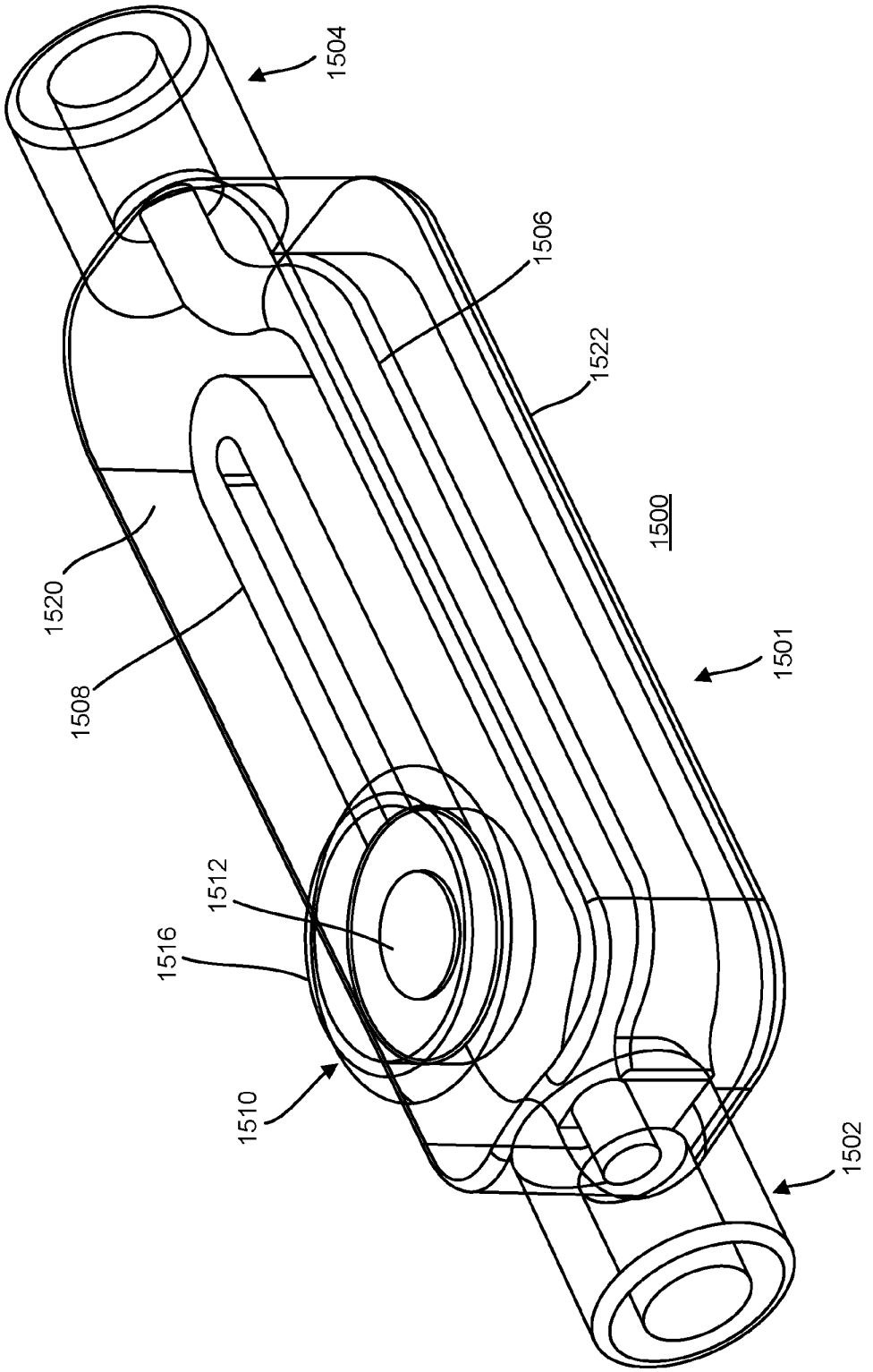


FIG. 15C

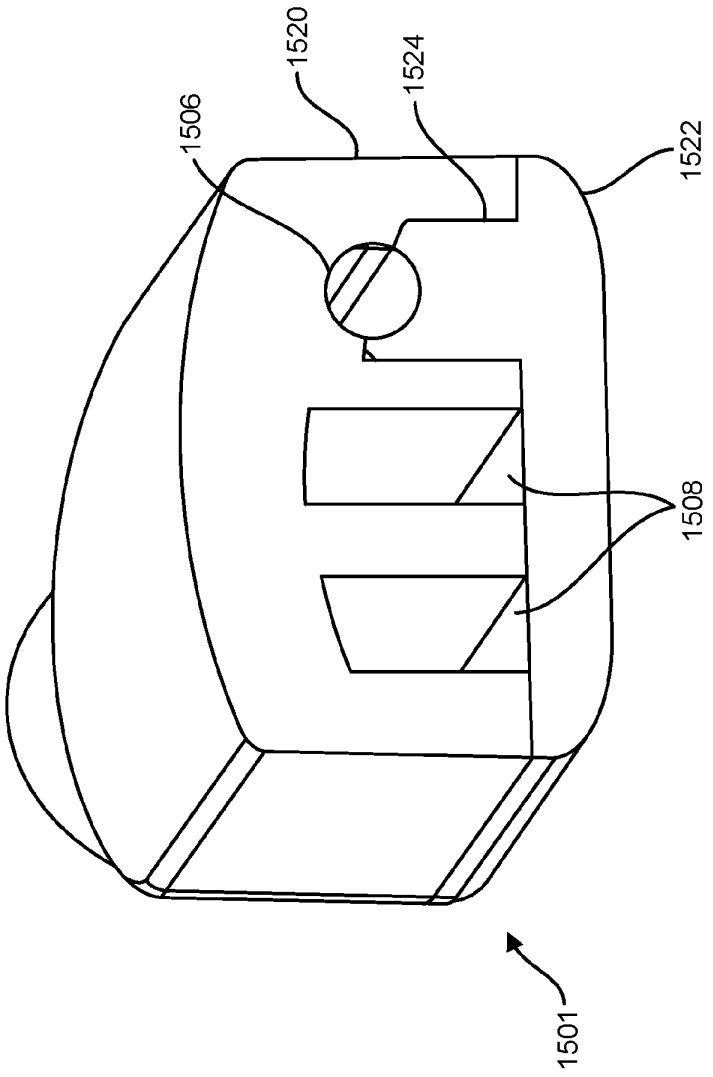


FIG. 15D

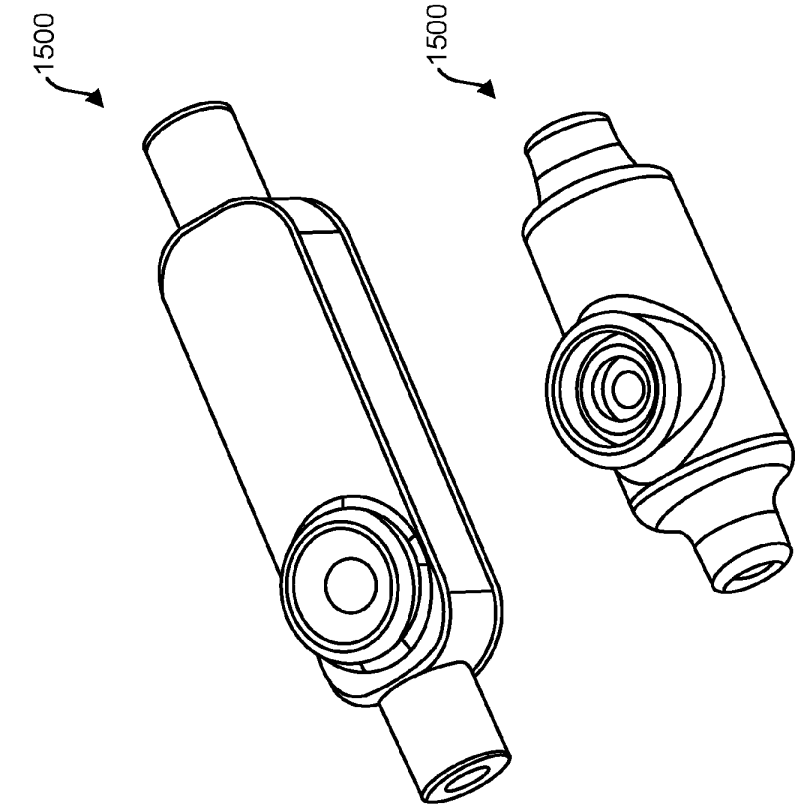


FIG. 15F

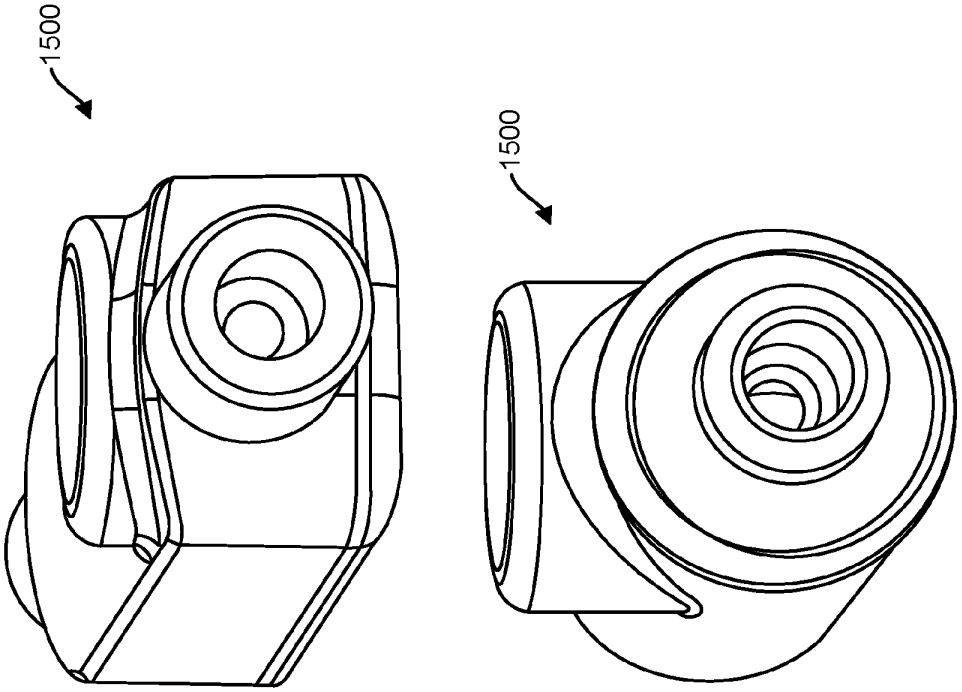


FIG. 15E

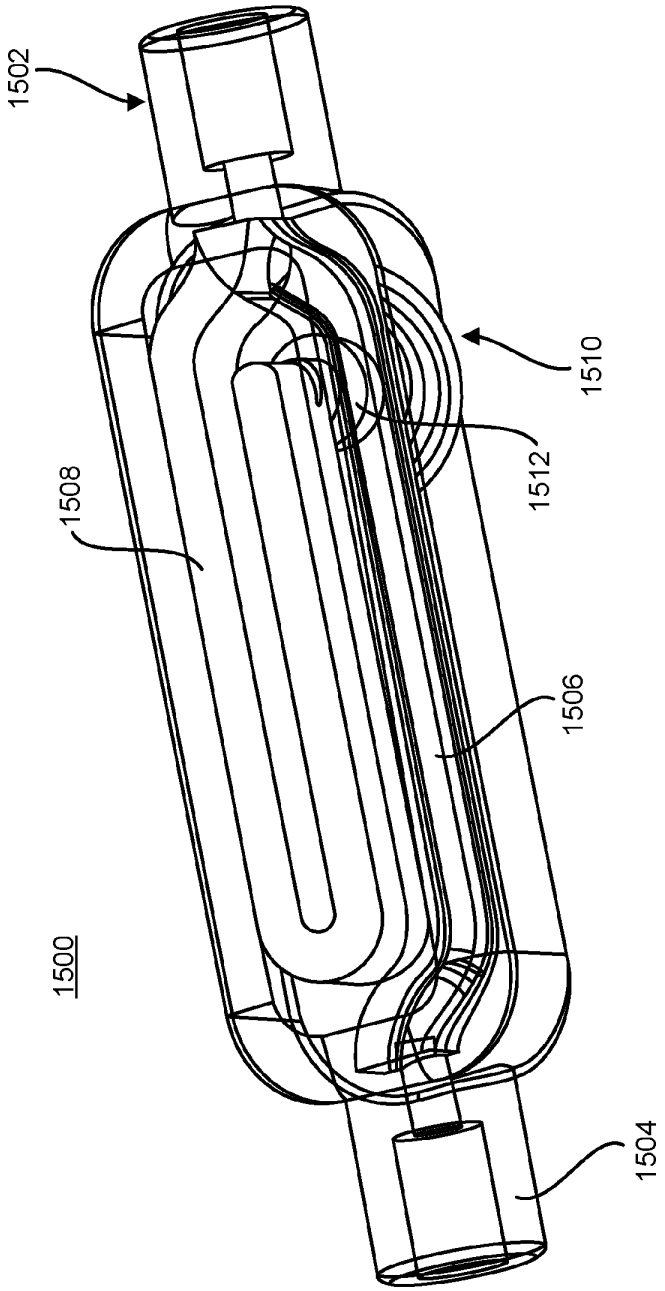


FIG. 15G

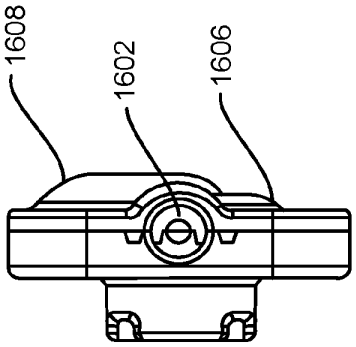


FIG. 16C

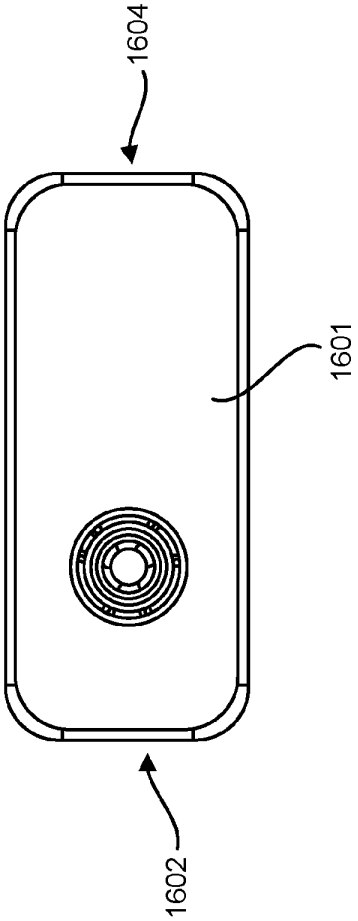


FIG. 16A

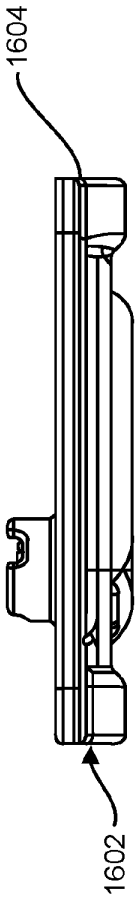


FIG. 16B

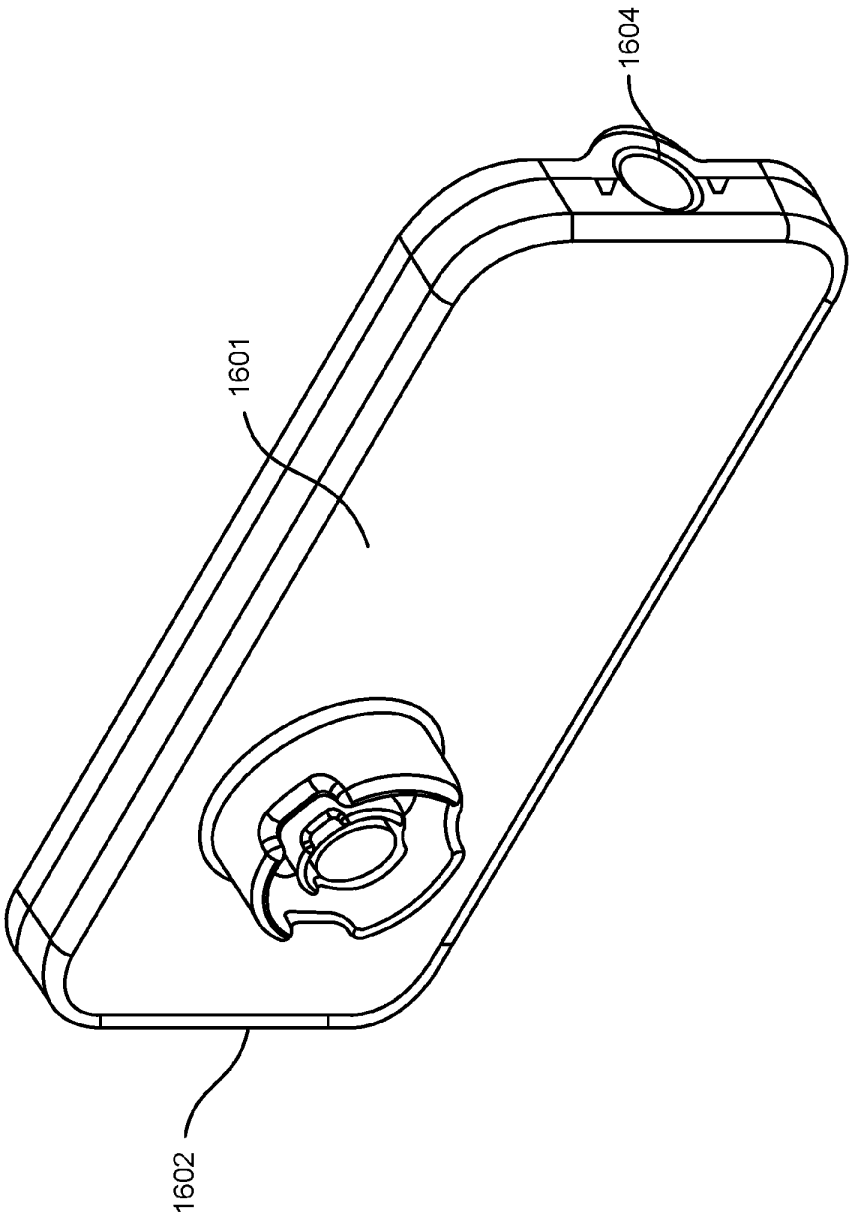


FIG. 16D

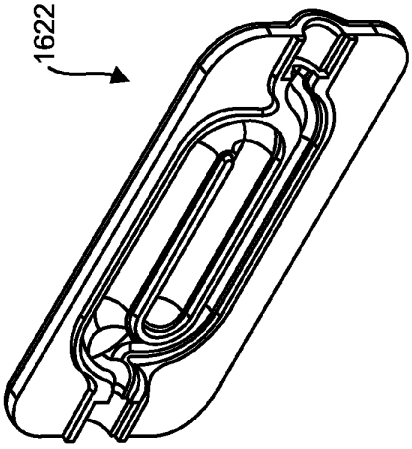


FIG. 17B



FIG. 17E

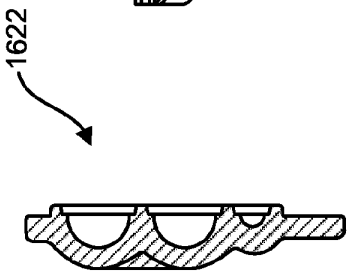


FIG. 17D

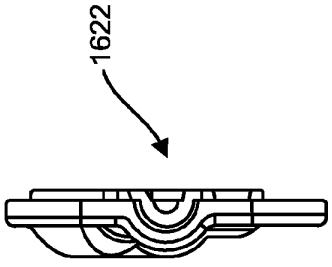


FIG. 17C

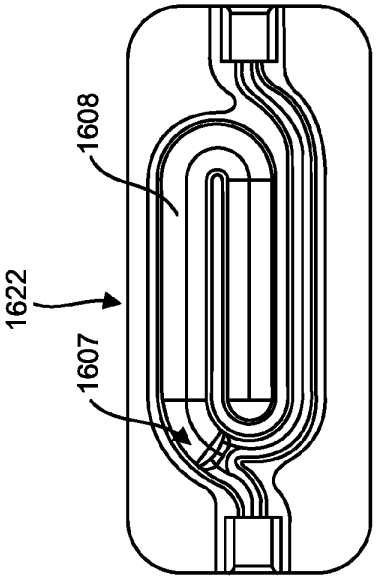


FIG. 17A

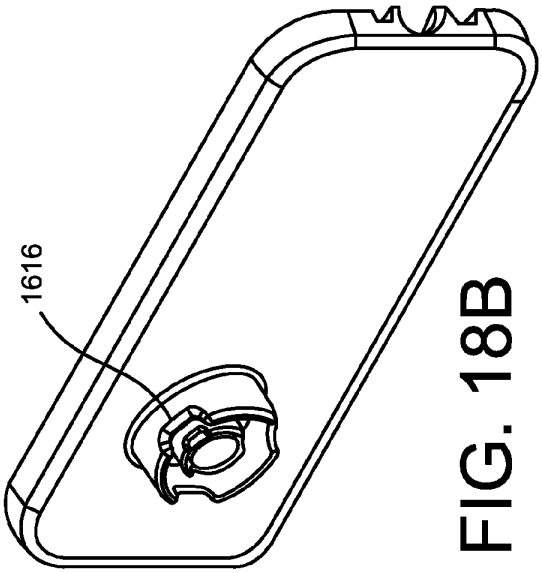


FIG. 18B

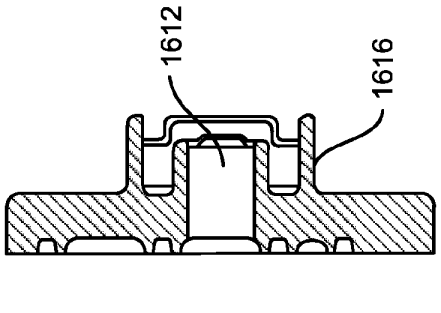


FIG. 18F

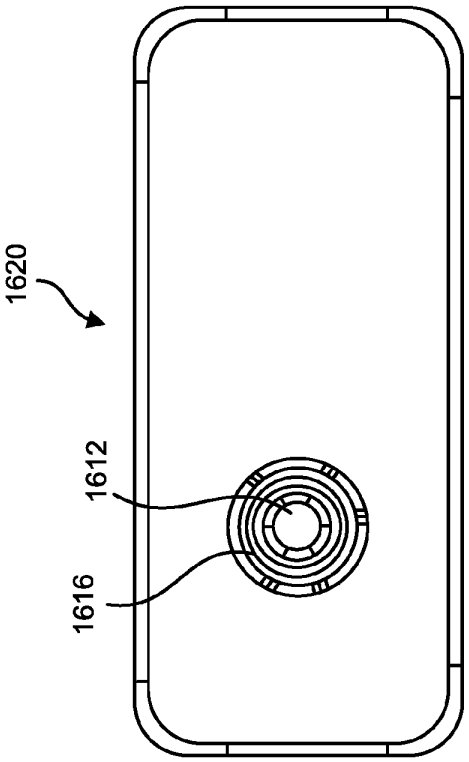


FIG. 18A

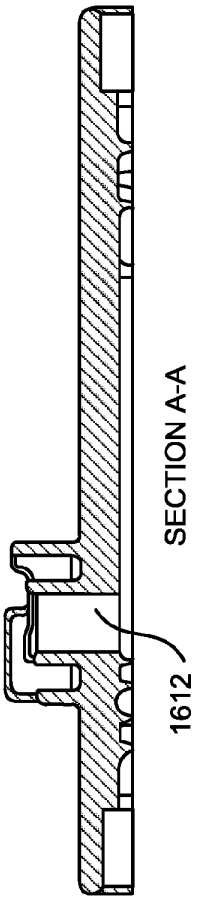


FIG. 18D

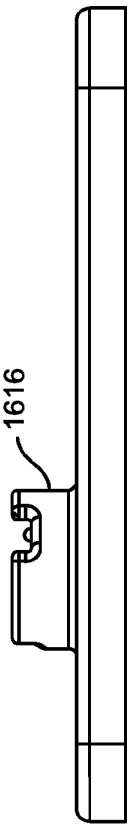


FIG. 18E

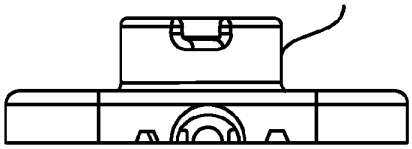


FIG. 18C

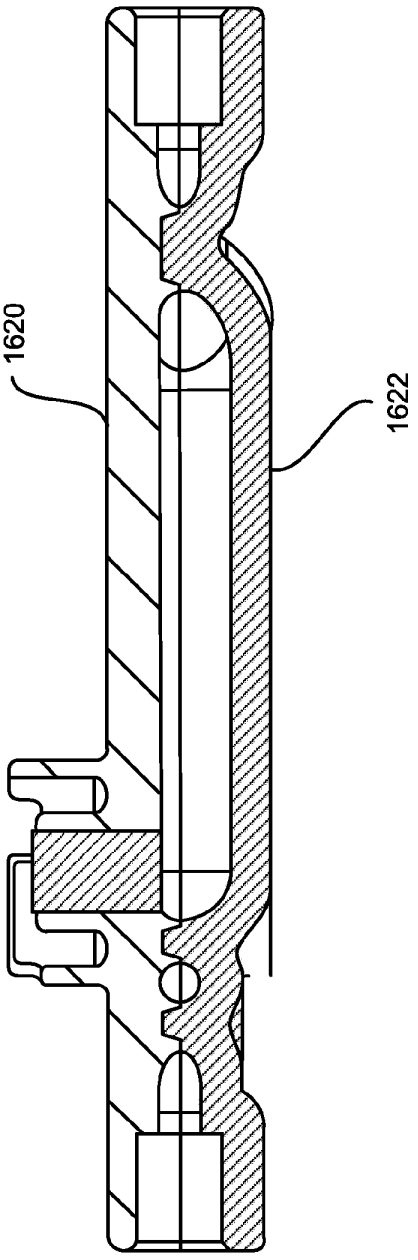


FIG. 19A

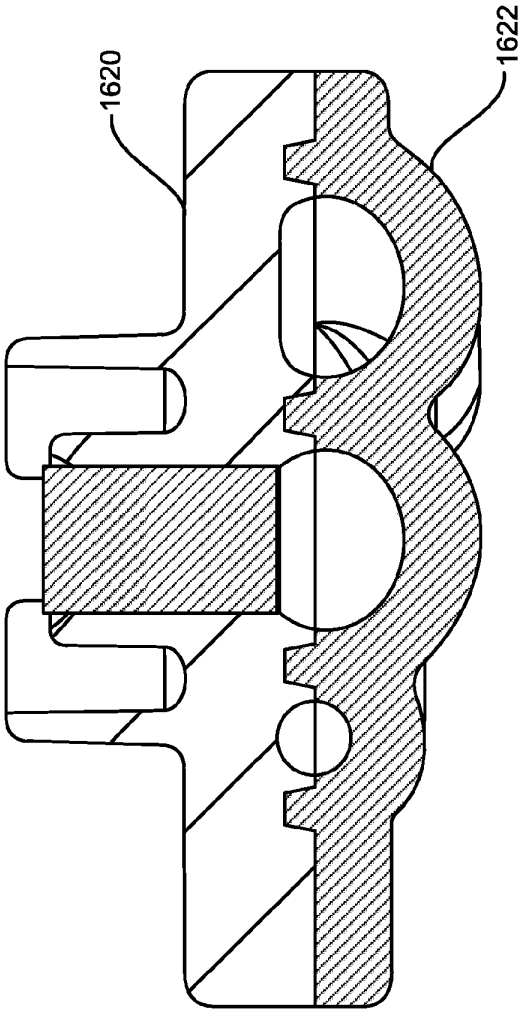


FIG. 19B

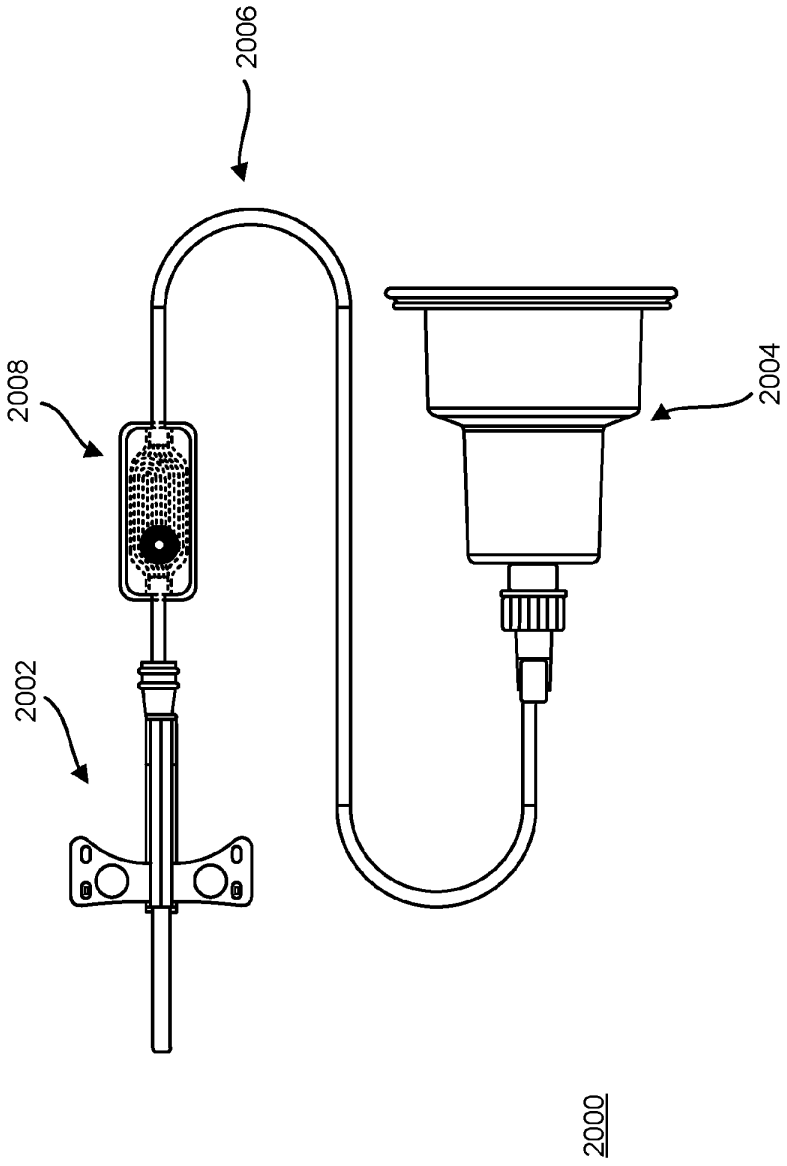


FIG. 20

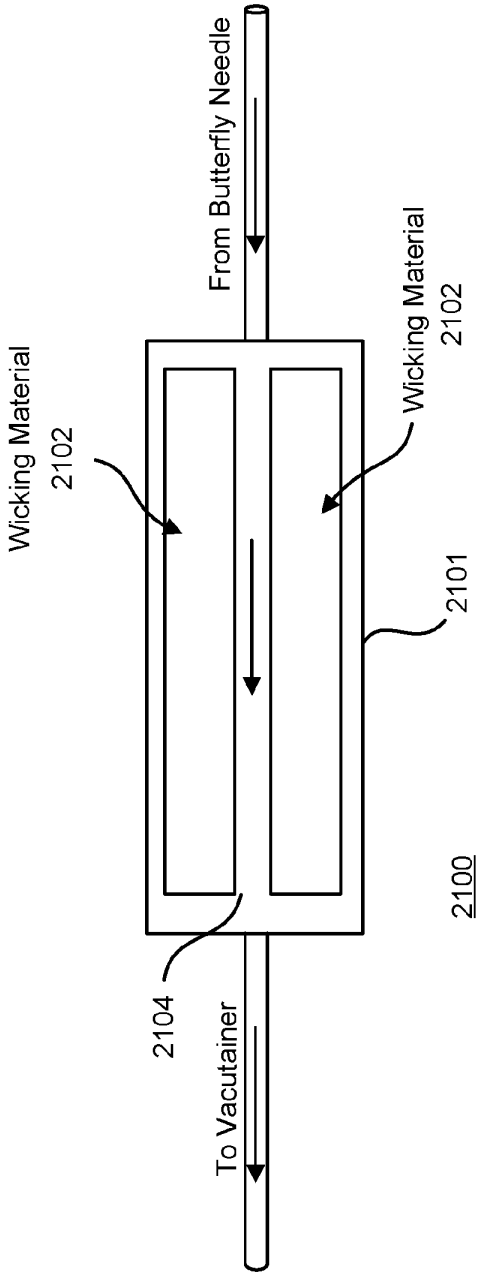

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

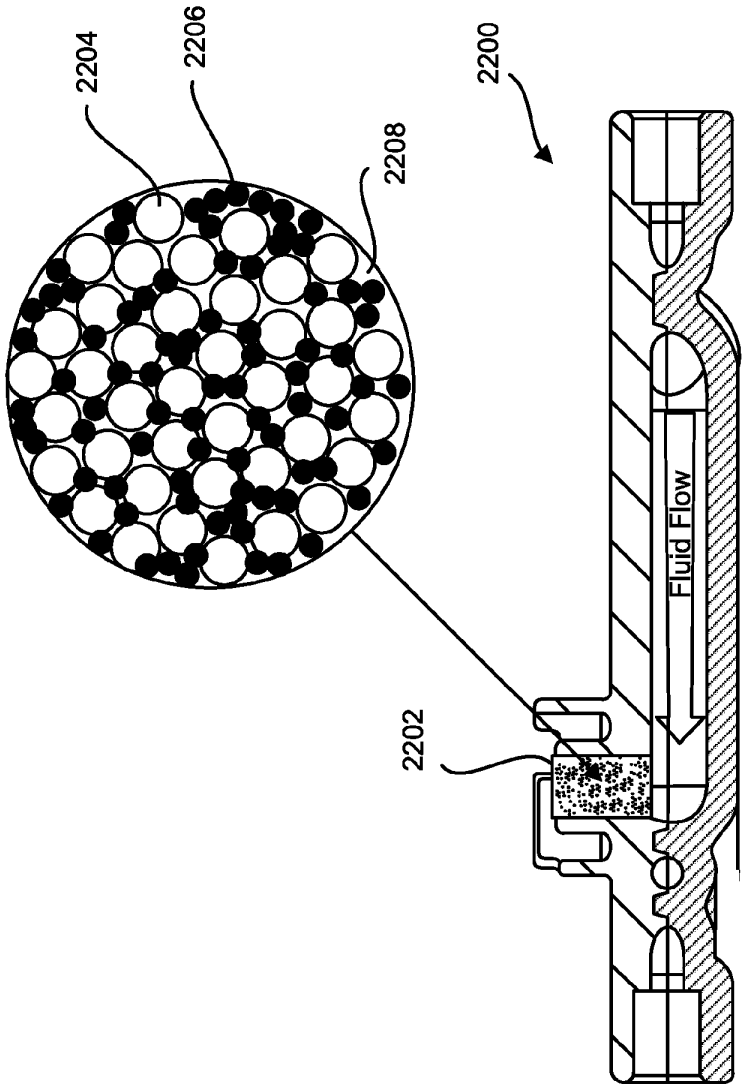


FIG. 22A

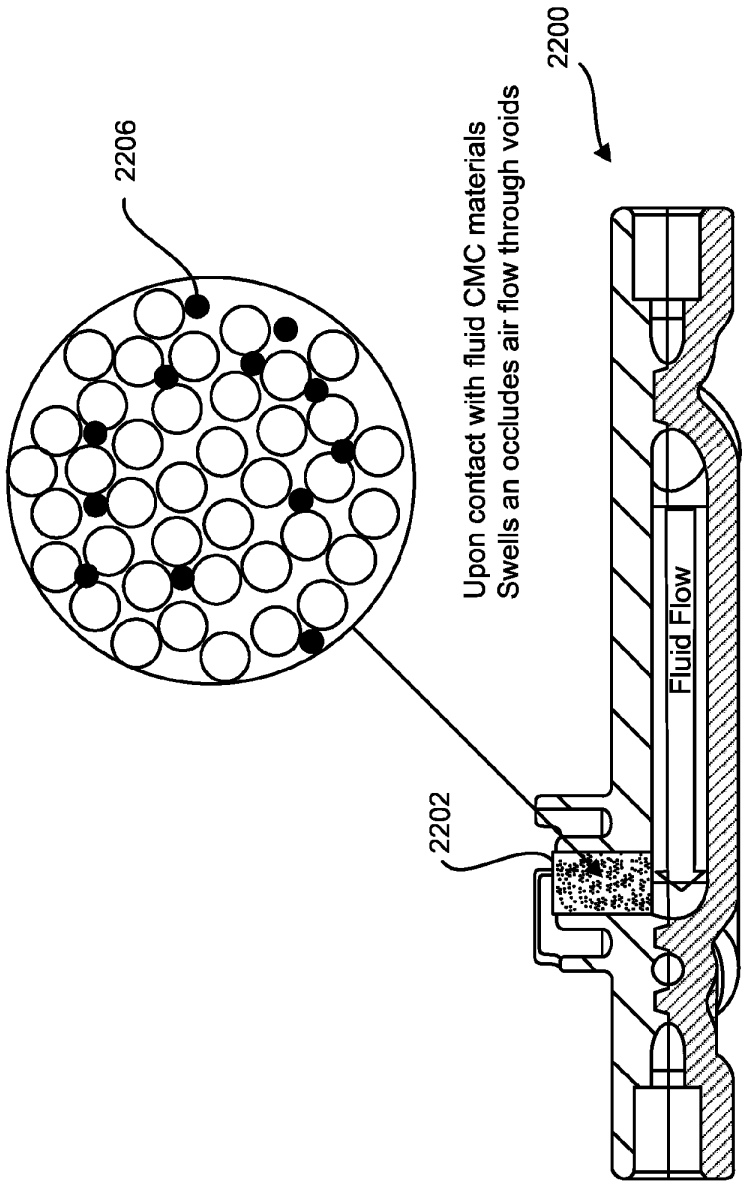

2200
2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
Fluid Flow
2202

FIG. 22B

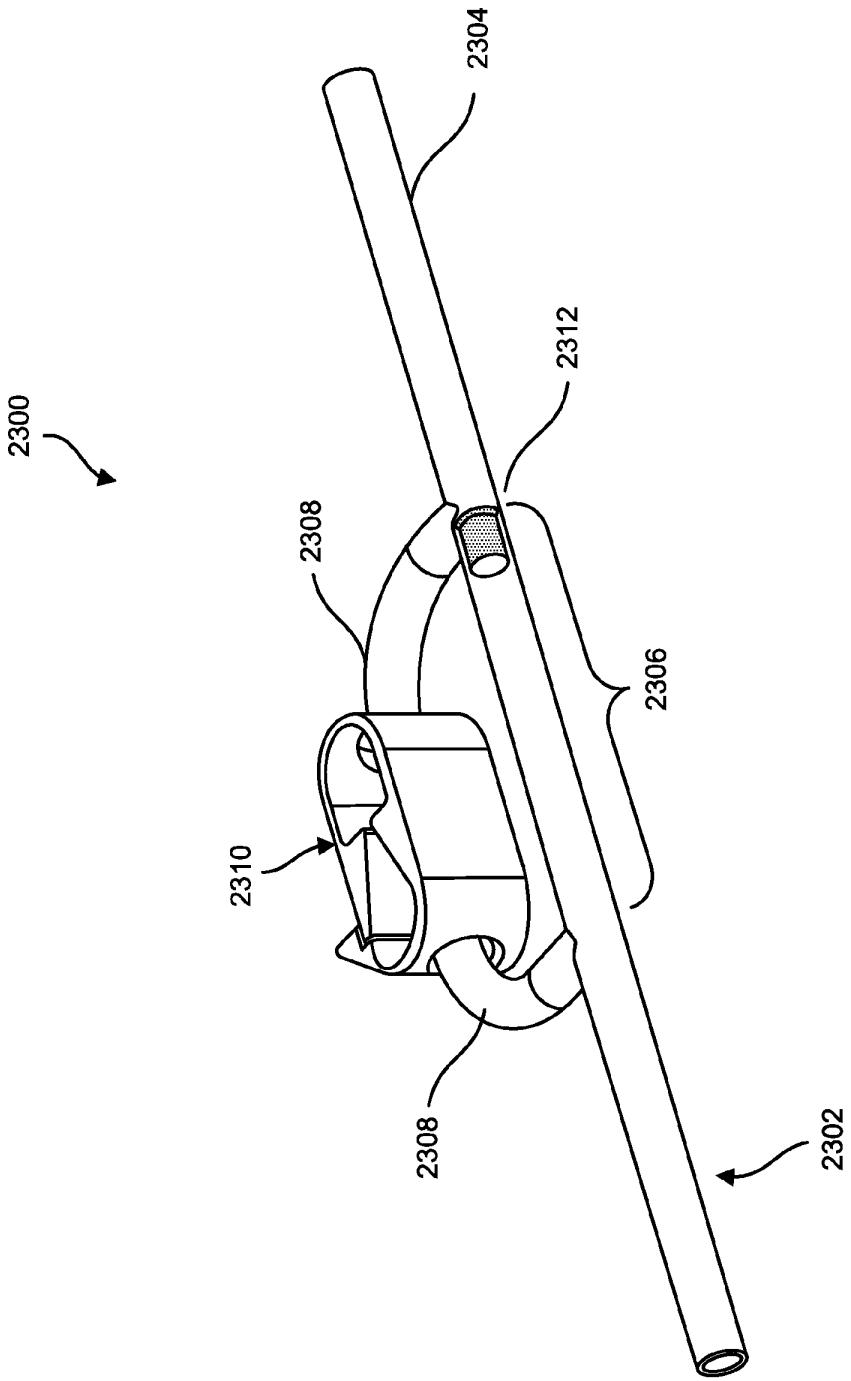


FIG. 23A

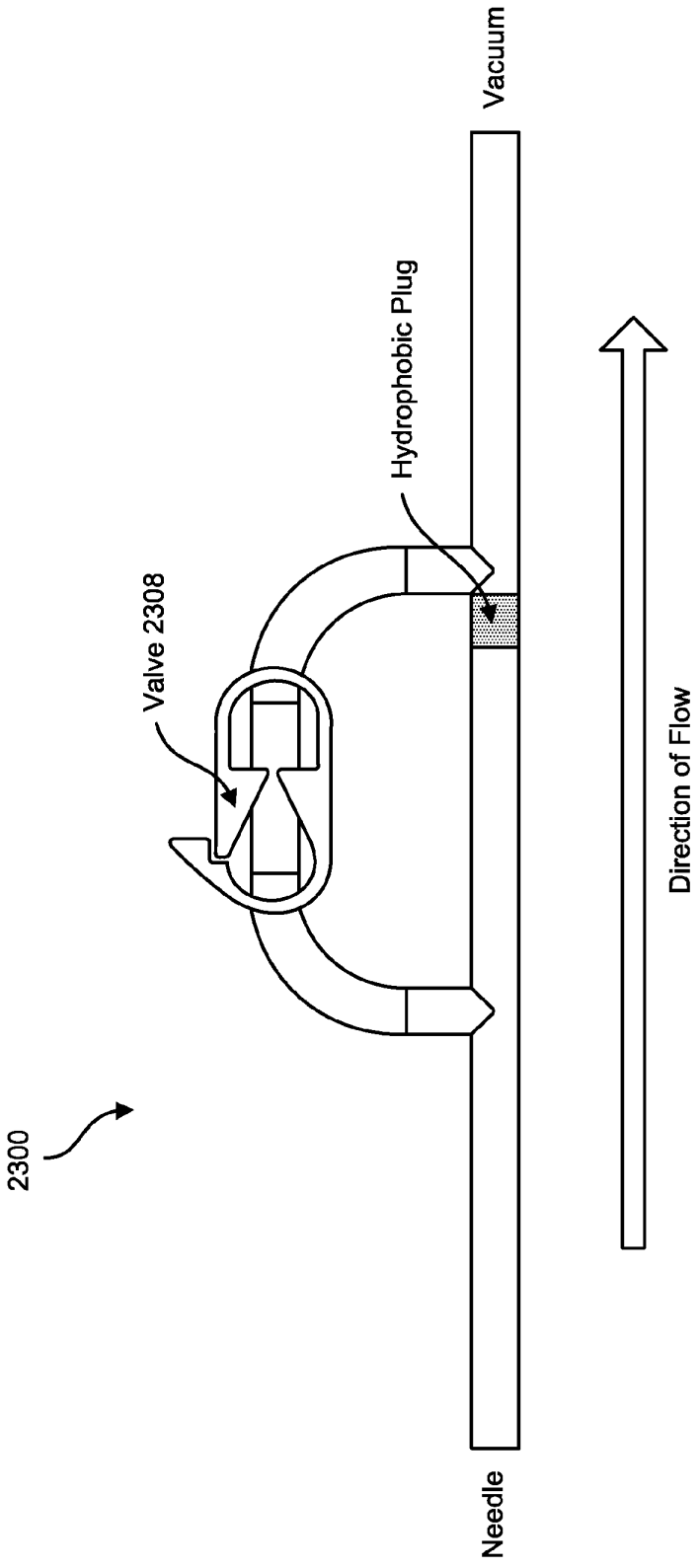

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

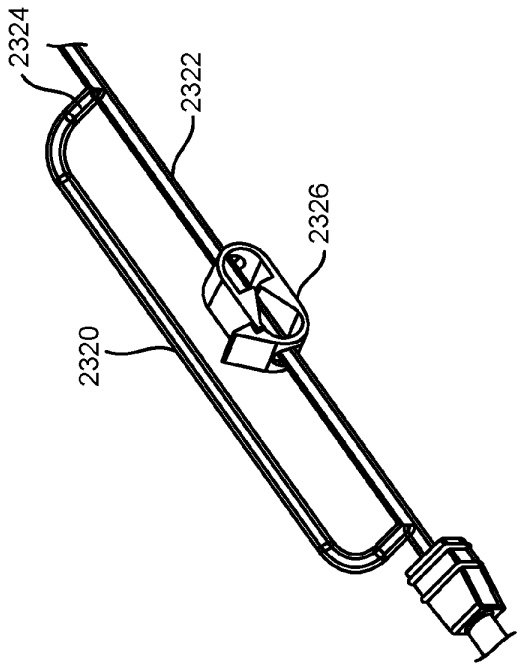


FIG. 23D

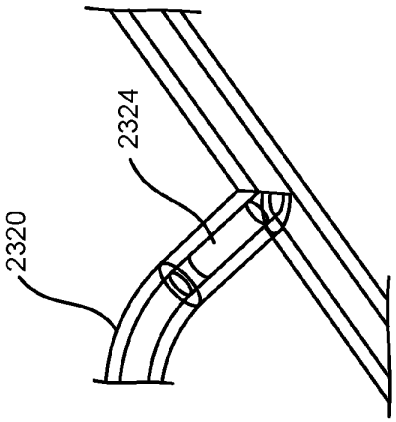


FIG. 23E

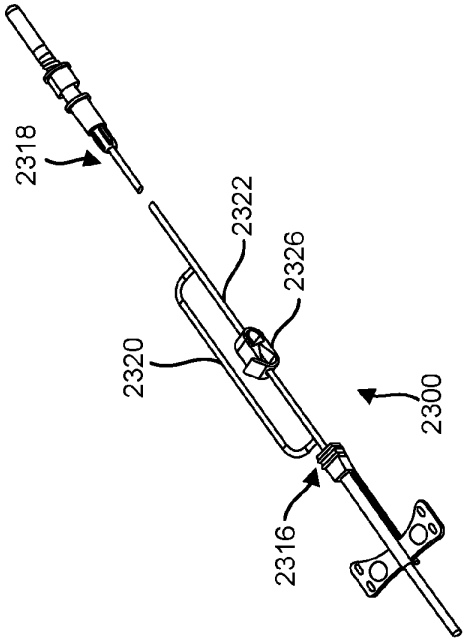


FIG. 23C

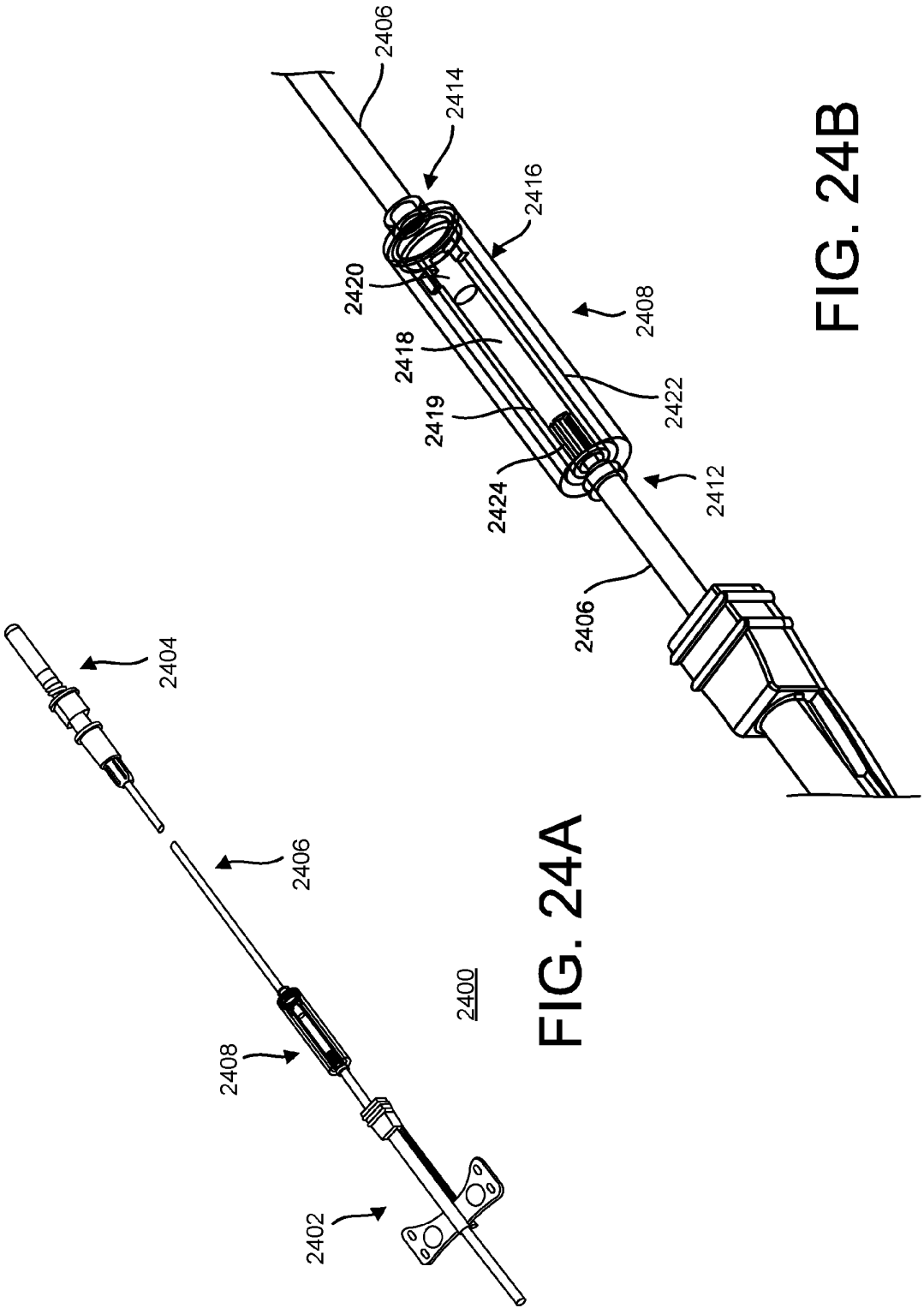


FIG. 24B

FIG. 24A

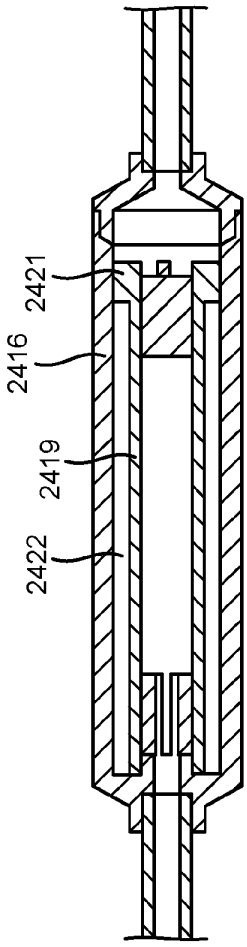


FIG. 24C

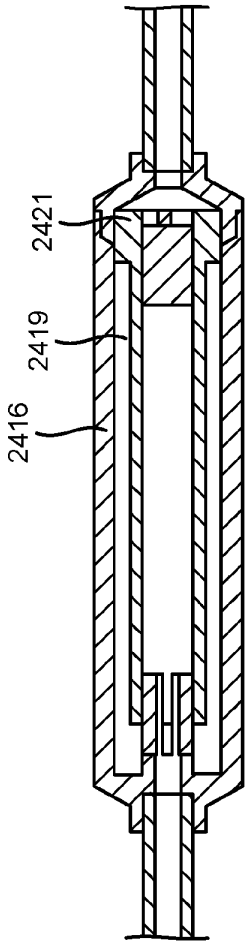


FIG. 24D

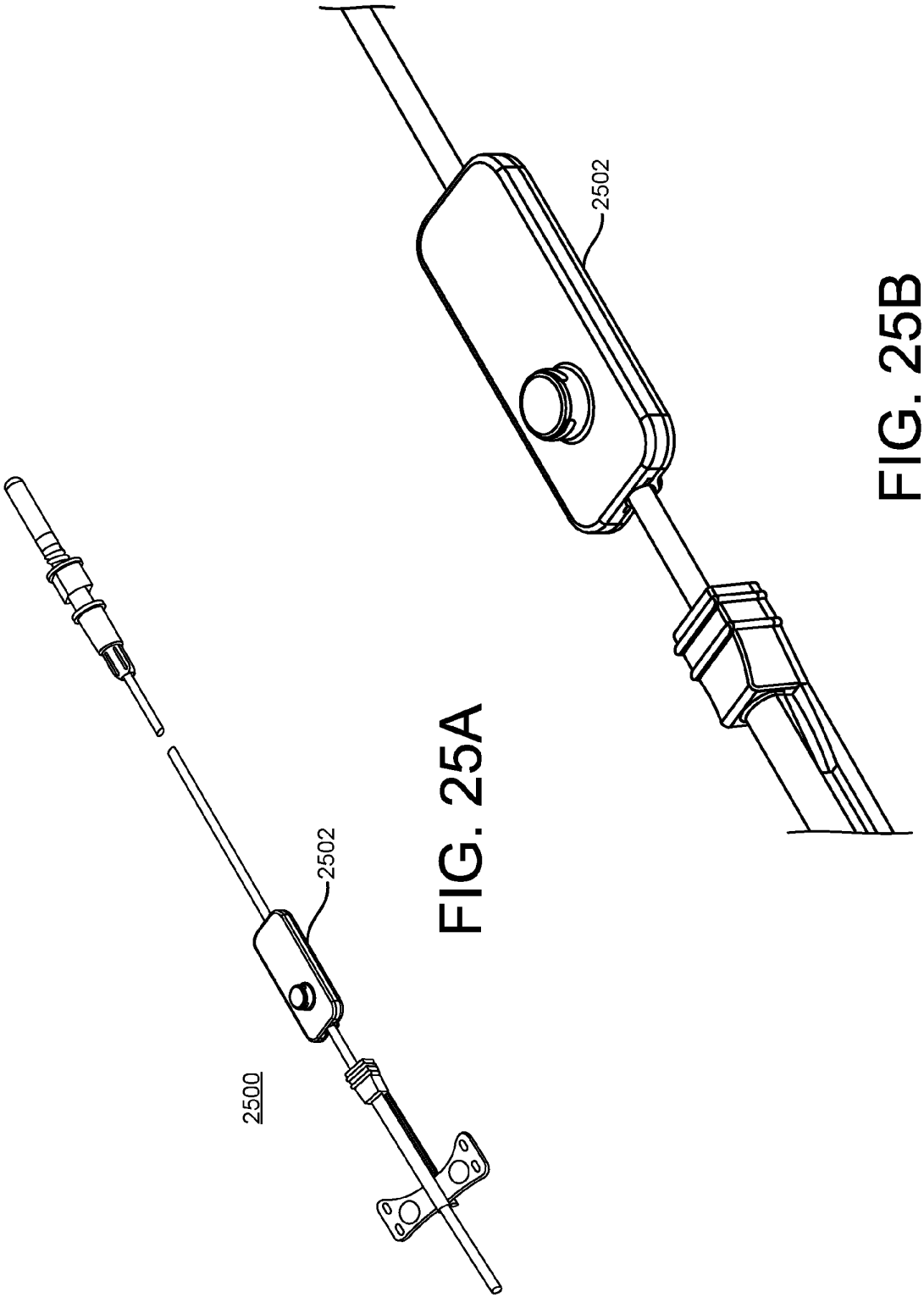


FIG. 25A

FIG. 25B

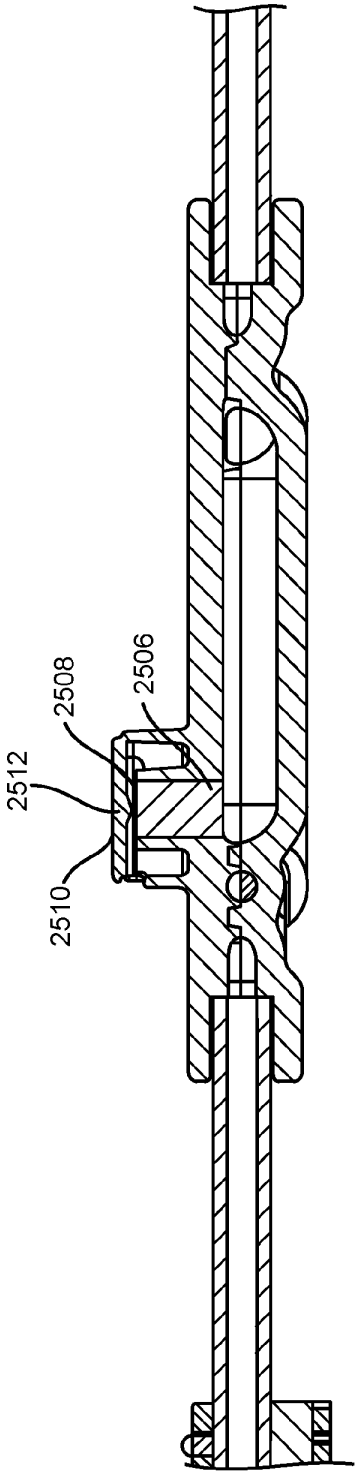


FIG. 25C

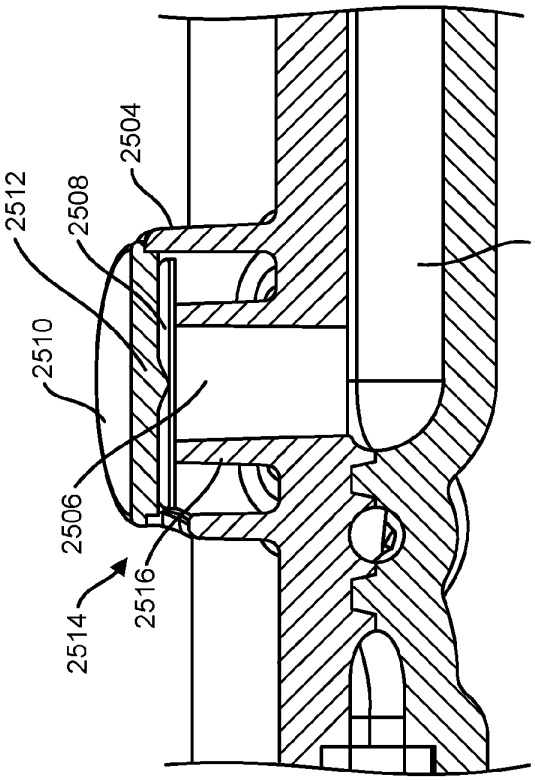


FIG. 25D

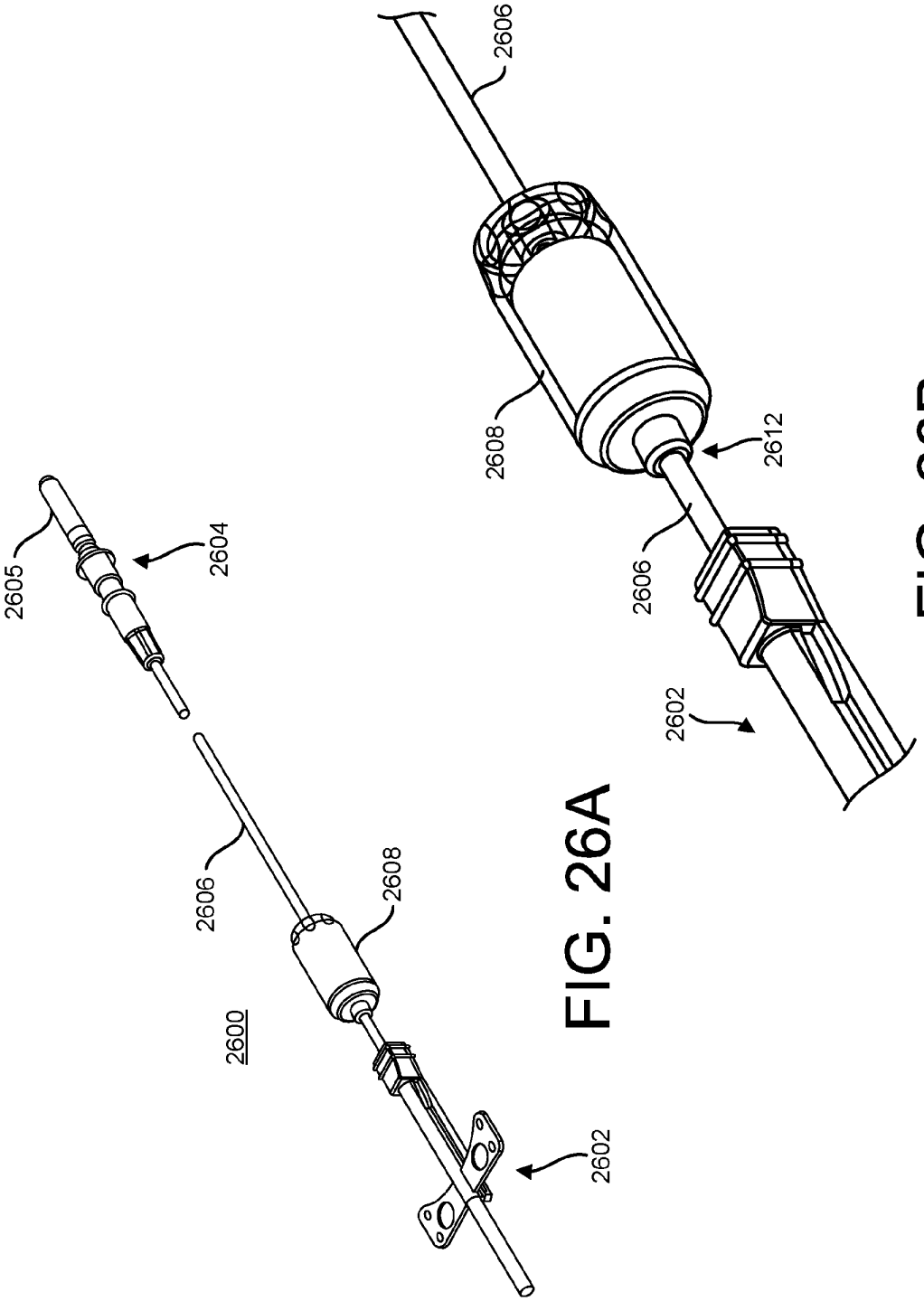


FIG. 26A

FIG. 26B

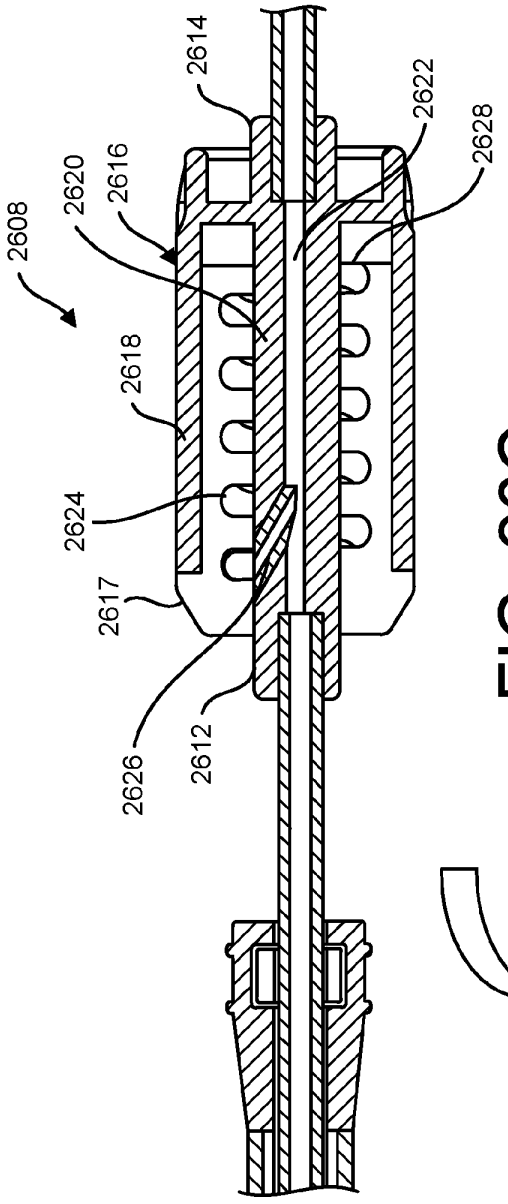


FIG. 26C

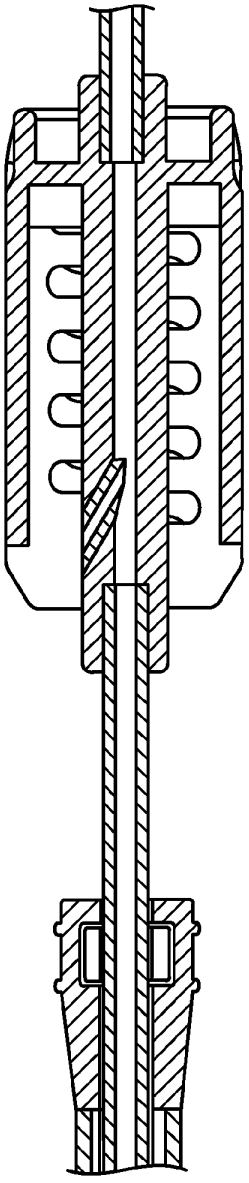


FIG. 26D

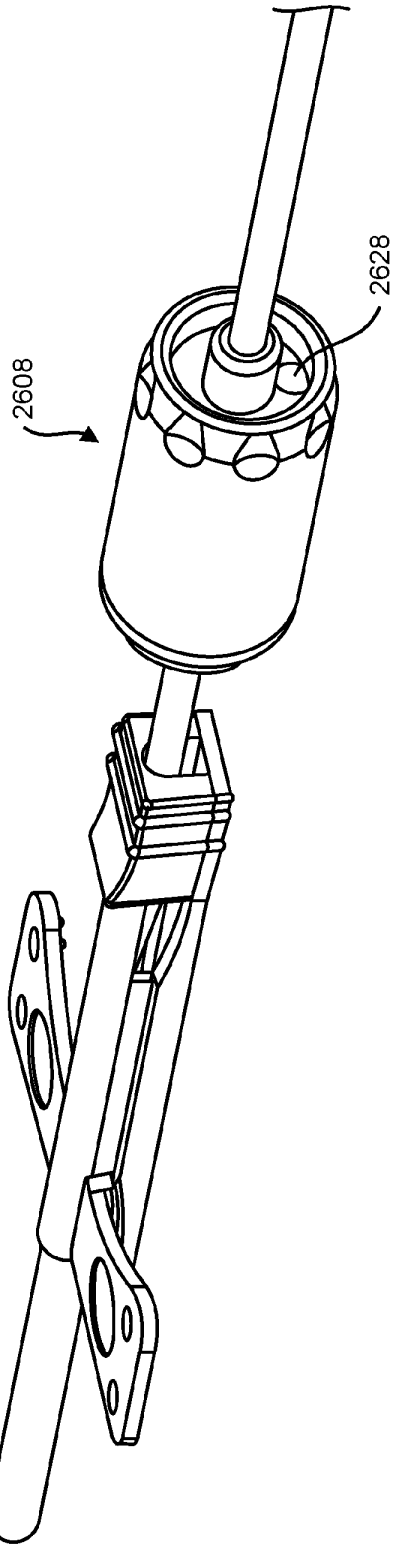


FIG. 26E

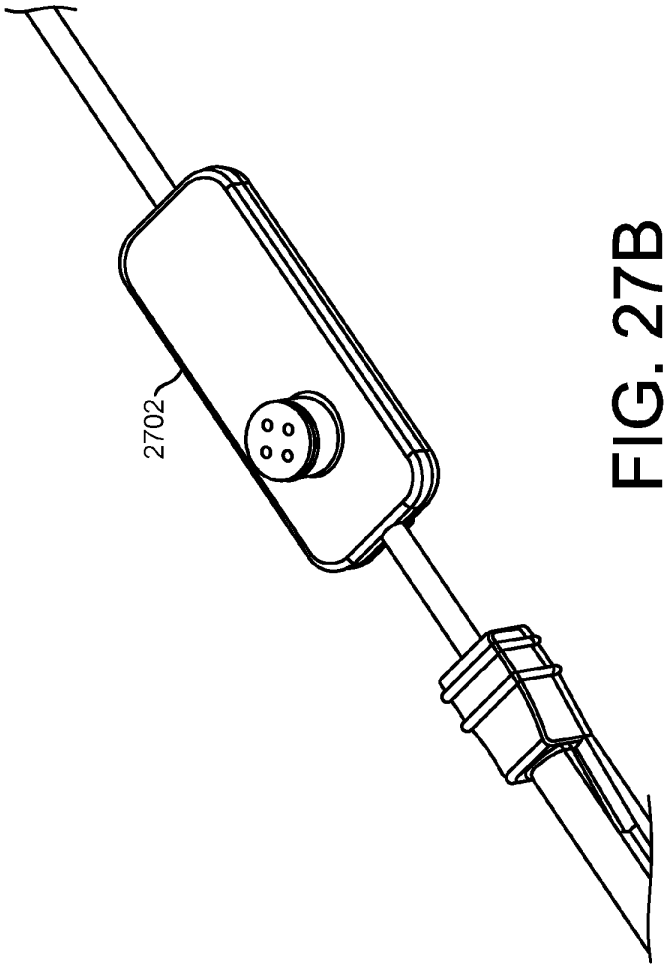


FIG. 27B

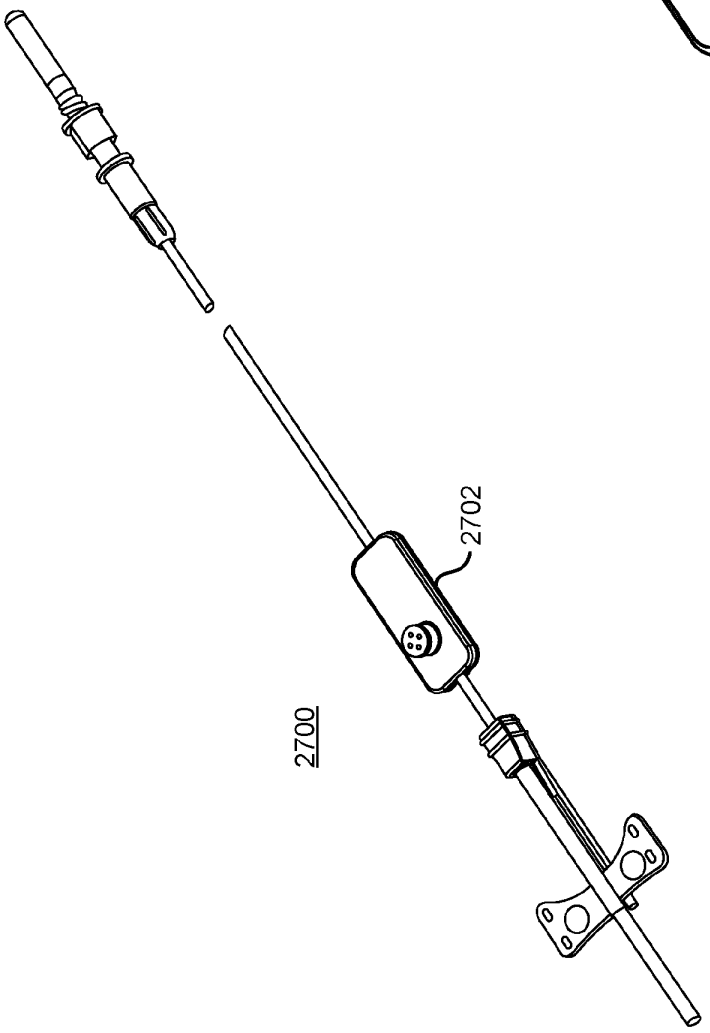


FIG. 27A

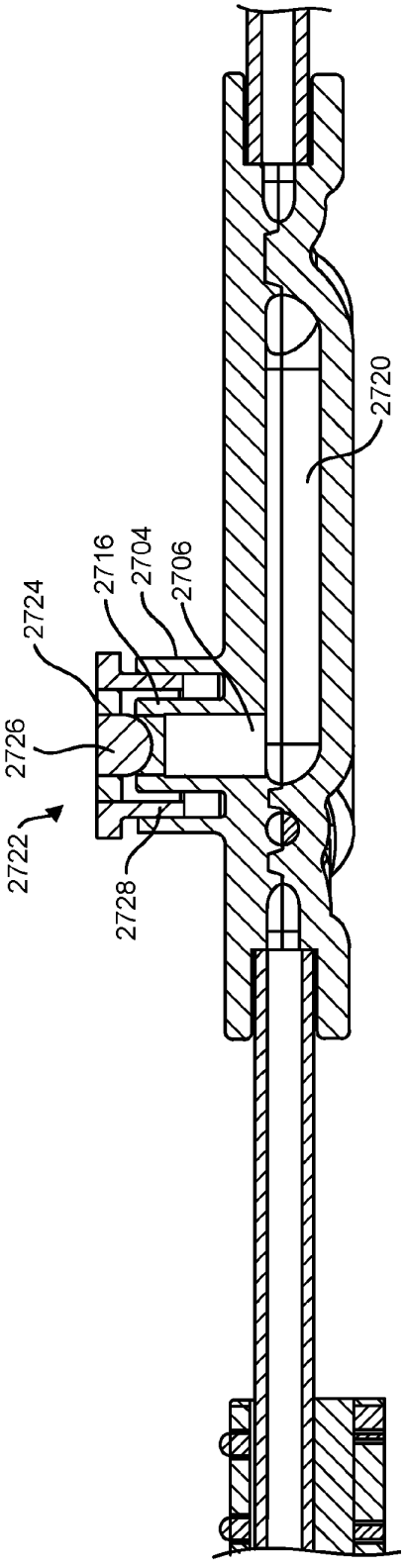


FIG. 27C

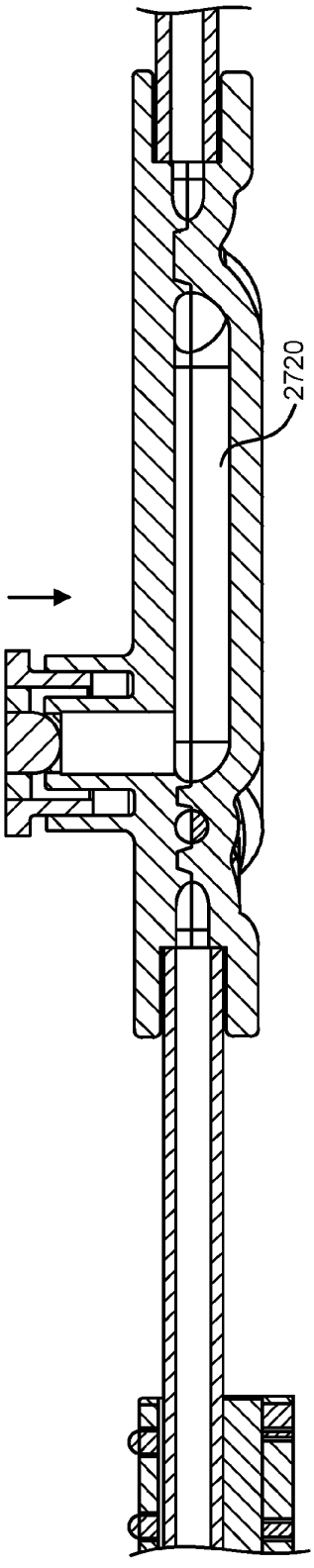


FIG. 27D

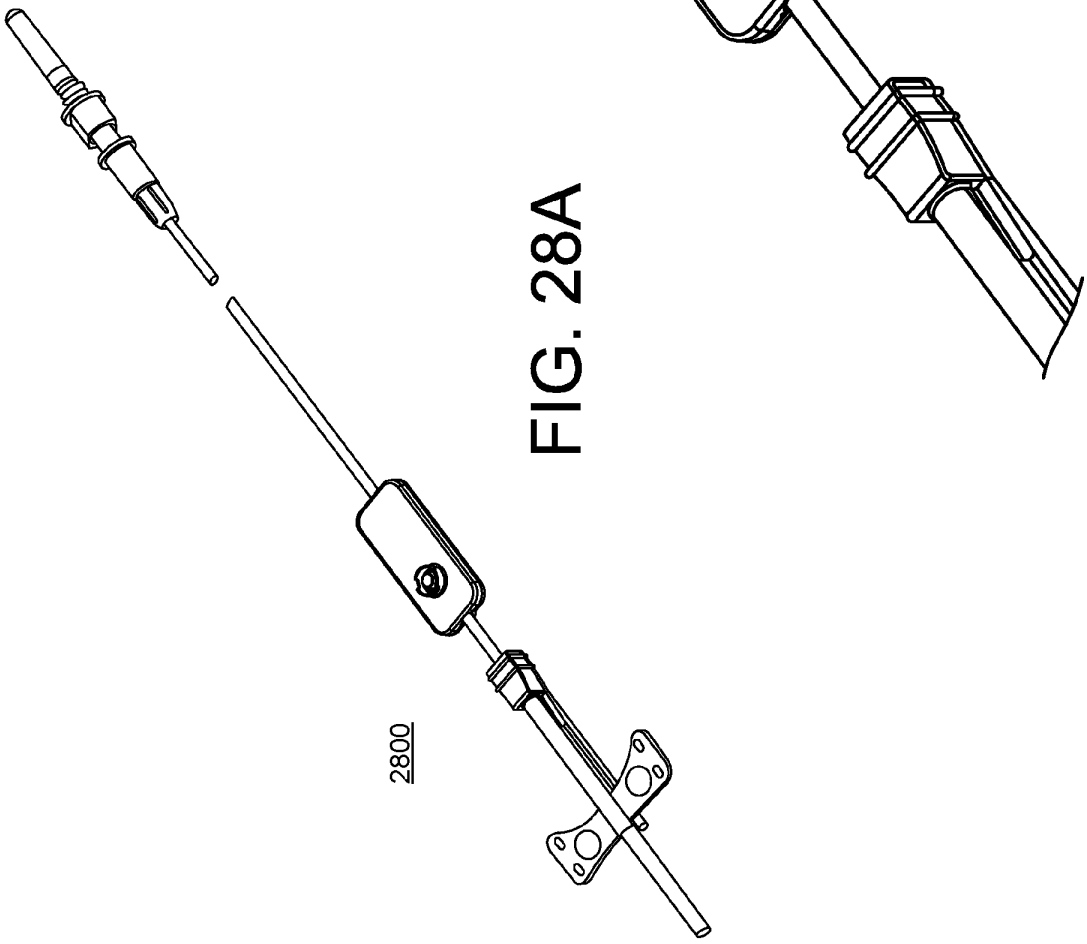


FIG. 28A

FIG. 28B

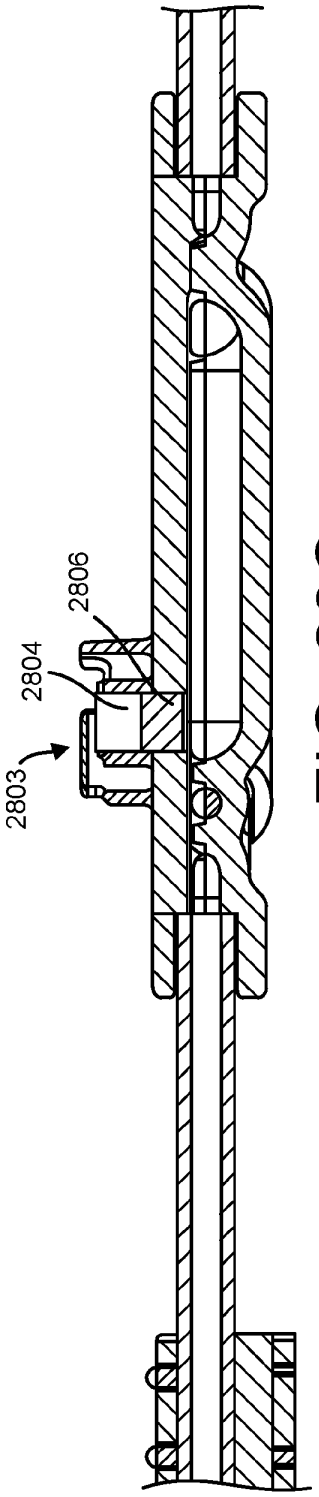


FIG. 28C

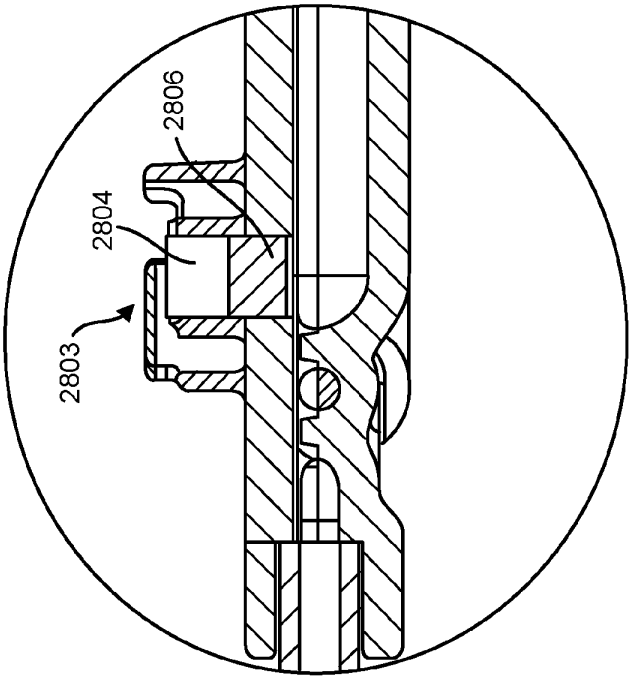


FIG. 28D

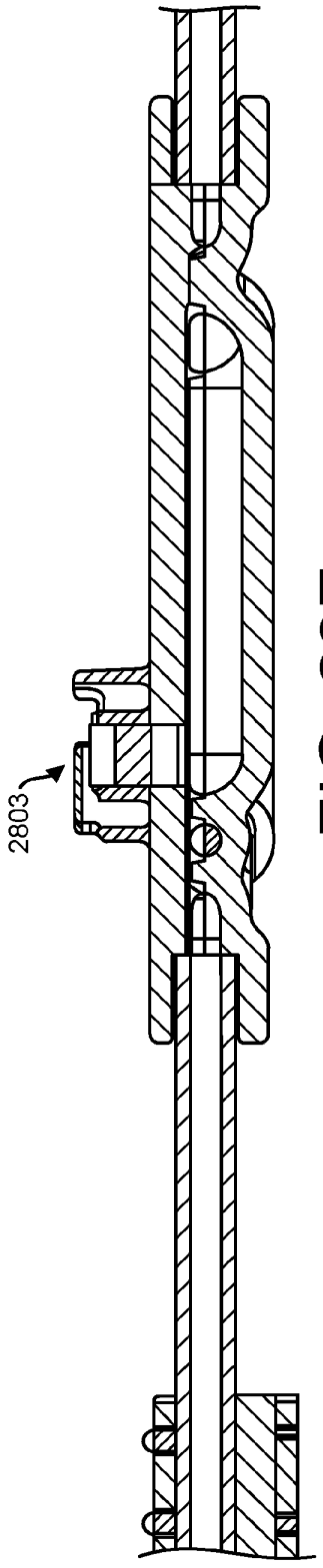


FIG. 28E

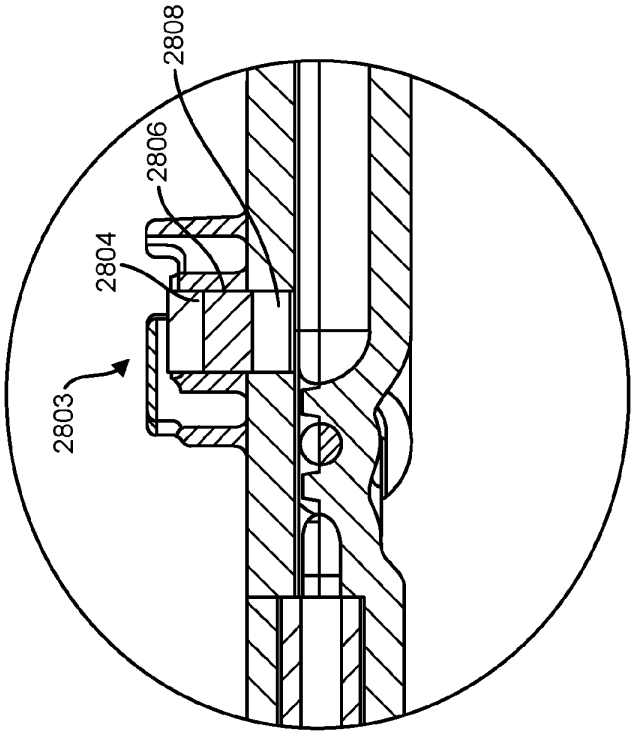


FIG. 28F

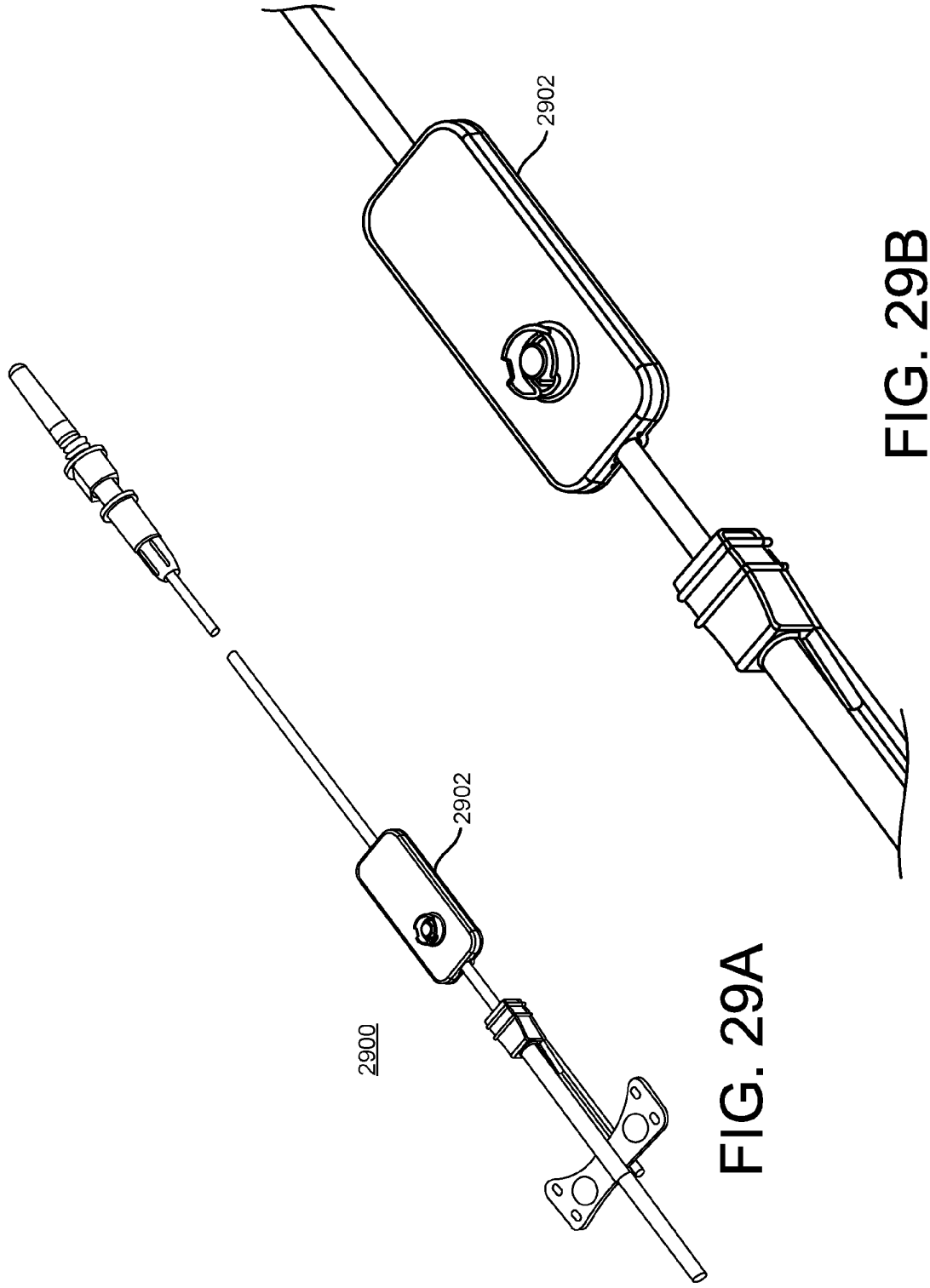


FIG. 29B

FIG. 29A

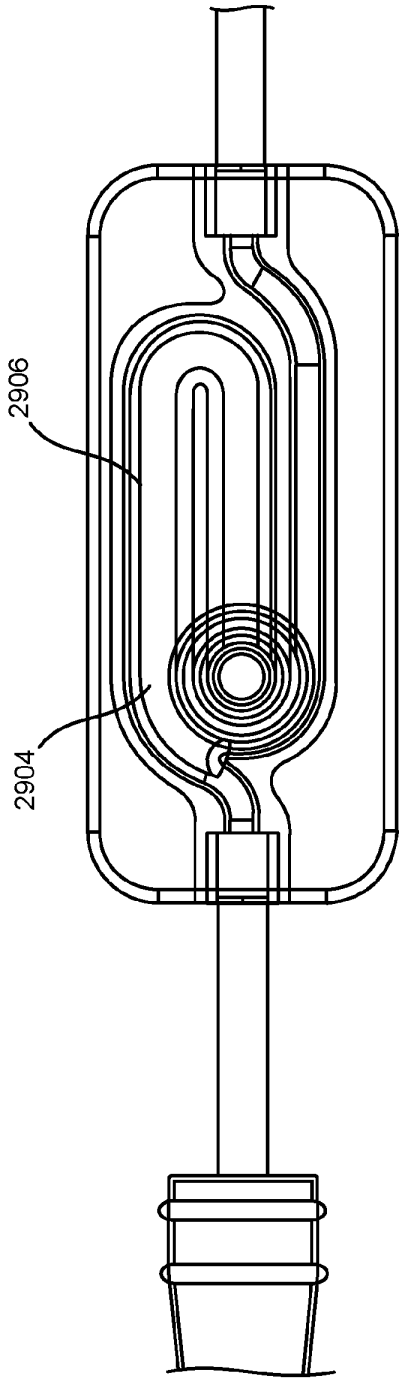


FIG. 29C

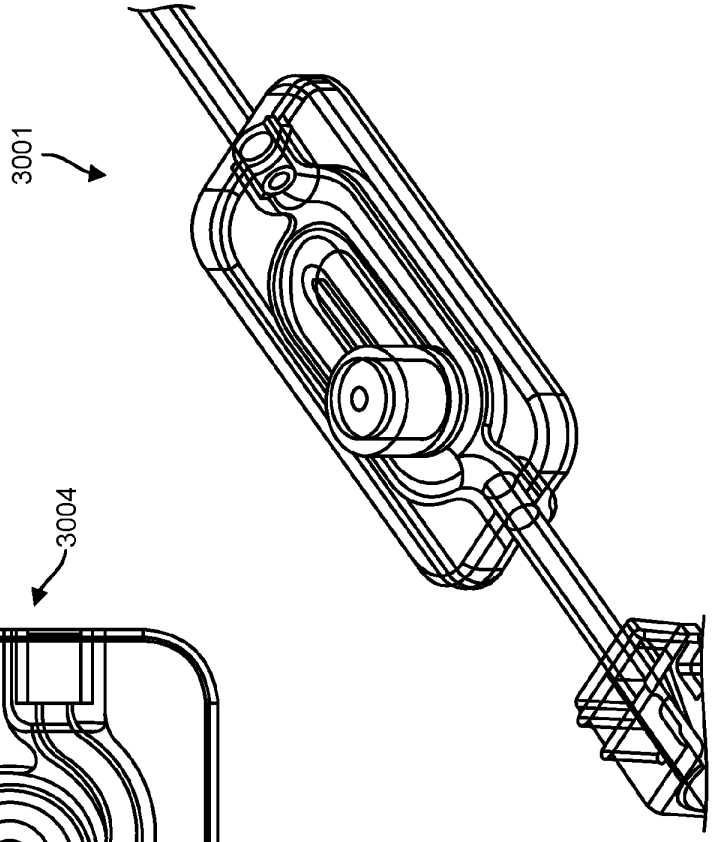


FIG. 30B

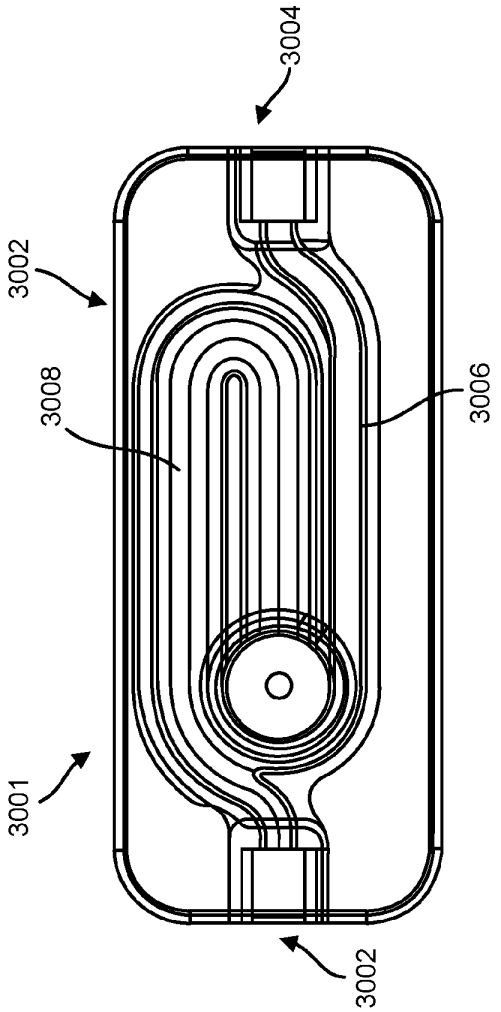


FIG. 30A

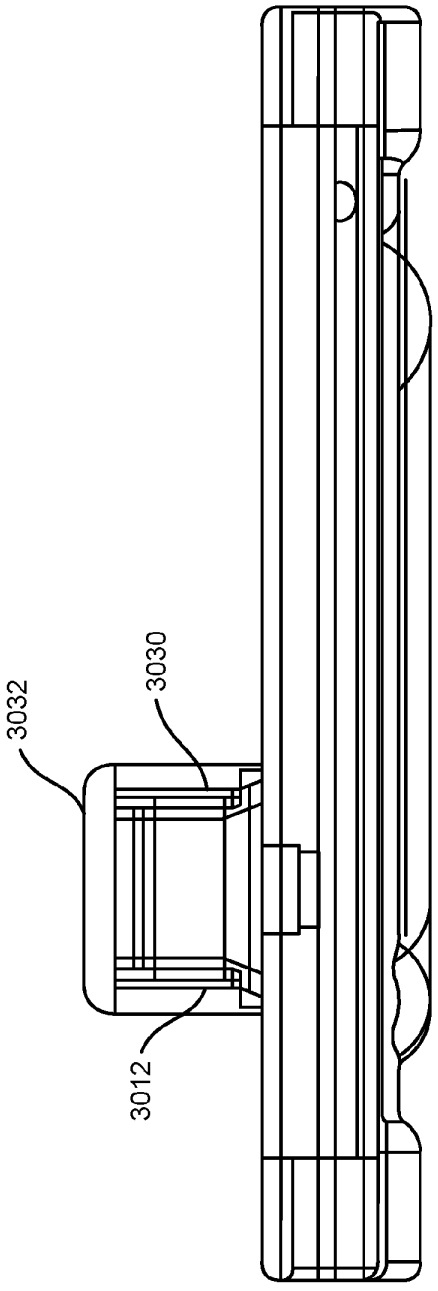


FIG. 30C

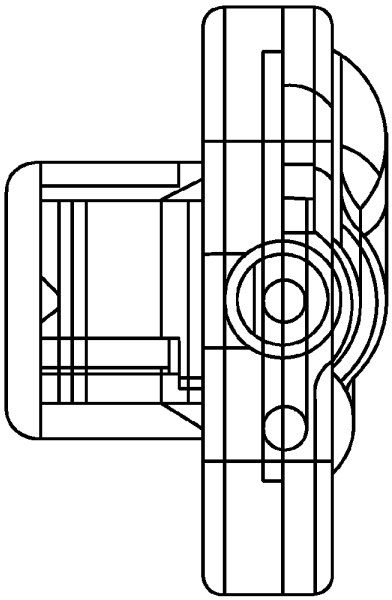


FIG. 30D

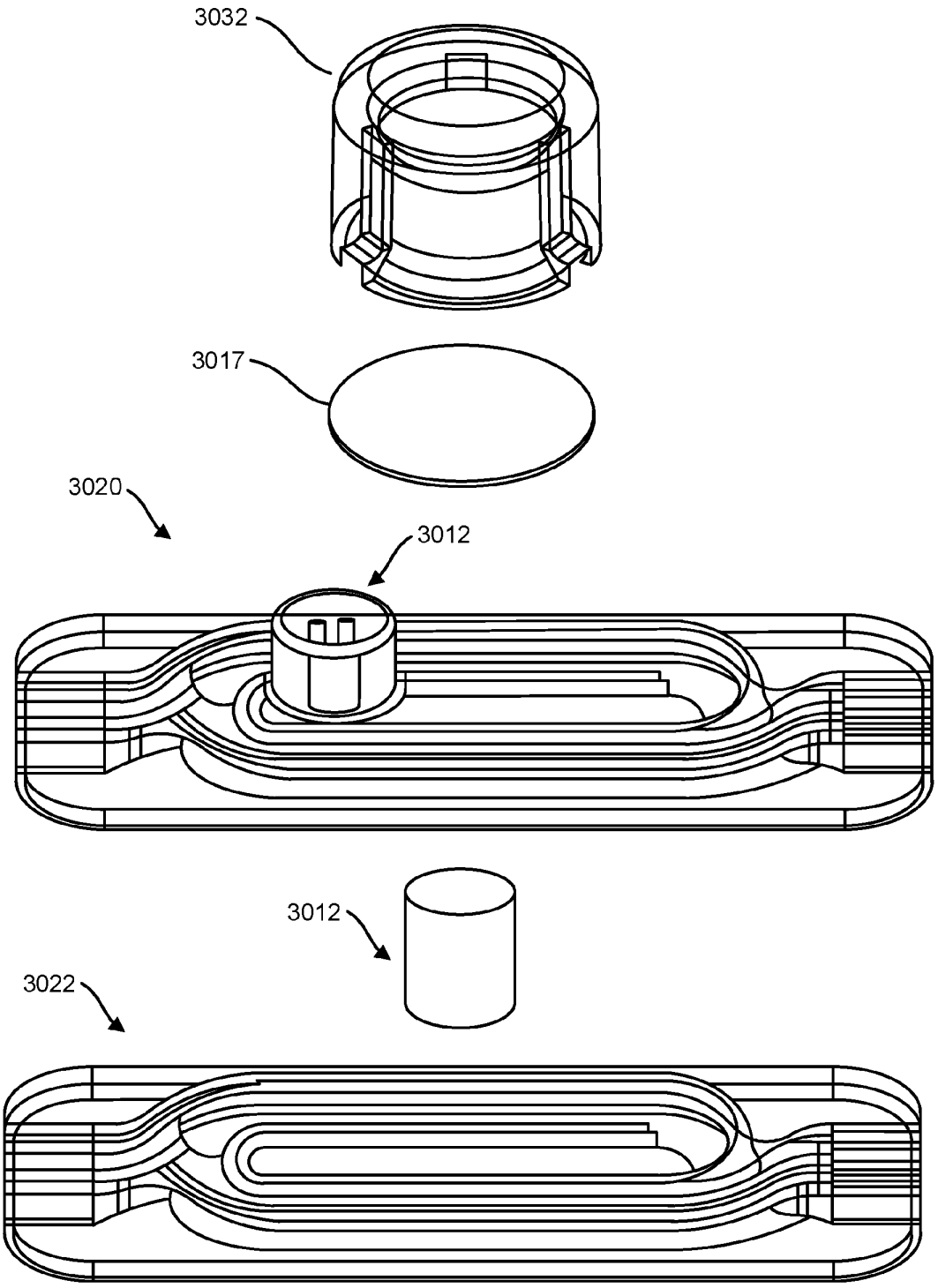


FIG. 30E

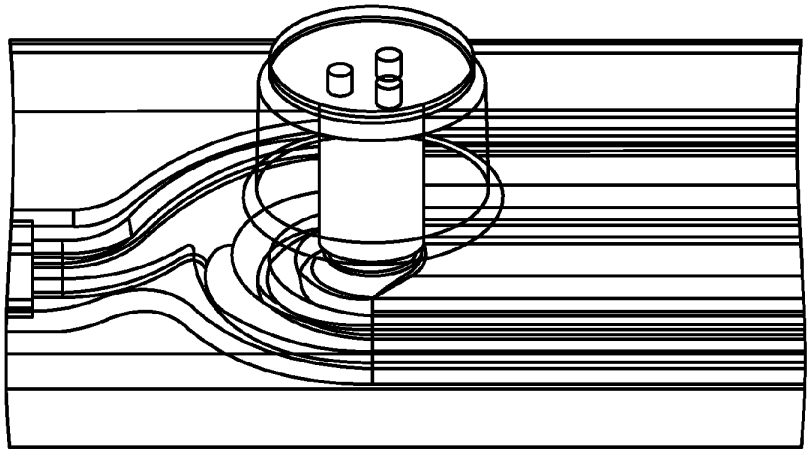


FIG. 30F

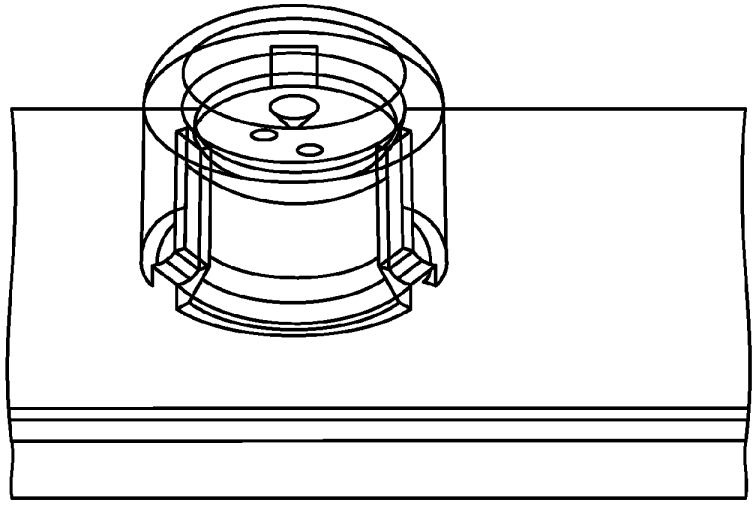


FIG. 30G

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/068569

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15 A61B5/153 A61B5/154 A61B5/157
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 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

-/--

[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)

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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

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INTERNATIONAL SEARCH REPORT

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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.

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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

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Closed Blood Conservation Device for Reducing Catheter-Related Infections in Children After Cardiac Surgery

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Abstract

Background Arterial catheters are potential sources of nosocomial infection.

Objective To investigate use of a closed blood conservation device in preventing catheter-related bloodstream infections in children after cardiac surgery.

Methods Children with an indwelling arterial catheter after cardiac surgery were randomly assigned to 2 groups: a control group with a conventional 3-way stopcock in the catheter system and an interventional group with the conservation device in the catheter system. Catheter tips, catheter intraluminal fluid, and blood samples obtained from the catheter and peripherally were cultured for microbiological analysis. RESULTS Intraluminal fluid contamination was significantly lower (P = .03) in the interventional group (3 of 147 catheters) than in the control group (10 of 137 catheters). The 2 groups did not differ significantly in the rate of tip colonization (9 of 147 vs 12 of 137, P = .40) or in the number of catheter-related bloodstream infections (0 of 147 vs 2 of 137, P = .21).

Conclusion Use of a closed blood conservation device could decrease the incidence of catheter-related contamination of intraluminal fluid.

This article has been designated for CNE credit. A closed-book, multiple-choice examination follows this article, which tests your knowledge of the following objectives:

1. Describe closed blood conservations devices
2. Identify the key findings of the study and implications on preventing catheter-related bloodstream infections in pediatric patients
3. Discuss the indications for use in the pediatric intensive care unit

Arterial catheters are routinely used in critically ill patients for continuous monitoring of arterial blood pressure and for obtaining blood samples for arterial blood gas analysis. Catheter-related bloodstream infections (BSIs) are a common and serious complication of intravascular catheters and are associated with increased morbidity, mortality, length of hospital stay, and medical costs.[1–5] Although previous studies[6–8] indicated a low risk for infections associated with use of arterial catheters, recent studies[9–11] showed that the risk for arterial catheter–related infection was high, comparable to the risk associated with short-term use of central venous catheters. Compared with adult patients, children are more susceptible to nosocomial infection, and catheter-related BSI is considered the most common nosocomial infection in pediatric intensive care units (PICUs).[12] Prevention of catheter-related BSI in PICU patients with multiple intravascular catheters has become a top priority.

Catheter-related BSI is the most common nosocomial infection in PICUs.

Unlike central venous catheters, arterial catheters have an open-loop design that allows backflow of blood into the pressure tubing. This backflow and frequent blood sampling are now considered the 2 major causes of catheter-related BSI.[13–15] Keeping the arterial catheter system closed could be an effective method to decrease the risk of catheter-related BSI. Several investigators have reported that the risk for blood contamination could be minimized for both central venous[14,16–18] and arterial[13,19] catheters in adult patients when closed-loop systems were used.

The venous arterial blood management protection (VAMP) device (Edwards Lifesciences Corporation) is a needleless closed-loop blood sampling system. The device has been introduced into clinical practice to eliminate discarding of blood during blood sampling.[20] Besides reducing blood loss, use of a VAMP device may also reduce the risk for catheter-related BSI by keeping the arterial catheter system closed. Oto et al[21] reported that the risk for contamination of intraluminal fluid in adult patients could be decreased by adding a VAMP device to the arterial catheter system. However, the potential benefit of using this type of device to prevent catheter-related BSI in children is still not well recognized. The objective of our study was to investigate the effect of a VAMP device in reducing the occurrence of catheter-related BSI in children after cardiac surgery.

Materials and Methods

Setting and Sample

The study was approved by the appropriate ethical committee, and informed written consent was obtained from patients' parents. The study sample consisted of children who had undergone open heart surgery and were admitted to the PICU. Patients were included if they were less than 12 years old, were expected to stay more than 48 hours in the PICU, and had an arterial catheter inserted. Patients were excluded if they were expected to stay less than 48 hours or die during the study period, had an apparent infection before admission to the PICU, had the arterial catheter removed within 48 hours of surgery, or had confirmed diagnosis of non–catheter-related infection (eg, pulmonary or surgical site infection). All arterial catheters were inserted in the operating room or reinserted in the PICU. Aseptic technique was used for all insertions, and all patients received prophylactic antibiotics for 48 hours after surgery.

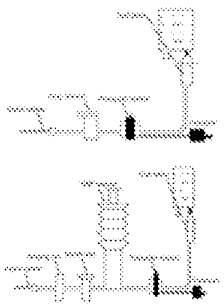
Samples and Randomization

A 2-sided test for randomized control trials indicated that for 80% power and $\alpha = .05$, a sample size of at least 130 patients in each group was needed. During the study period, each patient was randomly allocated to 1 of 2 groups by using a sealed-envelope method. The control group had a conventional 3-way stopcock system in the catheter, and the interventional group had a VAMP Plus device in the catheter. Both groups were followed up until removal of the arterial catheter, discharge from the PICU, or death.

The Figure shows the components of the blood sampling systems in the 2 groups. In the control group, the heparin cap of the 3-way stopcock was removed and a sterile syringe was inserted into the stopcock port after the port was cleaned with iodine swabs. After about 5 mL of blood was obtained, the first syringe was removed and another sterile syringe was inserted into the stopcock port for obtaining the required amount of blood. Then, the 5 mL of blood in the first syringe was injected back into the patient through the arterial catheter, and the stopcock port was cleaned again with iodine swabs. Finally, a new sterile heparin cap was reconnected to the 3-way stopcock, and the mixture of heparin and physiological saline in the flush device was infused into the arterial catheter system. Throughout the entire process, the heparin cap was off, leaving the 3-way stopcock port open to the outside. Also, 2 sterile syringes were needed, and blood obtained with the first syringe was injected back into the patient.

Figure

Schematic diagrams of the conventional 3-way stopcock arterial catheter system (top, control group) and the venous arterial blood management protection (VAMP, Edwards Life-Sciences) system (bottom, VAMP group). In



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the conventional 3-way stopcock system, key components are an arterial catheter, a 3-way stopcock capped with a sterile heparin cap, a pressurized reservoir, a transducer, and a continuous flush device containing a solution of heparin (6.25 IU/mL) in physiological saline. In the VAMP system, the 3-way stopcock is replaced by a VAMP device, a needleless closed-loop blood-sampling system, including a sampling port, a shutoff valve, and a closed-loop blood reservoir.

In the VAMP group, the inner cylinder of the blood reservoir was pulled back until blood passed the sample port and filled half of the blood reservoir, and then the shutoff valve was closed. The sampling port was disinfected twice with iodine swabs, an arterial blood collection syringe (Becton, Dickinson and Company) with an attached blood collection cap (VMP400, Edwards Life-sciences Corporation) was inserted into the sampling port, and the required blood sample was obtained. After collection of the blood sample, the syringe was removed and the sample port was disinfected with iodine swabs. Finally, the shutoff valve was opened, and the blood in the reservoir and the mixture of heparin and physiological saline in the flush device were reinjected into the patient. Throughout the entire process, no parts of the arterial catheter system were removed and the system was completely closed.

During the study period, each patient had an arterial catheter device in place for at least 48 hours. The heparin-saline solution in the flush device was replaced every 24 hours. Other components of the systems (including transducer, continuous flush device, and the tubing) were replaced at 96-hour intervals.[22] All medical personnel were strictly trained in the blood-sampling procedure and routine care of the arterial catheter system. The arterial catheter was removed if it was no longer necessary, the patient had signs of catheter-related BSI, or complications related to use of the catheter occurred.

Keeping the arterial catheter system closed is an effective method of decreasing the risk of catheter-related BSI.

Microbiological Analysis

The differential time to positivity between cultures of blood from the catheter and cultures of peripheral blood is a simple and reliable tool for diagnosis of catheter-related BSI.[23] Samples of blood from the arterial catheter and samples of peripheral blood were cultured simultaneously when a patient's temperature was greater than 38.5°C (101.3°F) and were monitored continually. A diagnosis of catheter-related BSI was made when cultures of the catheter blood became positive for microbial growth 2 hours earlier than did cultures of peripheral blood and cultures of both samples had the same microorganisms.

Arterial catheter tips were cultured after removal of the catheters. A 5-cm segment of the catheter (or the entire short catheter) was placed into a sterile tube and cultured by using a roll plate technique.[24] Colonization of a tip was defined as a growth of 15 or more colony-forming units in a semiquantitative culture.

Intraluminal fluid from both arterial catheter systems was also cultured. After aseptic removal of the arterial catheter, sampling port, and transducer, a sterile syringe containing 10 mL of sterile physiological saline was inserted at the proximal connection of the transducer, and the saline was injected into the arterial catheter. In the catheters with the VAMP device, the 10 mL of saline was also used to flush the VAMP reservoir. Finally a 10-mL aliquot of the mixture of saline and intraluminal fluid was drained into a sterile culture bottle and cultured in trypticase soy broth for 7 days at 37°C (98.6°F). The cultures were examined daily; if the broth was cloudy, standard laboratory subculturing was performed.

Data Collection

Patient demographic data included age, sex, and score on the Acute Physiology and Chronic Health Evaluation II at PICU admission. Data on the arterial catheters included the location of the catheter, date of insertion, site of any reinsertion, and final date of removal. Data on cultures of catheter tips, intraluminal fluid from the catheter, and samples of blood obtained simultaneously from the catheter and peripherally also were noted.

Statistical Analysis

Statistical analysis was performed by using SPSS, version 16.0 (IBM SPSS). Quantitative variables were expressed as means and standard deviations unless stated otherwise and were compared by using a *t* test or the Mann-Whitney test. Categorical data were compared between groups by using χ^2 analysis or the Fisher exact test. Logistic regression analysis was used to evaluate the direct relationship between arterial catheter–related infection and patients' demographic or catheter characteristics. A bidirectional hypothesis was applied, and a *P* less than .05 was considered significant.

Results

Characteristics of the Patients and the Arterial Catheters

From March 2010 to December 2012, 260 children were enrolled in the study. A total of 12 patients were excluded because of death (3 patients), confirmed pulmonary infection (7 patients), or removal of the arterial catheter within 48 hours after surgery (2 patients). The final sample consisted of 248 children and 284 placements of an arterial catheter. The VAMP group included 128 patients with 147 arterial catheters inserted. The control group consisted of 120 patients with 137 arterial catheters inserted. The median duration of insertion for both groups was 7 days. The 2 groups did not differ significantly in age, sex, score on the Acute Physiology and Chronic Health Evaluation II, insertion site of the arterial catheter, and length of time the catheter was in place (Table 1).

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Table 1

Basic characteristics of patients in the venous arterial blood management protection (VAMP) and control groups

Microbiological Analysis

Intraluminal fluid contamination was significantly lower (*P*=.03) in the interventional group (3 of 147 catheters) than in the control group (10 of 137 catheters). The 2 groups did not differ significantly in the rate of colonization of the catheter tip (9 of 147 vs 12 of 137; *P*=.40) or in the number of catheter-related BSIs (0 of 147 vs 2 of 137; *P*=.21; Table 2). Logistical regression analysis indicated that the incidence of colonization of the catheter tip was significantly related to both the length of time the catheter was in place (odds ratio, 0.737; 95% CI, 0.580–0.936; *P*=.01) and the score on the Acute Physiology and Chronic Health Evaluation II (odds ratio, 0.879; 95% CI, 0.781–0.989; *P*=.03). Contamination of intraluminal fluid was also significantly associated with the length of time the catheter was in place (odds ratio, 0.506; 95% CI, 0.350–0.731; *P*<.001), and use of the VAMP device was a strong predictor of a decrease in the risk for contamination of intraluminal fluid (odds ratio, 0.069; 95 CI, 0.013–0.592; *P*=.01; Table 3).

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Table 2

Results of microbiological analysis of the 2 types of arterial catheter systems

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Table 3

Risk factors associated with the occurrence of catheter tip colonization and intraluminal fluid contamination

Microorganisms Identified

In the VAMP group, all colonization of catheter tips and contamination of intraluminal fluid was caused by coagulase-negative staphylococci. In the control group, various species of microorganisms were detected, but coagulase-negative staphylococci were still the most common bacteria found in the arterial catheter systems. Table 4 indicates microorganisms identified for each group.

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Table 4

Results of microbiological analysis of the 2 types of arterial catheter systems

Discussion

Arterial catheters are commonly used for hemodynamic monitoring and for collecting samples of arterial blood. Previously, the risk for infection associated with use of arterial catheters was considered low.[6–8] The 2002 guidelines[22] of the Centers for Disease Control and Prevention even commented that arterial catheters had a "low infection risk" and were "rarely associated with bloodstream infection." However, in a prospective study[25] of 212 intensive care unit patients with placement of both arterial and central venous catheters, the cumulative incidence of catheter-related BSI for arterial catheters was 7.7%, comparable to an incidence of 9.4% for central venous catheters (P=.45). Several studies[9–11] confirmed that risk for infection associated with arterial catheters was similar to the risk associated with central venous catheters. Thus, prevention of catheter-related BSI has become an important issue in medical practice. Effective methods to minimize the risk of arterial contamination or infection include use of a rigorous aseptic technique for placement of the catheter, selection of an optimal site for the catheter, prompt removal of any unnecessary catheter, and keeping the catheter system closed.[13,19,21,26]

Coagulase-negative staphylococci are the most common bacteria found in arterial catheter systems.

Unlike adult patients, children in the intensive care unit are more susceptible to nosocomial infection. Because most studies[13,21] on catheter-related BSI were done in adults, we investigated the effect of using a VAMP device in the management of critically ill children. Although we found no significant difference between the VAMP group and the control group in colonization of catheter tips or occurrence of catheter-related BSI, contamination of intraluminal fluid was significantly lower in the group with the VAMP device. This result is similar to the findings of Oto et al[21] and Crow et al.[13] Oto et al found that catheter-related contamination of intraluminal fluid decreased from 8.4% for an arterial catheter system with a conventional 3-way stopcock to 1.8% when an arterial catheter with a VAMP device was used (P=.03). Crow et al reported that the incidence of contamination of intraluminal fluid was lower with a closed blood-sampling system (7%) than with a 3-way stopcock system (61%).

As mentioned earlier, frequent opening of the arterial catheter system for blood sampling and backflow of blood into the pressure tubing are 2 important causes of catheter-related BSI.[13–15] When the conventional 3-way stopcock system is used, frequent acquisition of blood samples through the open arterial catheter system, reinjection of blood into the artery, and the inevitable presence of residual blood within the stopcock port could lead to a high risk for microbial contamination of the catheter. In contrast, an arterial catheter system with a VAMP device is a completely closed infusion system. No part of the VAMP system must be opened when a blood sample is obtained, so no pathway exists for transfer of microorganisms to intravascular fluid

Although microbial contamination of intraluminal fluid was significantly lower in the VAMP group than in the control group in our study, use of the VAMP system did not decrease the incidence of colonization of catheter tips. This result agrees with the findings of Oto et al,[21] who observed no significant difference (P=.48) in the rate of colonization of catheter

tips: 7.3% in the test group and 10.3% in the control group. We can only speculate that the reason for this result in our study is the short length of time the catheters were in place and a relatively low rate of colonization of catheter tips. Researchers[7,27,28] have reported that colonization of catheter tips may be more closely related to the insertion site of the arterial catheter and the length of time the catheter is in place than to the catheter system. In our study, further logistic regression analysis indicated that the length of time the catheter was in place was an important factor in the colonization of catheter tips, and we found no significant difference between the 2 groups in the length of time the catheter was in place. Meanwhile, the rate of colonization of catheter tips in our study was relatively low. In a study by Thorpe and Thomas,[29] the contamination rate was higher than the rate in our investigation for both a blood conservation system (30%) and a traditional 3-way stopcock system (37%). Infections of short-term catheters (those in place <10 days) are due mainly to microbial colonization of the skin around the insertion site.[21] In our study, the microorganisms detected on the catheter tips (median time in place, 7 days) in both groups were mostly coagulase-negative staphylococci, organisms primarily found on the skin.

The occurrence of catheter-related BSI for arterial catheters did not differ significantly between the 2 groups in our study. We identified 2 instances of catheter-related BSI in the control group and no instances in the VAMP group. Although no conclusion can be made about the direct effect of a VAMP device in preventing catheter-related BSI in arterial catheter systems, we speculate that use of a VAMP device could lower the risk for catheter-related BSI in children. Because of the unique closed-loop design, use of a VAMP device has obvious advantages in children, especially children who have had heart surgery who require repeated blood sampling and continuous blood pressure monitoring. Use of a VAMP device could prevent microbial contamination of intraluminal fluid and save the blood normally discarded when blood samples are obtained for blood gas analysis. Because children, especially infants, are more susceptible than adults to nosocomial infections such as catheter-related BSI in the intensive care unit,[12,30,31] a small step forward in preventing catheter-related BSI could be highly beneficial for patients in the PICU. Our results did not directly prove the effect of a VAMP device in reducing catheter-related BSI in children after cardiac surgery, but the VAMP device could be still used as part of "bundle care" for use of intravascular catheters to minimize the risk of catheter-related contamination.

The VAMP device could be used as part of "bundle care" for use of intravascular catheters to minimize the risk of catheter-related contamination.

Limitations

Our investigation had several major limitations. First, the study was done at a single center and with a limited study cohort. Further large-scale, well-designed, randomized control trials are needed to verify the validity of our results. Second, although we tried to ensure equal treatment of both groups with the blood-sampling technology and routine care, physicians and nurses were aware of the device, and they might have been more careful or cautious with patients in the VAMP group. In addition, with the semiquantitative method described by Maki et al,[24] only the external surface of a catheter tip is sampled, and the VAMP device might prevent internal colonization better than it prevents external colonization because the device forms a closed system. The quantitative catheter segment culture technique reported by Cleri et al[32] might be a more suitable method for investigating the effect of a VAMP device on colonization of catheter tips.

Conclusion

In conclusion, compared with the conventional 3-way stopcock device, use of a VAMP device could decrease the incidence of arterial catheter–related contamination of intraluminal fluid. The VAMP device may be an effective method of preventing catheter-related BSI in the PICU. CCN

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Footnotes

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Financial Disclosures

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To learn more about reducing the risk for catheter-related infections, read "Simulation-Based Training for Nurses in Sterile Techniques During Central Vein Catheterization" by Gerolemou et al in the *American Journal of Critical Care*, January 2014;23:40–48. Available at **www.ajcconline.org**.

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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.		

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

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A61B

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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

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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
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A	US 3 648 684 A (BARNWELL CLEORA W ET AL) 14 March 1972 (1972-03-14) abstract; figures	1-20
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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

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Information on Search Strategy - Pilot phase (see OJ 2015, A86)
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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

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(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

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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.

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Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

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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.

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Re Item VII

Certain defects in the international application

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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).

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Re Item VIII

Certain observations on the international application

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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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Original Article

Quality of Processed Blood for Autotransfusion

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Keywords: red cell mass flow rate, speed, plasma washout, quality

Presented at the American Society of Extra-Corporeal Technology 37th International Conference, April 8–11, 1999, New Orleans, Louisiana

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.

$$\text{Albumin elimination rate (\%)} = \left[\left| - \frac{\text{Total Albumin}_{PRBC}}{\text{Total Albumin}_{blood}} \right| \right] * 100$$

$$= \left[\left| - \frac{\text{Volume PRBC} * (1 - \text{HCT}_{PRBC}) * \text{Albumin}_{PRBC}}{\text{Volume Blood} * (1 - \text{HCT}_{blood}) * \text{Albumin}_{blood}} \right| \right] * 100$$

$$\text{Residual Albumin transfusion rate (mg/dL RCM)} = \frac{\text{Albumin}_{PRBC} * (1 - \text{HCT}_{PRBC})}{\text{HCT}_{PRBC}}$$

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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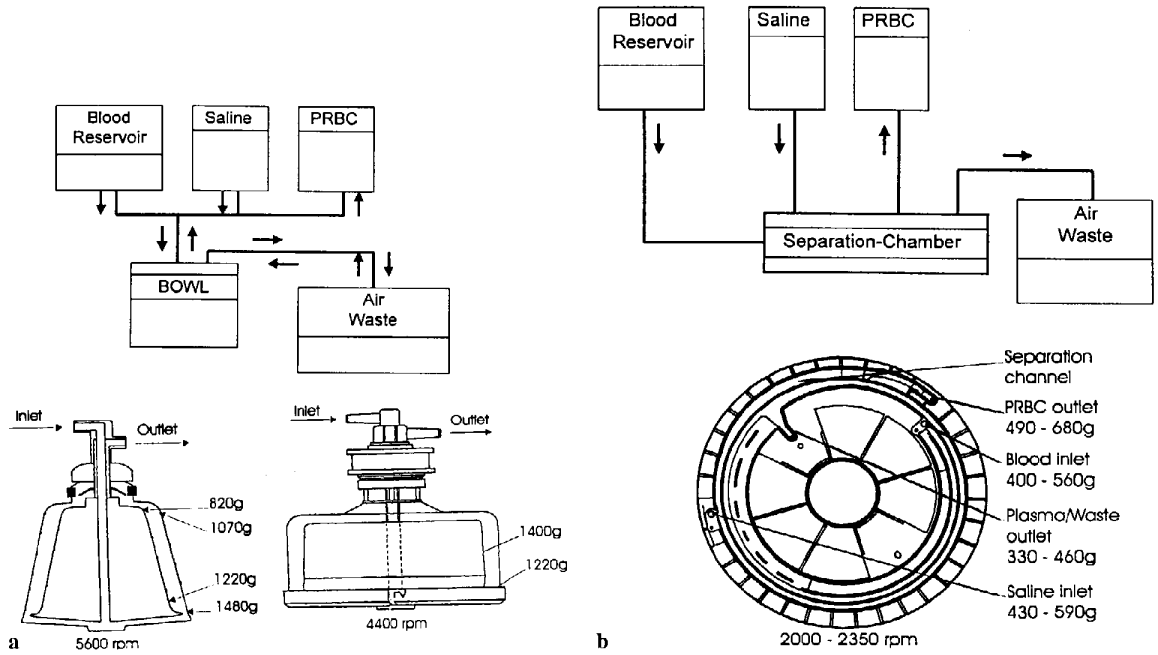


Figure 1: Diagrammatic representations of the flow in systems devised for intraoperative autologous transfusion in (a) discontinuous and (b) continuous flow procedures.

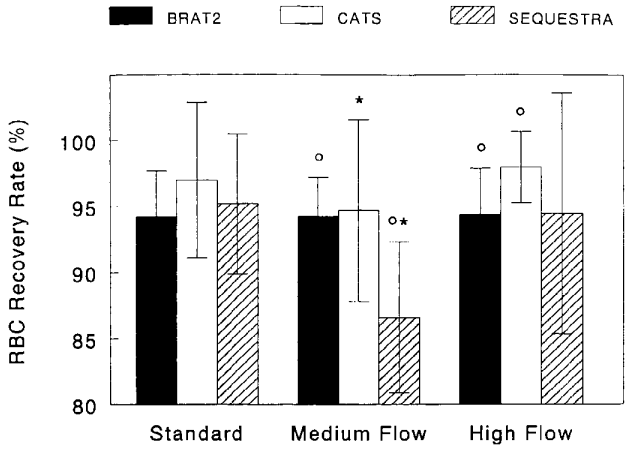


Figure 2: Mean red blood cell recovery rates ± standard deviations for three replicate processing runs using three autotransfusion devices in three programs; ° * = $p < .05$; $N = 9$.

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.

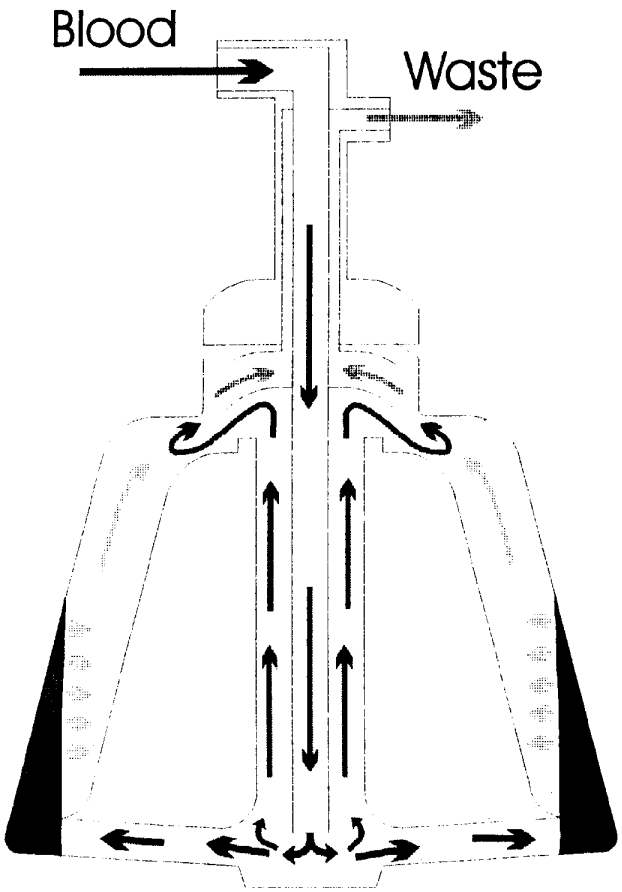


Figure 3: Processing with the conical centrifuge bowl at high flow rates showing red cell loss to waste, presumably due to pressure buildup.

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.

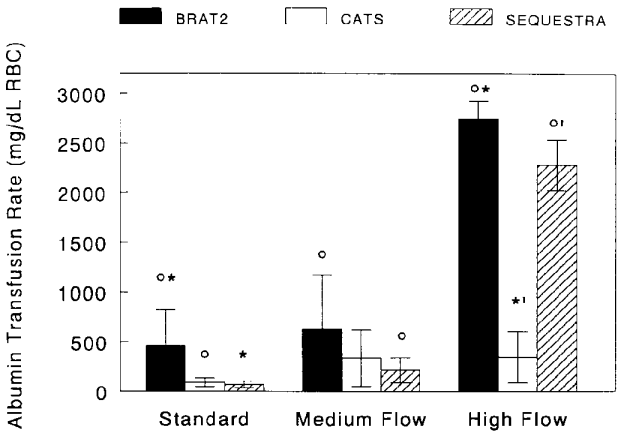


Figure 4: Mean holding bag supernatant albumin transfusion rates ± standard deviations (mg/dL/RCM) for three replicate processing runs using three autotransfusion devices in three programs; ° * = $p < .05$; $N = 9$.

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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Date
09.12.20

Reference	Application No./Patent No.
EPA-150 670	20197213.0 - 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: 30B

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.

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Application No.: 20 197 213.0

The application and the invention to which it relates seem to meet the requirements of the EPC. Upon presence of a valid request for examination and consideration by the examining division, a communication under Rule 71(3) EPC may be issued.

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EUROPEAN SEARCH REPORT

Application Number
EP 20 19 7213

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 2014/039348 A1 (BULLINGTON GREGORY J [US] ET AL) 6 February 2014 (2014-02-06) * the whole document *	1-7	INV. A61B5/15 A61B5/153 A61B5/154 A61B5/157
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A	US 4 813 433 A (DOWNEY JOHN M [US]) 21 March 1989 (1989-03-21) * the whole document *	1-7	
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 *	1-7	
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 *	1-7	TECHNICAL FIELDS SEARCHED (IPC) A61B

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	19 November 2020	Nielsen, Michael

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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19-11-2020

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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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.

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☐ 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

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EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Berlin	18 November 2019	Schultz, Ottmar

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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O : non-written disclosure
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EUROPEAN SEARCH REPORT

Application Number
EP 19 20 0766

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 19 20 0766

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18-11-2019

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		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

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.

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Doing It Right the First Time: Quality Improvement and the Contaminant Blood Culture

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The aim of the project was to determine whether the rate of contaminant blood cultures could be reduced by using a team of dedicated phlebotomists. Comparisons were made between adult patients requiring blood cultures for suspected bacteremia on medical and surgical units before and after the introduction and withdrawal of a dedicated blood culture team. The results showed that a significant reduction in the contaminant blood culture rate was achieved by the blood culture team ($P < 0.001$; χ^2 test). Therefore, in our experience, the rate of contaminant blood cultures can be reduced in a teaching hospital by using a team of dedicated phlebotomists. Calculations made with our data and those published by others suggest that cost savings from reducing false-positive blood cultures are greater than the cost of the blood culture team.

The costs of correcting a defective product often exceed the costs of designing a system to avoid producing a defect (5). For hospitals, these costs are not only monetary but also carry a burden of human suffering. The contaminant blood culture can be regarded as a "defective product." The cost of correcting this defect far exceeds the cost of repeating the blood culture itself (2, 6). Contaminant blood cultures are common events in teaching hospitals (1, 2, 10). They are associated with increased length of stay, inappropriate administration of antibiotics, and use of further testing (2, 6), resulting in more than 50% greater total hospital charges (2).

Standards published by the American Society of Microbiology indicate that the rate of blood culture contamination should not exceed 3% (8). Nevertheless in many teaching hospitals the contamination rate exceeds 6% (2, 10). A recent publication suggested that this could be reduced to less than 4% by using a different method of skin preparation (10). In our institution the contamination rate reported to our quality assessment and improvement committee was 4.7%, and this was identified as an opportunity for improvement.

When quality concerns occur, there is a natural tendency to blame the line worker (3). For many teaching hospitals, the line worker who collects blood for culture is usually an intern or resident. Our initial effort was to educate the house staff on proper performance and provide guidelines for appropriate test use. Despite this effort, the contamination rate remained the same. To achieve a quality improvement breakthrough, we questioned the system rather than blaming the line worker. We hypothesized that our house staff had numerous clinical responsibilities and could not possibly dedicate the time and energy required to perform the process of collecting blood for culture without the result being a contamination rate that is unacceptable. We instituted a trial of a blood culture team (BCT) consisting of dedicated phlebotomists. We hypothesized that this would lead to a significant reduction in the rate of contaminant blood cultures. Published data (2) indicated that saving the true costs of contaminant blood cultures would make this initiative economically advantageous. The subsequent quality improvement would pay for the cost of the program, confirming the contention of industry consultants that for some goals quality is free (4). We report a significant reduction in the rate of blood culture contamination achieved by a team of dedicated phlebotomists ($P < 0.001$; χ^2 test).

MATERIALS AND METHODS

Patient population. The New York Hospital Medical Center of Queens is an acute-care community hospital with 487 beds. There are independent medical and surgical residency programs. The patient units chosen for this study were adult general medical and surgical care units. All patients on these units requiring a blood culture for suspected bacteremia during the study periods were included. No consents were obtained, and patients were not informed of this study. Institutional review board approval was not deemed necessary.

Study design. A BCT consisting of three full-time phlebotomists was established. Blood samples for culture were collected by the BCT after orders were written by house staff or attending physicians by a standardized protocol based on methods published previously (9). Briefly, a commercially available skin preparation kit (prep kit) with isopropanol and tincture of iodine (Cepti-seal blood culture prep kit II; Mediflex Hospital Systems, Overland Park, Kans.) was used according to the manufacturer's specifications, and two sets of blood samples for culture were collected from separate sites of each patient. Each was inoculated into one anaerobic and one aerobic culture bottle (BACTEC NR 7A and 6A, respectively; Becton-Dickinson Diagnostic Systems, Sparks, Md.). Blood samples were collected by house staff when the BCT was not available to the patient care unit.

The house staff were educated in proper technique by conventional methods (alcohol and povidone-iodine swabs), but no attempt was made to verify their use. Commercial prep kits were not available to the house staff initially. These were made available on one patient unit after the BCT was withdrawn and the house staff was educated regarding their use. This was done to evaluate the effect of the commercial prep kit.

Blood cultures were evaluated by using BACTEC NR-660 (Becton-Dickinson Diagnostic Systems). Blood cultures were considered contaminated if microorganisms derived from common skin flora were cultured: *Corynebacterium* spp., *Bacillus* spp., *Propionibacterium* spp. (e.g., *Propionibacterium acnes*), and coagulase-negative staphylococci.

The presence of coagulase-negative staphylococci was closely monitored since it may represent true infection. Culture sets in which only one of four bottles or two of four bottles (one set) were positive were analyzed. Coagulase-negative staphylococci present in three of four and four of four bottles were not considered contaminants for the purposes of this study to avoid including true positives.

The following criteria were used in combination to confirm contamination for cultures positive for coagulase-negative staphylococci: (i) subsequent (and often prior) cultures were negative and (ii) physician review of the medical record indicated that contamination was present.

Two patient care units (designated units A and B) were selected for sequential

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TABLE 1. Comparison of blood culture collection techniques by house staff and phlebotomy team (BCT)

Blood culture collection technique	Unit A			Unit B		
	Duration of study (mo)	No. of contaminated cultures/total no. of cultures (%)[a]	*P* value	Duration of study (mo)	No. of contaminated cultures/total no. of cultures (%)	*P* value
A. House staff without prep kits	3	24/287 (8.4)	<0.001[b]	2	15/312 (4.8)	<0.001[b]
B. BCT with prep kits	6	11/956 (1.2)	<0.001[c]	3	8/799 (1.0)	
C. House staff with prep kits	3	10/208 (4.8)				

[a] For comparison of techniques A and C, $P = 0.173$.
[b] Comparison of techniques A and B.
[c] Comparison of techniques B and C.

introduction of the BCT. Unit A was a large, busy general medical floor and was heavily weighted toward emergency admissions. This area had been noted in the past to have a high rate of blood culture contamination. Unit B consisted of a smaller general medical floor and a general surgical floor. Historically, the rate of blood culture contamination on unit B was similar to that for the institution as a whole. Blood culture data were collected for 3 months prior to the introduction of the BCT on unit A and for 2 months prior to the introduction of the BCT on unit B. Data were collected for a subsequent 6 months for unit A and 3 months for unit B after the introduction of the BCT. The BCT was then withdrawn from unit A and the commercial prep kits made available to the house staff, who were instructed to use them according to specifications. Data were then collected for 3 subsequent months for unit A.

Statistical methods. The Mantel-Haenszel chi-square test was performed with True Epistat software (Epistat Services, Richardson, Tex.) on an International Business Machines Corporation-compatible desktop computer. Two-tailed *P* values were used.

RESULTS

Effects of BCT and commercial skin prep. The results of studies examining the effects of the BCT and the commercially available skin prep are presented in Table 1 and are displayed graphically in Fig. 1. Unit A had a high baseline rate of blood culture contamination (8.4%), a rate that exceeded that seen in the hospital as a whole (4.7%; unpublished data). This high rate was thought to be due to the character of the unit, a busy, high-turnover, general medical floor heavily weighted toward emergency admissions, and the effect that this had on the house staff workload. Unit B had a lower baseline rate of contamination of blood cultures (4.8%), and this result was similar to that for the whole institution. After the introduction of a BCT, the rate of contamination decreased significantly for unit A to 1.2% ($P < 0.001$; χ^2 test) and decreased significantly for unit B to 1% ($P < 0.001$; χ^2 test). When the BCT was withdrawn from unit A, commercial blood culture kits with isopropanol and tincture of iodine were supplied and the house staff were educated in their use. Despite the use of the prep kits, there was a significant increase in the contamination rate to 4.8% compared to that observed with the BCT, 1.2% ($P < 0.001$; χ^2 test). The performance of the house staff on unit A did exhibit a trend toward improvement with the use of the commercial prep kits compared to that at the baseline (4.8 versus 8.4%), but this was not statistically significant ($P = 0.173$; χ^2 test). Others have found significant improvements with improved methods of skin preparation (9, 10).

Calculations of economic benefits. Data establishing the true consequences of false-positive blood cultures have been published by Bates et al. (2). The median hospital charges for patients with false-positive blood cultures were reported to be more than 50% greater than those for similar patients with true-negative blood cultures. This was accounted for by increased length of stay and increases in pharmacy and laboratory charges, with an increase in total median charges of more $4,000 per patient. In our hospital, costs account for greater than 98% of charges. If we assume a 50% increase in actual hospital costs and average diagnosis-related group charges of approximately $5,000, then each contaminant blood culture costs our institution $2,500. If we accept this conservative estimate, then the following calculation can be made. For unit A, over 6 months, 11 of 956 cultures of blood collected by the BCT with a commercial skin prep kit were contaminated. Without blood collection by the BCT and with the use of the commercial skin prep kit, 4.8%, or 45 contaminant blood cultures, would have been expected. This represents elimination of 34 contaminant cultures or a calculated savings of $85,000. The cost of the BCT, with three full-time equivalent salaries and benefits, for 6 months was $45,000. The savings resulting from this improvement, $40,000, does not include further cost reductions that the BCT achieved simultaneously on unit B, which were also substantial, as well as other productive work that the team performed (collection of blood at appropriate intervals for determination of antibiotic levels for patients on aminoglycosides). More than 14,000 blood culture sets were collected in our institution for the year 1994. We would predict that at least 650 sets would have been contaminated on the basis of an institutional contamination rate of 4.7%. A reduction of the contamination rate to 1.2% would eliminate more than 480 contaminant cultures, with potential savings of $1,200,000.

DISCUSSION

Our data have indicated that a significant reduction in the rate of contaminant blood cultures was achieved in two patient care units by a BCT using commercial prep kits ($P < 0.001$) compared to the results obtained by house staff. Improved

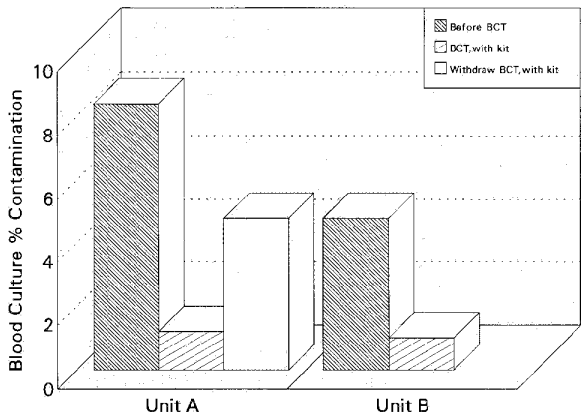


FIG. 1. Effect of BCT and commercial prep kits on rate of blood culture contamination.

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results occurred when house staff used a commercial prep kit, although the difference from the baseline data was not statistically significant ($P = 0.173$; χ^2 test). Others have shown that significant benefits result from improved methods of skin preparation (9, 10). The trend that we observed would corroborate those reports. Conservative estimates of the cost savings achieved by reductions in contaminant blood cultures indicated that the BCT was economically advantageous.

Quality can be defined for some products as conformance to specifications measured by the number of defects divided by the number of opportunities to produce a defect (7). The contaminant blood culture is an easily measured example of a defect produced by a process within a hospital. Unfortunately, the implications of producing this defect are not merely economic. Human suffering results from the increased use of diagnostic testing and additional hospital days with treatment with unnecessary antibiotics. Improving quality in hospital settings is a valid goal, regardless of cost. Nevertheless, pressures to reduce costs from consumers and government exist independently of consideration of quality. In other industries, when the cost of error is calculated, it is clear that improving quality by designing systems to reduce the production of defects results in substantial savings (7). Calculations made by using our results and those reported by others (2) indicate that this is the case for contaminant blood cultures.

Quality improvement can reduce costs in medicine as well as in other industries. Incentives to do so are already present. Organizations that harness the tools of quality improvement theory should be well equipped to meet this challenge. An appropriate goal for hospitals is to control costs by improving quality. To do otherwise risks the substantial achievements of generations of physicians and scientists.

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Direct labeling and visualization of blood vessels with lipophilic carbocyanine dye DiI

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Direct labeling and visualization of blood vessels with lipophilic carbocyanine dye DiI

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Abstract

We describe a protocol to rapidly and reliably visualize blood vessels in experimental animals. Blood vessels are directly labeled by cardiac perfusion using a specially formulated aqueous solution containing 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (DiI), a lipophilic carbocyanine dye, which incorporates into endothelial cell membranes upon contact. By lateral diffusion, DiI also stains membrane structures, including angiogenic sprouts and pseudopodial processes that are not in direct contact. Tissues can be immediately examined by conventional and confocal fluorescence microscopy. High-quality serial optical sections using confocal microscopy are obtainable from thick tissue sections, especially at low magnification, for three-dimensional reconstruction. It takes less than 1 h to stain the vasculature in a whole animal. Compared with alternative techniques to visualize blood vessels, including space-occupying materials such as India ink or fluorescent dye-conjugated dextran, the corrosion casting technique, endothelial cell-specific markers and lectins, the present method simplifies the visualization of blood vessels and data analysis.

INTRODUCTION

We describe here a direct labeling protocol[1,2] to visualize blood vessels in small experimental animals rapidly and reliably using a lipophilic carbocyanine dye, DiI ($DiIC_{18}(3)$). Lipophilic carbocyanine dyes, including DiI, have been widely used to label cell membranes[3–8] and to trace neuronal connections in live and fixed tissues[7–14]. In the cell membrane, a DiI molecule has its two hydrocarbon chains buried in the lipid bilayer parallel to the phospholipid acyl chains, and the chromophores are on the surface of the bilayer[15].

The direct labeling technique takes advantage of the lipophilic property of DiI. A special aqueous DiI solution is formulated to have the maximum sodium chloride concentration without causing precipitation of DiI. Glucose is added to maintain the physiological osmolarity. Labeling is achieved by bringing DiI solution in direct contact with endothelial cells through cardiac perfusion. A simple perfusion device is assembled with two three-way stopcocks, a butterfly needle and three 10-ml disposable syringes for phosphate-buffered saline (PBS), DiI solution and fixative, respectively (Fig. 1).

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Note: Supplementary information is available via the HTML version of this article.

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During perfusion, DiI partitions quickly into the cell membrane (lipid) phase, the endothelial cell membrane lining the blood vessels, resulting in instantaneous labeling of blood vessels (Fig. 2). Once in the membrane, DiI molecules diffuse laterally within the lipid bilayer[3]. The lateral diffusion helps to stain membrane structures that are not in direct contact with the DiI solution, including angiogenic sprouts and psuedopodial processes of angiogenic endothelial cells (Fig. 3c,d).

As DiI is directly delivered to the endothelial cell membrane, it is possible to achieve high concentration in cell membrane and thus high signal intensities, which dramatically increases the signal-to-noise ratio. In addition, the dye itself is intensely fluorescent with slow fading when exposed to the excitation light[7,8]. The strong intensity and slow fading feature are ideal for serial optical sections using laser scanning confocal microscopy, especially at low magnification. Images can be obtained throughout the entire thickness of a tissue sample of 100 μm without noticeable deterioration of image quality. The vasculature in the inner surface of a hollow organ like the eye can be scanned as a single stack of confocal images at very low magnification (×5 objective lens). Digitized data of thick tissue sections can be used to reconstruct 3-dimemsional (3-D) images of vascular network in the samples of interest and/or to perform other analyses with suitable software. The 3-D images have the advantage of viewing the vascular network in its entirety (Fig. 3; Supplementary Movies 1–3 online). In addition, the use of thick tissue sections would save time and effort, as fewer tissue sections need to be prepared to cover the entire tissue sample. This is especially important when many samples are to be examined.

Many alternative techniques are available to visualize blood vessels. Space-occupying high-contrast materials, including India ink[16] and fluorescent dye-conjugated dextran (e.g., fluorescein isothiocyanate or FITC)[17], are used to fill blood vessels to render them visible. However, the dye molecules are not bound to blood vessels but move freely in the filling solution. When a tissue sample is compressed, especially during sample preparation, the filling solution can be squeezed out of blood vessels, resulting in interrupted or 'broken' vascular patterns. This method, however, directly stains the endothelial cell membranes.

The corrosion casting technique using low-viscosity plastics, another type of space-occupying material, to make casts of blood vessel network has been employed to study the three dimensionality of vasculature[18,19] in combination with scanning electron microscopy (SEM) [20,21]. The casts are viewed with SEM to obtain 3-D images of the vasculature. It is technically demanding to make casts and requires access to SEM[20,21]. It is also difficult to visualize angiogenic sprouts and pseudopodial processes. In comparison, the method described here is technically much simpler in sample preparation and data collection.

Blood vessels can also be visualized by endothelial cell-specific markers, including factor VIII (see ref. [22]) or CD34 (see ref. [23]). Lectins have been used as surrogate markers for endothelial cells. For example, *Ulex europaeus* I lectin recognizes human endothelial cells[24], and *Griffonia simplicifolia* isolectin B_4 specifically labels endothelial cells in mouse, rat and other laboratory animals[25,26]. Use of these markers usually requires multistep procedures. In addition, it is difficult for these techniques to achieve the high signal intensities that can be achieved by direct labeling methods described here.

The direct labeling technique with DiI provides an efficient, reliable and low-cost (the amount of DiI used per rat is less than 1 mg that costs less than USD $2) alternative to obtain high intensity, high signal-to-noise ratio labeling of blood vessels in the entire body for both low- and high-power microscopic observation. It can also be used to study angiogenic sprouts and pseudopodial processes. Although described here for use in rodents, this procedure can be adapted easily to the study of vasculature in other vertebrate animals including rabbits, either

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for the vasculature of the entire body or for *ex vivo* perfusion of a particular organ, such as rabbit kidneys.

In this method, DiI molecules are directly incorporated into the membrane of endothelial cells. As it is a lipophilic dye, the molecules in the membrane could be washed away by lipophilic solvents. It is therefore not easy to combine DiI staining with other techniques, such as immunohistochemical analysis, if the subsequent procedures involve those lipophilic solvents. This issue could be overcome by using a fixable DiI derivative, CM-DiI (C-7001, Invitrogen/Molecular Probes). CM-DiI is particularly useful in experiments that combine membrane labeling with subsequent immunohistochemical analysis, fluorescence *in situ* hybridization or electron microscopy. DiI staining is, however, compatible with the nuclear dye DAPI (4′-6-diamidino-2-phenylindole).

MATERIALS

REAGENTS

- DiI (D-282, Invitrogen/Molecular Probes; 42364, Sigma-Aldrich)
- Ethanol (100% vol/vol)
- NaCl (S7653, Sigma-Aldrich)
- KCl (P9333, Sigma-Aldrich)
- Na_2HPO_4 (S8282, Sigma-Aldrich)
- NaH_2PO_4 (S7907, Sigma-Aldrich)
- Glucose (G7568, Sigma-Aldrich)
- HCl (1 M) (13-1700, Sigma-Aldrich)
- NaOH (5 M) (S8263, Sigma-Aldrich)
- Glycerol (G6279, Sigma-Aldrich)
- Paraformaldehyde (158127, Sigma-Aldrich)
- Agarose (A5939, Sigma-Aldrich)
- Superglue (can be obtained from regular hardware stores)
- Experimental animals (rats and mice, Charles River)

▲ CRITICAL All animal experiments must comply with national laws and institutional regulations.

EQUIPMENT

- 25 gauge butterfly needles
- Microscope slides
- Standard BK7 glass coverslip (no. 1.5, 170 μm thickness)
- Three-way stopcocks
- 10-ml disposable syringes
- Aluminum boats
- Vibratome (VT1000S, Leica Microsystems)

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REAGENT SETUP

DiI stock solution—Dissolve 100 mg of DiI crystal in 16.7 ml of 100% ethanol on a rocker overnight (covered with aluminum foil when rocking) and store in the dark at room temperature (RT, 20–25 °C) for up to 1 year. ⁑ CAUTION DiI solution stains easily on skin and other surfaces. If accidental staining occurs, it can be wiped off easily by 70% ethanol.

PBS (pH 7.4)—Dissolve 8 g of NaCl, 0.2 g of KCl, 1.44 g of Na_2HPO_4 and 0.23 g of NaH_2PO_4 in 800 ml of distilled water. Adjust pH to 7.4 with HCl. Add water to 1,000 ml, filter through a 0.22-μm bottle-top filter. Store at RT for up to 1 year.

5% (wt/vol) glucose—Dissolve 50 g of glucose in 1,000 ml of distilled water. Filter through a 0.22-μm bottle-top filter. Store at RT for up to 1 year.

Diluent—Mix PBS and 5% glucose at a ratio of 1:4. Store at RT for up to 1 year.

DiI work solution—Immediately before use, add 200 μl of DiI stock solution into 10 ml of diluent, mix by quick shaking. DiI work solution should be freshly made under room lighting.

Phosphate buffer (pH 7.4)—Prepare separately a solution of 0.2 M NaH_2PO_4 and another one of 0.2 M Na_2HPO_4. Mix the two solutions at a ratio of 19:81. Check the pH with a pH meter. Adjust pH with either HCl or NaOH. Store at RT for up to 1 year.

8% (wt/vol) paraformaldehyde—Under a chemical hood, add 8 g of paraformaldehyde to 90 ml of distilled water in a beaker with a magnetic stirrer. Heat to 65 °C and adjust the pH to 7.4 (using pH paper) with 5 M NaOH. Add distilled water to adjust the final volume to 100 ml. Cool the solution and filter. Store at 4 °C for up to 1 month.

4% (wt/vol) paraformaldehyde solution—Mix 8% paraformaldehyde with 0.2 M phosphate buffer at a ratio of 1:1 before use. Store at 4 °C for up to 1 month.

80% (vol/vol) glycerol—Add 1 ml of distilled water into 4 ml of glycerol and mix well. Store at RT for up to 1 year.

5% (wt/vol) agarose—Add 20 ml of distilled water to a beaker, and add 1 g of agarose. Heat on a heat place until agarose melts. Keep 5% agarose to 60 °C. Agarose (5%) can be stored at 4 °C for up to 1 month. To use the agarose again, heat until it melts and keep it at 60 °C.

EQUIPMENT SETUP

Perfusion device—The perfusion device is assembled with two three-way stopcocks, a 25 gauge butterfly needle and three 10-ml syringes (Fig. 1). First, connect the two three-way stopcocks in series (Fig. 1, inset) and then the 25-gauge butterfly needle to the outflow port of the stopcocks (Fig. 1). Load the three syringes with 2 ml of PBS, DiI solution (5 ml for a mouse, 10 ml for a rat) and 10 ml of fixative (4% paraformaldehyde), respectively. Connect the syringe with fixative to the first inflow port and inject solution until there is no air in the line; turn the stopcock to block the port. Then, connect the DiI syringe to the second inflow port, inject solution until there is no air in the line, and turn the stopcock to block the port. Finally, connect the PBS syringe to the last inflow port and inject solution until there is no air in the line. Assembly is under room lighting. ⁂ CRITICAL Make sure that no air is trapped in the line or the syringes before proceeding to perfusion. Once in the circulation system, air will block blood vessels, resulting in poor perfusion.

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Aluminum boats—Cut a piece of Styrofoam into the shape and size of the samples of interest. Wrap the Styrofoam with a piece of aluminum foil, leaving one side open. Remove the Styrofoam and store the aluminum boats appropriately at RT.

PROCEDURE

Perfusion ● TIMING **~45 min**

▲ CRITICAL All steps are carried out under ambient lighting unless specified.

1¦ Assemble the perfusion device as described in EQUIPMENT SETUP.

? TROUBLESHOOTING

2¦ Kill a mouse or rat by CO_2 overdose in a CO_2 chamber, or by sodium phenobarbital overdose (120 mg kg^{-1}, i.p).

▲ CRITICAL STEP All animal experiments must comply with national laws and institutional regulations.

3¦ In a glass tray with an absorbing blue pat or several paper towels, position the animal on its back. Make a transverse incision to open the abdominal cavity. Expose and cut the diaphragm. Cut the chest wall on both sides up to the first or the second rib.

4¦ Take a small hemostat to hold the lower tip of the sternum and the turn the anterior chest wall toward the head of the animal to expose the chest cavity.

5¦ (Optional) If the tissues of interest are in the upper body, such as the brain or the eye, there is no need to perfuse the lower body. If this is the case, load half amount of the regular perfusion solutions in Step 1 and clamp the descending aorta to block the flow to the lower body before perfusion. This is not necessary for mice.

6¦ Insert the butterfly needle of the perfusion device into the left ventricle and then puncture the right atrium with a 16-gauge needle.

▲ CRITICAL STEP Make sure that the needle is in the left ventricle, which appears lighter than the right ventricle. Do not penetrate the opposite side of the ventricular wall. Such penetration will result in a leak in the left ventricle, making perfusion difficult.

? TROUBLESHOOTING

7¦ Inject 2 ml of PBS from the perfusion device at the rate of 1–2 ml min^{-1} (total 1–2 min). A sign of good perfusion is bleeding from the right atrium. After injection, turn the switch to block the port of PBS syringe and open the port to the DiI syringe.

? TROUBLESHOOTING

8¦ Inject 5–10 ml of the DiI solution at the rate of 1–2 ml min^{-1} (total 5–10 min). Monitor color change in the ears, nose and palms. DiI appears purple in visible light. During perfusion with DiI solution, the ears, nose and palms will turn slightly purple. After injection, turn the switch to block the port of DiI syringe and open the port to the fixative syringe.

9¦ Inject 5–10 ml of the fixative at the rate of 1–2 ml min^{-1} (total 5–10 min).

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10| Harvest tissues of interest. To make eyecup preparation, eyes are enucleated and the anterior segments are removed. The retinas are further dissected from eyecups[1]. Other tissues of interest can be harvested by directly removing them from the body.

PAUSE POINT Samples can be left in the fixative or PBS in the dark for up to 1 month at 4 °C.

CRITICAL STEP Be sure to place the used needles into a sharp container and to dispose of the animal and waste appropriately.

TROUBLESHOOTING

Tissue sectioning TIMING ~1–2 h, depending on the size of the tissue to be sectioned

11| Rinse samples in PBS 2× 15 min.

12| Embed tissue sample in 5% agarose: heat agarose in a 100-ml beaker to 60 °C and pour it (about one-third of the volume required to submerge the sample) into an aluminum boat that fits the sample. Submerge the tissue sample into the agarose and adjust the orientation. Add more agarose into the boat to keep the sample totally submerged. Samples can be kept at 4 °C in the dark up to 1 month when wrapped in plastic wrap to prevent dehydration. Remove the sample block from the aluminum boat before sectioning. Embedding is not necessary for solid tissue such as the brain and the liver.

TROUBLESHOOTING

13| Trim off excess agarose. Glue the sample to the section stage of the Vibratome using Superglue. Secure the section stage in the section chamber and adjust the sample to the appropriate orientation. Fill the sectioning chamber with PBS to submerge the sample.

TROUBLESHOOTING

14| Set the start and the end point of sectioning (for additional information regarding operating the Leica VT1000S Vibratome, please read the manufacturer's manual).

TROUBLESHOOTING

15| Set the thickness of the section to 100 μm (for additional information regarding operating the Leica VT1000S Vibratome, please read the manufacturer's manual).

TROUBLESHOOTING

16| Section the tissue and collect a section with a small (no. 6 or 8) round watercolor brush; put it on a glass slide. One slide may hold several sections.

TROUBLESHOOTING

17| Use a larger watercolor brush to remove excess PBS, add a small amount of 80% glycerol to the sections and cover with no. 1.5 cover slip. Seal it with nail polish.

PAUSE POINT Sections are better viewed as soon as possible but can be kept for several days at 4 °C in the dark.

TROUBLESHOOTING

View sections TIMING Depending largely on the number of the sections and the area of interest to be examined, ~1 h to 1 d

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18| View tissue sections under a fluorescence microscope or a confocal microscope using the filter set for rhodamine.

19| Collect a stack of confocal images. Reconstruction of 3-D images can be achieved using any image analysis software that has such a function. We used AutoVisualize 3-D (version 5.5, AutoQuant Image Inc.) and Leica Application Suite Advanced Fluorescence (LAS AF, TCS-SP5) (Leica).

● TIMING

Steps 1–10: ~45 min

Steps 11–17: ~1–2 h, depending on the size of the tissue to be sectioned

Steps 18 and 19: depending largely on the number of the sections and the area of interest to be examined, ~1 h to 1 d

? TROUBLESHOOTING

Troubleshooting advice can be found in Table 1.

ANTICIPATED RESULTS

Perfusion with DiI solution delivers dye molecules to endothelial cells lining blood vessels in the entire circulation system, thus blood vessels in the whole body are stained. DiI appears purple in color under visible light, so tissues that are well stained should appear slightly purple. Large blood vessels on the surface should be visible. Blood vessels appear intensely red under a fluorescence microscope using a rhodamine filter set (Fig. 2). Stacks of confocal images could be obtained and used to reconstruct 3-D images in hollow organs like the eye (Fig. 3a) and thick tissue samples (Fig. 3b). Because of lateral diffusion, DiI also stains membrane structures that are not in direct contact with the dye solution, including angiogenic sprouts and pseudopodial processes. Images of angiogenic sprouts with their extruding processes (3-D reconstruction) are shown in Figure 3c,d. Thick tissue sections allow efficient screening of the entire tissue of interest at low magnifications for relatively rare events, which can then be studied in detail at high magnifications and/or using an electronic zoom. For example, to study choroidal neovascularization, it is important to find the site where new blood vessels from the choriocapillaris penetrate the Bruch's membrane. In our study on choroidal neovascularization in a subretinal Matrigel model of choroidal neovascularization in the rat[1], we routinely screen the entire Matrigel-injected area (20–25 sections of 100 μm thick) to identify the penetration sites and then to carefully study them. One such site is shown in Figure 4. The combined DiI staining and DIC (differential interference contrast) image shows the site at which a new blood vessel originated in the choriocapillaris penetrated the Bruch's membrane and entered the space between the retinal pigment epithelium and the Bruch's membrane.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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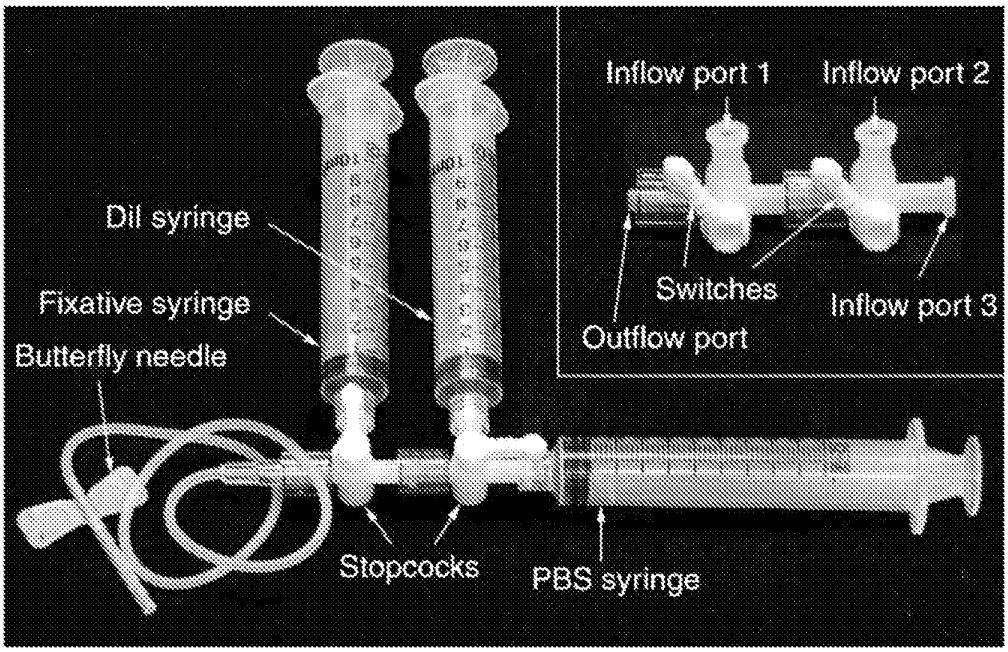


Figure 1.
Perfusion device. The main body of the perfusion device is two three-way stopcocks connected in series (inset). The output port of the stopcocks is connected to a butterfly needle. The inflow ports are connected to three 10-ml disposable syringes for PBS, DiI solution and fixative, respectively. The positions of the three syringes depend on the specific stopcock used, as stopcocks of different brands may have different configurations. It is also possible to use a single stopcock for the device. In that case, it will require change of syringes after perfusion with DiI solution. During syringe change, it is important to avoid air from entering the perfusion line.

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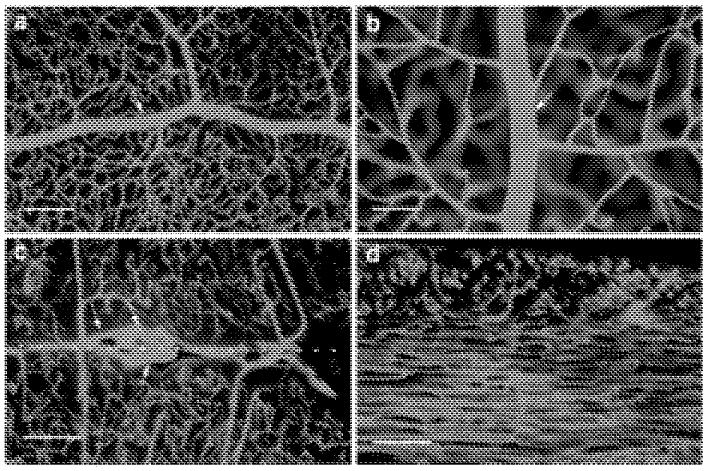


Figure 2.

Vasculature visualized by DiI labeling. (**a**) Retinal whole-mount showing an artery (arrow) on the retinal inner surface along with its branches connecting to the deep capillaries, which are also visible, although out of focus (10 objective lens). (**b**) Retinal whole-mount-showing another artery (arrow) at a higher magnification (×20 objective lens). The nuclei of endothelial cells are identifiable as oval spots in both **a** and **b**. (**c**) A brain section (100 μm thick, ×10 objective lens) showing three large blood vessels (arrows) located in the midline (dashed line) between the two hemispheres and the vascular network in the tissue. (**d**) A heart section (left ventricle, 100 μm thick, ×10 objective lens) showing capillaries in the left ventricle wall. In the outer layer (upper part), they are perpendicular to the section plane and appear as bright dots, whereas in the inner layer (lower part), they are parallel to the section plane. Tissues were viewed by fluorescence microscopy (Nikon Eclipse E800 fluorescence microscope with plan fluo ×10/0.3 numerical aperture (**NA**) or plan fluo ×20/0.5 NA objective lens and Chroma 34,000 rhodamine filter set, with the excitation wavelength of 570 nm and the emission of 590). Scale bars, 200 μm for **a**, **c** and **d**, and 100 μm for **b**.

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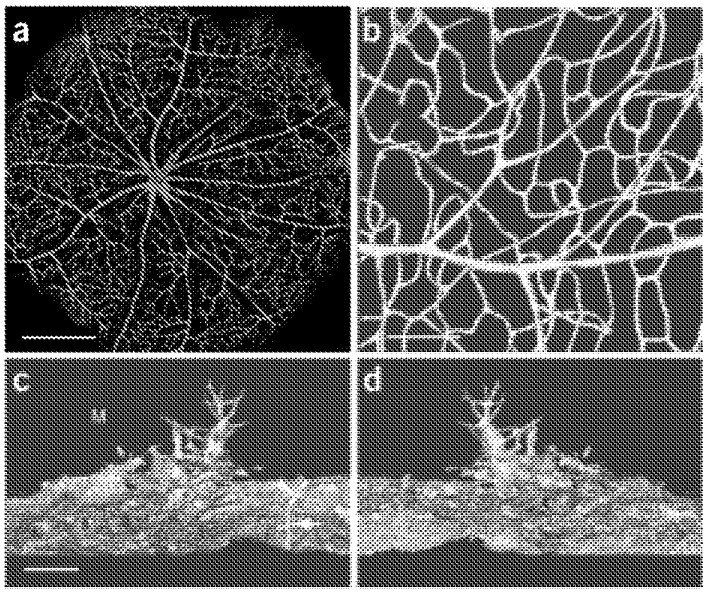


Figure 3.

Three-dimensional reconstructed images of retinal vasculature and angiogenic sprouts and pseudopodial processes. (**a**) A 3-D reconstructed image of the eyecup as a 'bird's eye' view of the vasculature of the posterior retina. The eyecup was placed in a holder and submerged in PBS for direct imaging. A ×5/0.15 NA objective lens was used to take a stack of confocal images, which were used for the reconstruction. DiI signal was detected using Leica DM6000B microscope with the ×5 objective (HC PL Fluotar/0.15) (Leica). Images were acquired by a Leica Application Suite Advanced Fluorescence (LAS AF), 1.7.0, Build 1240 software TCS-SP5 (Leica). The same software was used to create 3-D reconstruction of images and a movie clip, which shows the retinal vasculature rotated around the *x* axis (Supplementary Movie 1). (**b**) A 3-D image showing an artery on the retinal surface connected to the deep capillaries. A movie clip shows the artery and its network rotated around the *y* axis (Supplementary Movie 2). (**c**) A 3-D image of angiogenic sprouts and pseudopodial processes in a subretinal Matrigel of choroidal neovascularization[1] at a viewing angle of 0° (from the coverslip side downward). The vertical line (arrow) indicates the cross section of the choroid. Another line (arrowhead) indicates the surface of the choroicapillaris. Several sprouts from the choriocapillaris invaded the Matrigel layer (M) in the subretinal space. Their pseudopodial processes protruded into the Matrigel deposit (M) in different directions. (**d**) 3-D image of angiogenic sprouts and pseudopodial processes at a viewing angle of 180°. A movie clip shows the sprouts rotated around the *y* axis (Supplementary Movie 3). Scale bar, 400 μm for **a**, 100 μm for **b** and 20 μm for **c** and **d**.

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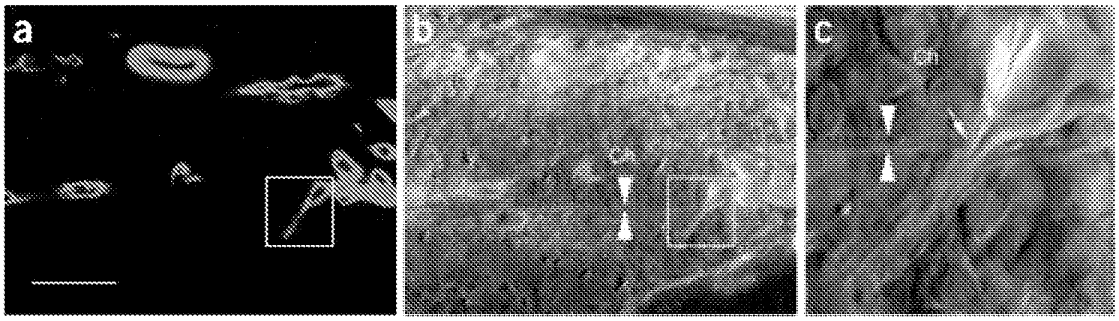


Figure 4.

Penetration of Bruch's membrane by choroidal neovascularization. Choroidal neovascularization was induced by subretinal injection of Matrigel[1]. To locate the penetration sites of choroidal neovascularization, serial tissue sections (100 μm thick each) were cut through the entire Matrigel injected area (about 2 mm in diameter). Tissue sections were screened at low power (×10 objective) under a fluorescence microscope. Potential penetration sites were further examined by confocal microscopy. (**a**) A confocal image of a new blood vessel that had penetrated the Bruch's membrane (square). (**b**) A superimposed image of DIC (differential interference contrast) and fluorescence (red) shows the penetrating blood vessel (square) relative to Bruch's membrane (between two arrowheads). (**c**) The penetration site (arrow) at higher magnification to show Bruch's membrane (between two arrowheads). Ch, choroid. Scale bar, 50 μm for **a** and **b**; 7 μm for **c** .

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TABLE 1

Troubleshooting table

Problem	Possible reason	Possible solution
Weak signal	Poor perfusion due to air trapped in the system (Steps 1 and 6)	Make sure no air is trapped in the perfusion line before perfusion. When inserting the needle into the left ventricle, slightly press the PBS syringe to allow a fluid drop to appear at the needle tip
	Poor perfusion because of a leak in the left ventricle (Step 6)	Do not penetrate the opposite side of the ventricle when inserting the butterfly needle. Using a small hemostat to clamp the leaking point sometimes works
	Poor staining because of too much PBS perfusion (Step 7)	Make sure not more than 2 ml of PBS is used before DiI perfusion
'Leak' staining	The inner lining of blood vessels are broken because of rough handling of tissue preparation and sectioning (Steps 10, 12–17)	DiI will not 'leak' to the surrounding tissues if blood vessels are intact. Be gentle during tissue harvesting. View tissue sections as soon as possible

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FLUID CONTROL DEVICES AND METHODS OF USING THE SAME

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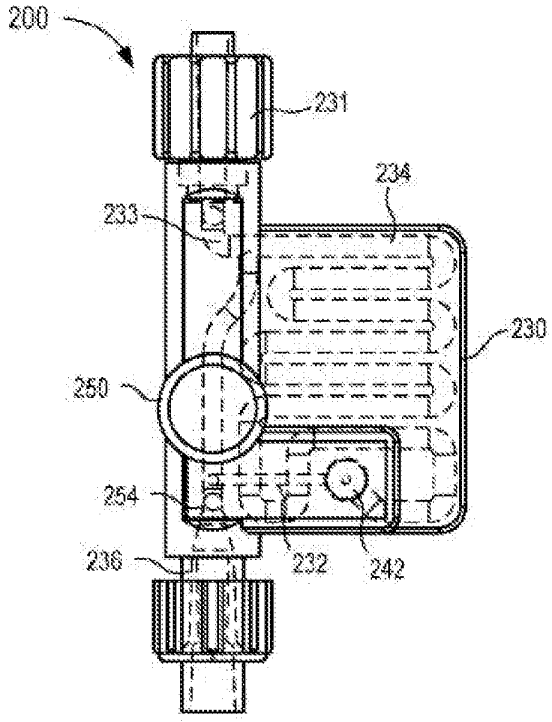
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Abstract of WO2019055487 (A1)

A fluid control device includes an inlet configured to be placed directly or indirectly in fluid communication with a bodily fluid source and an outlet configured to be placed in fluid communication with a fluid collection device. The fluid control device has a first state in which a negative pressure differential produced from an external source such as the fluid collection device is applied to the fluid control device to draw an initial volume of bodily fluid from the bodily fluid source, through the inlet, and into a sequestration portion of the fluid control device. The fluid control device has a second state in which (1) the sequestration portion sequesters the initial volume, and (2) the negative pressure differential draws a subsequent volume of bodily fluid, being substantially free of contaminants, from the bodily fluid source, through the fluid control device, and into the fluid collection device.


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(54) Title: FLUID CONTROL DEVICES AND METHODS OF USING THE SAME

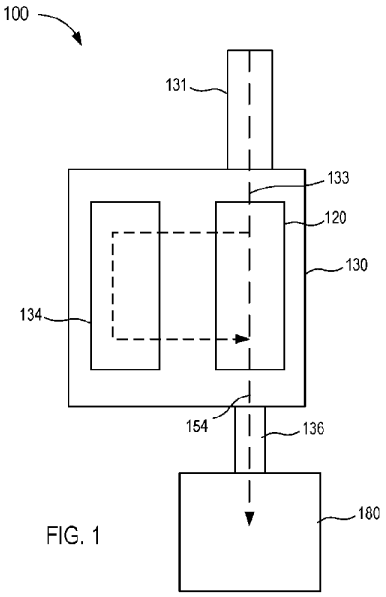


FIG. 1

(57) Abstract: A fluid control device includes an inlet configured to be placed directly or indirectly in fluid communication with a bodily fluid source and an outlet configured to be placed in fluid communication with a fluid collection device. The fluid control device has a first state in which a negative pressure differential produced from an external source such as the fluid collection device is applied to the fluid control device to draw an initial volume of bodily fluid from the bodily fluid source, through the inlet, and into a sequestration portion of the fluid control device. The fluid control device has a second state in which (1) the sequestration portion sequesters the initial volume, and (2) the negative pressure differential draws a subsequent volume of bodily fluid, being substantially free of contaminants, from the bodily fluid source, through the fluid control device, and into the fluid collection device.

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FLUID CONTROL DEVICES AND METHODS OF USING THE SAME

Cross-Reference to Related Applications

[1001] This application claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 62/557,530 entitled, "Fluid Control Devices and Methods of Using the Same," filed September 12, 2017, the disclosure of which is incorporated herein by reference in its entirety.

[1002] This application also claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 62/634,569 entitled, "Fluid Control Devices and Methods of Using the Same," filed February 23, 2018, the disclosure of which is incorporated herein by reference in its entirety.

[1003] This application also claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 62/678,632 entitled, "Fluid Control Devices and Methods of Using the Same," filed May 31, 2018, the disclosure of which is incorporated herein by reference in its entirety.

Background

[1004] The invention relates generally to the parenteral procurement of bodily fluid samples, and more particularly to fluid diversion, sequestration, and/or isolation devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source.

[1005] Health care practitioners routinely perform various types of microbial as well as other broad diagnostic tests on patients using parenterally obtained bodily fluids. As advanced diagnostic technologies evolve and improve, the speed, accuracy (both sensitivity and specificity), and value of information that can be provided to clinicians continues to improve. Maintaining the integrity of the bodily fluid sample during and/or after collection also ensures that analytical diagnostic results are representative of the in vivo conditions of a patient. Examples of diagnostic technologies that are reliant on high quality, non-contaminated, and/or unadulterated bodily fluid samples include but are not limited to microbial detection, molecular diagnostics, genetic sequencing (e.g., deoxyribonucleic acid (DNA), ribonucleic acid (RNA), next-generation sequencing (NGS), etc.), biomarker identification, and the like. When biological matter, which can include cells external to the intended source for sample procurement, and/or other external contaminants are inadvertently included in the bodily fluid

sample that is to be analyzed, there is an opportunity for inaccurate test results to be derived. In short, when the purity of the sample intended to be derived or collected from a specific bodily fluid source is compromised during the specimen procurement process, resultant analytical test results may be inaccurate, distorted, adulterated, falsely positive, falsely negative, and/or otherwise not representative of the actual condition of the patient, which in turn, can inform faulty, inaccurate, confused, unsure, low-confidence, and/or otherwise undesired clinical decision making.

[1006] In some instances, patient samples (e.g., bodily fluids) are tested for the presence of one or more potentially undesirable microbes, such as bacteria, fungi, or yeast (e.g., Candida). In some instances, microbial testing may include incubating patient samples in one or more sterile and/or non-sterile vessels that may contain culture media, common additives, and/or other types of solutions that are conducive to microbial growth. In other instances, the sample in the vessel may be analyzed directly (i.e., not incubated) and may not contain culture media or additives associated with incubating the specimen. In still other instances, various technologies can be employed to assist in the detection of the presence of microbes as well as other types of biological matter, specific types of cells, biomarkers, proteins, antigens, enzymes, blood components, and/or the like during diagnostic testing. Examples include but are not limited to molecular polymerase chain reaction (PCR), magnetic resonance and other magnetic analytical platforms, automated microscopy, spatial clone isolation, flow cytometry, whole blood ("culture free") specimen analysis (e.g. NGS) and associated technologies, morphokinetic cellular analysis, and/or other common or evolving and advanced technologies utilized in the clinical laboratory environment to characterize patient specimens and/or to detect, identify, type, categorize, and/or characterize specific organisms, antibiotic susceptibilities, and/or the like.

[1007] In some instances, the detection of the presence of microbes includes allowing the microbes and/or organisms to grow for an amount of time (e.g., a variable amount of time from less than an hour to a few hours to several days – which can be longer or shorter depending on the diagnostic technology employed). The microbe and/or organism growth can then be detected by automated, continuous monitoring, and/or other methods specific to the analytical platform and technology used for detection, identification, and/or the like.

[1008] In culture testing, for example, when microbes are present in the patient sample, the microbes flourish over time in the culture medium and, in some instances, automated monitoring technologies can detect carbon dioxide produced by organism growth. The presence of microbes in the culture medium (as indicated by observation of carbon dioxide

and/or via other detection methods) suggests the presence of the same microbes in the patient sample which, in turn, suggests the presence of the same microbes in the bodily fluid of the patient from whom the sample was obtained. Accordingly, when microbes are determined to be present in the culture medium (or more generally in the sample used for testing), the patient may be diagnosed and prescribed one or more antibiotics or other treatments specifically designed to treat or otherwise remove the undesired microbes from the patient.

[1009] Patient samples, however, can become contaminated during procurement and/or otherwise can be susceptible to false positive or false negative results. For example, microbes from a bodily surface (e.g., dermally residing microbes) that are dislodged during the specimen procurement process (which can include needle insertion into a patient, specimen procurement via a lumen-containing device such as a peripheral IV catheter (PIV), a central line (PICC) and/or other indwelling catheter(s), collection with a syringe or any other suitable means employed to collect a patient specimen), either directly or indirectly via tissue fragments, hair follicles, sweat glands, and other skin adnexal structures, can be subsequently transferred to a culture medium, test vial, or other suitable specimen collection or transfer vessel with the patient sample and/or included in the specimen that is to be analyzed for non-culture based testing. Another possible source of contamination is from the person drawing the patient sample (e.g., a doctor, phlebotomist, nurse, technician, etc.). Specifically, equipment, supplies, and/or devices used during a patient sample procurement process often include multiple fluidic interfaces (by way of example, but not limited to, patient to needle, needle to transfer adapter, transfer adapter to sample vessel, catheter hub to syringe, syringe to transfer adapter, needle/tubing to sample vessels, and/or any other fluidic interface or any combination thereof) that can each introduce points of potential contamination. In some instances, such contaminants may thrive in a culture medium and/or may be identified by another non-culture based diagnostic technology and eventually may yield a false positive and/or a false negative microbial test result, which may inaccurately reflect the presence or lack of such microbes within the patient (i.e., in vivo).

[1010] Such inaccurate results because of contamination and/or other sources of adulteration that compromise the purity of the sample are a concern when attempting to diagnose or treat a wide range of suspected illnesses, diseases, infections, patient conditions or other maladies of concern. For example, false negative results from microbial tests may result in a misdiagnosis and/or delayed treatment of a patient illness, which, in some cases, could result in the death of the patient. Conversely, false positive results from microbial tests may result in the patient being unnecessarily subjected to one or more anti-microbial therapies,

which may cause serious side effects to the patient including, for example, death, as well as produce an unnecessary burden and expense to the health care system due to extended length of patient stay and/or other complications associated with erroneous treatments. The use of diagnostic imaging equipment attributable to these false positive results is also a concern from both a cost as well as patient safety perspective as unnecessary exposure to concentrated radiation associated with a variety of imaging procedures (e.g., CT scans) has many known adverse impacts on long-term patient health.

[1011] In some instances, devices and/or systems can be used to reduce the likelihood of contamination, adulteration, and/or the like of bodily fluid samples for testing. For example, some known devices can be configured to collect, divert, separate, and/or isolate or sequester an initial volume of bodily fluid that may be more likely to contain contaminants such as dermally residing microbes or the like. Some such devices, however, can be cumbersome, non-intuitive, perceived as difficult to use, inappropriate or unusable as intended for the target patient population, etc. In addition, some such devices can require training, user observation, intervention by more than one user, and/or can otherwise present challenges that can lead to limited efficacy based on variables including environmental, educational, clinician skill, patient condition, and/or the like. In some instances, such challenges can complicate the collection of consistently high quality samples that are non-contaminated, sterile, unadulterated, etc., which in turn, can impact the validity of test result outcomes.

[1012] On the other hand, some known passive diversion devices and/or systems (e.g., systems that do not specifically utilize or rely on direct user intervention, interaction, manipulation, and/or the like) may fail to adequately divert, sequester, and/or isolate a clinically desired and efficacious pre-sample volume of bodily fluid due to clinical realities such as, for example, the time required to fill a sequestration reservoir with a meaningful volume of fluid. In some instances, the operation of some known passive devices is dependent on a positive pressure applied by a bodily fluid source (e.g., a patient's blood pressure). The positive pressure applied by the bodily fluid source, however, may be insufficient to result in flow dynamics and/or flow rates that makes use of such devices practical in various clinical settings (including emergency rooms and other intensive settings). For example, the patient population with symptoms requiring diagnostic testing noted above commonly are in such physical condition that attaining vascular access and/or collection of bodily fluid samples can be difficult due to a hypotensive state (i.e., low blood pressure), hypovolemic state (i.e., low blood volume), and/or other physical challenges (e.g., severe dehydration, obesity, difficult and/or inaccessible vasculature, etc.). Such states or physical conditions can result in difficulty

in providing sufficient blood flow and/or pressure to achieve passive filling of a sequestration chamber, channel, reservoir, container (or other diversion volume) consistently with sufficient volume to meet clinically validated, evidence-based efficacy and results in diverting, sequestering, and/or isolating contaminants which otherwise can lead to distorted, inaccurate, falsely positive, falsely negative, and/or otherwise adulterated diagnostic test results. The challenges associated with this approach (e.g., relying on a positive pressure differential applied by the bodily fluid source without utilizing a specific external energy source and/or negative pressure to facilitate collection of an appropriate and clinically efficacious initial volume of bodily fluid) can render it impractical as failure rates can be unacceptably high for the fragile patient population from whom these samples are collected.

[1013] As such, a need exists for fluid diversion devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source that result in consistent bodily fluid collection (e.g., from a general patient population and/or a challenging patient population). Some such devices and methods can include, for example, bodily fluid collection with the assistance of various sources of external energy and/or negative pressure. Furthermore, a need exists for such devices that are user-friendly, demonstrate consistent efficacy, and address the challenges associated with collecting samples from patients with challenging health circumstances and/or physical characteristics that impact the ability to collect bodily fluid samples.

Summary

[1014] Devices and methods for procuring bodily fluid samples with reduced contaminants such as dermally residing microbes and/or other contaminants exterior to the bodily fluid source are described herein. In some embodiments, a system includes a housing, a flow controller, and a fluid collection device. The housing has an inlet and an outlet, and forms a sequestration portion. The inlet is configured to be placed in fluid communication with a bodily fluid source. The sequestration portion is configured to receive an initial volume of bodily fluid from the bodily fluid source. The flow controller is at least partially disposed in the sequestration portion of the housing and is configured to transition from a first state to a second state. The fluid collection device is configured to be fluidically coupled to the outlet to produce a negative pressure differential within at least a portion of the housing. The negative pressure differential is operable to draw the initial volume of bodily fluid into the sequestration portion when the flow controller is in the first state and is operable to draw the sample volume of bodily

fluid through the outlet and into the fluid collection device when the flow controller is in the second state.

Brief Description of the Drawings

[1015] FIG. 1 is a schematic illustration of a fluid control device according to an embodiment.

[1016] FIGS. 2-5 are various views of a fluid control device according to an embodiment.

[1017] FIGS. 6-8 are various views of a fluid control device according to an embodiment.

[1018] FIGS. 9 and 10 are front view illustrations of a fluid control device in a first operating mode and a second operating mode, respectively, according to an embodiment.

[1019] FIGS. 11 and 12 are front view illustrations of a fluid control device in a first operating mode and a second operating mode, respectively, according to an embodiment.

[1020] FIGS. 13-15B are various views of a fluid control device according to an embodiment.

[1021] FIGS. 16-18 are various views of a fluid control device according to an embodiment.

[1022] FIGS. 19-25 are various views of a fluid control device according to an embodiment.

[1023] FIGS. 26-28 are each a perspective view of a fluid control device according to different embodiments.

[1024] FIGS. 29-34 are various views of a fluid control device according to an embodiment.

[1025] FIGS. 35-40 are various views of a fluid control device according to an embodiment.

[1026] FIGS. 41-44 are various views of a fluid control device according to an embodiment.

[1027] FIGS. 45-50 are various views of a fluid control device according to an embodiment.

[1028] FIGS. 51 and 52 are cross-sectional views of a fluid control device according to an embodiment.

[1029] FIG. 53 is a flowchart illustrating a method of using a fluid control device according to an embodiment.

Detailed Description

[1030] Devices and methods for collecting, diverting, sequestering, isolating, etc. an initial volume of bodily fluid to reduce contamination in subsequently procured bodily fluid samples are described herein. Any of the fluid control devices described herein can be configured to receive, procure, and/or transfer a flow, bolus, volume, etc., of bodily fluid. A first reservoir, channel, flow path, or portion of the device can receive an initial amount of the bodily fluid flow, which then can be substantially or fully sequestered (e.g., contained or retained, circumvented, isolated, segregated, vapor-locked, separated, and/or the like) in or by the first reservoir or first portion of the device. In some instances, contaminants such as dermally residing microbes or the like can be included and/or entrained in the initial amount of the bodily fluid and likewise are sequestered in or by the first reservoir or first portion of the device. Once the initial amount is sequestered, any subsequent amount of the bodily fluid flow can be diverted, channeled, directed, flow controlled (e.g., manually, automatically, and/or semi-automatically) to a second reservoir, second portion of the device, and/or any additional flow path(s). Thus, with the initial amount sequestered, any additional and/or subsequent amount(s) of bodily fluid flow are substantially free from contaminants that may otherwise produce inaccurate, distorted, adulterated, falsely positive, falsely negative, etc., results in some diagnostics and/or testing. In some instances, the initial amount of bodily fluid also can be used, for example, in other testing such as those less affected by the presence of contaminants, can be discarded as a waste volume, can be infused back into the patient, and/or can be used for any other suitable clinical application.

[1031] In some embodiments, a feature of the fluid control devices and/or methods described herein is the use of an external negative pressure source (e.g., provided by a fluid collection device or any other suitable means) to (1) overcome physical patient challenges which can limit and/or prevent a sufficient pressure differential (e.g., a differential in blood pressure to ambient air pressure) to fully engage the sequestration chamber and/or to transition fluid flow to the fluid collection device; (2) result in proper filling of the sequestration chamber with a clinically validated and/or desirable volume of bodily fluid; (3) result in efficient, timely, and/or user-accepted consistency with bodily fluid collection process; and/or (4) provide a means of manipulating and/or automatically transitioning fluid flow (e.g., movement of physical components of the system or changing, switching, engaging, and/or otherwise employing or achieving desired fluid flow dynamics) to enable sequestration and/or isolation of the initial sample and collection of a subsequent sample.

[1032] In some embodiments, a fluid control device includes an inlet and an outlet. The inlet is configured to be placed in fluid communication with a bodily fluid source or an intermediary bodily fluid transfer device and the outlet is configured to be placed in fluid communication with a fluid collection device such as, for example, a sample reservoir, a syringe, a lumen-containing device, and/or any other suitable bodily fluid collection and/or transfer device. The fluid control device has a first state in which a negative pressure differential produced from an external source (e.g., the fluid collection device such as a sample reservoir, a syringe, a vessel, and/or any suitable intermediary fluid reservoir) is applied to the fluid control device to draw an initial volume of bodily fluid from the bodily fluid source, through the inlet, and into a sequestration and/or diversion portion of the fluid control device (which can be formed by or in the fluid control device or coupled thereto). The fluid control device has a second state in which (1) the sequestration chamber sequesters the initial volume, and (2) the negative pressure differential draws a subsequent volume of bodily fluid, being substantially free of contaminants, from the bodily fluid source, through the fluid control device, and into the fluid collection device.

[1033] In some embodiments, a system includes a housing, a flow controller, and a fluid collection device. The housing has an inlet and an outlet, and forms a sequestration portion. The inlet is configured to be placed in fluid communication with a bodily fluid source. The sequestration portion is configured to receive an initial volume of bodily fluid from the bodily fluid source. The flow controller is at least partially disposed in the sequestration portion of the housing and is configured to transition from a first state to a second state. The fluid collection device is configured to be fluidically coupled to the outlet to produce a negative pressure differential within at least a portion of the housing. The negative pressure differential is operable to draw the initial volume of bodily fluid into the sequestration portion when the flow controller is in the first state and is operable to draw the sample volume of bodily fluid through the outlet and into the fluid collection device when the flow controller is in the second state.

[1034] In some embodiments, an apparatus includes a housing and an actuator coupled to the housing. The housing has an inlet configured to be placed in fluid communication with a bodily fluid source and an outlet configured be placed in fluid communication with a fluid collection device. The housing forms a sequestration portion that is configured to receive an initial volume of bodily fluid from the bodily fluid source. The actuator has a first configuration in which a first fluid flow path places the inlet in fluid communication with the sequestration portion and a second configuration in which a second fluid flow path places the

inlet in fluid communication with the outlet. The fluid collection device is configured to be placed in fluid communication with the outlet to produce a negative pressure differential (1) within the first fluid flow path that is operable to draw the initial volume of bodily fluid into the sequestration portion when the actuator is in the first configuration, and (2) within the second fluid flow path that is operable to draw a sample volume of bodily fluid into the fluid collection device when the actuator is in the second configuration.

[1035] In some embodiments, a method of using a fluid control device to obtain a bodily fluid sample with reduced contamination includes establishing fluid communication between a bodily fluid source and an inlet of the fluid control device. A fluid collection device is coupled to an outlet of the fluid control device and is configured to produce a negative pressure differential within at least a portion of the fluid control device. An initial volume of bodily fluid is received from the inlet and into a sequestration portion of the fluid control device in response to the negative pressure differential. In response to contact with a portion of the initial volume of bodily fluid, a flow controller disposed in the sequestration portion is transitioned from a first state in which the flow controller allows a flow of a gas through the flow controller and prevents a flow of bodily fluid through the flow controller, to a second state in which the flow controller prevents a flow of gas and bodily fluid through the flow controller. The initial volume of bodily fluid is sequestered in the sequestration portion after the flow controller is transitioned to the second state and a subsequent volume of bodily fluid is transferred from the inlet to an outlet in fluid communication with a fluid collection device.

[1036] As used in this specification and the claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, the term "a member" is intended to mean a single member or a combination of members, "a material" is intended to mean one or more materials, or a combination thereof.

[1037] As used herein, the terms "about," "approximate," and/or "substantially" when used in connection with stated value and/or other geometric relationships is intended to convey that the structure so defined is nominally the value stated and/or the geometric relationship described. In some instances, the terms "about," "approximately," and/or "substantially" can generally mean and/or can generally contemplate plus or minus 10% of the value or relationship stated. For example, about 0.01 would include 0.009 and 0.011, about 0.5 would include 0.45 and 0.55, about 10 would include 9 to 11, and about 1000 would include 900 to 1100. While a value stated may be desirable, it should be understood that some variance may occur as a result of, for example, manufacturing tolerances or other practical considerations (such as, for example, the pressure or force applied through a portion of a device, conduit,

lumen, etc.). Accordingly, the terms "about," "approximately," and/or "substantially" can be used herein to account for such tolerances and/or considerations.

[1038] As used herein, "bodily fluid" can include any fluid obtained directly or indirectly from a body of a patient. For example, "bodily fluid" includes, but is not limited to, blood, cerebrospinal fluid, urine, bile, lymph, saliva, synovial fluid, serous fluid, pleural fluid, amniotic fluid, mucus, sputum, vitreous, air, and the like, or any combination thereof.

[1039] As used herein, the words "proximal" and "distal" refer to the direction closer to and away from, respectively, a user who would place the device into contact with a patient. Thus, for example, the end of a device first touching the body of the patient would be the distal end, while the opposite end of the device (e.g., the end of the device being manipulated by the user) would be the proximal end of the device.

[1040] As described in further detail herein, any of the devices and methods can be used to procure bodily fluid samples with reduced contamination by, for example, diverting a "pre-sample" volume of bodily fluid prior to collecting a "sample" volume of bodily fluid. Each of the terms "pre-sample," "first," and/or "initial," can be used interchangeably to describe and/or refer to an amount, portion, or volume of bodily fluid that is transferred, diverted, and/or sequestered prior to procuring the "sample" volume. In some embodiments, the terms "pre-sample," "first," and/or "initial" can refer to a predetermined, defined, desired, or given volume, portion, or amount of bodily fluid. For example, in some embodiments, a predetermined and/or desired pre-sample volume of bodily fluid can be about 0.1 milliliter (mL), about 0.2 mL, about 0.3 mL, about 0.4 mL, about 0.5 mL, about 1.0 mL, about 2.0 mL, about 3.0 mL, about 4.0 mL, about 5.0 mL, about 10.0 mL, about 20 mL, about 50 mL, and/or any volume or fraction of a volume therebetween. In other embodiments, the pre-sample volume can be greater than 50 mL or less than 0.1 mL. In some specific embodiments, a predetermined and/or desired pre-sample volume can be between about 0.1 mL and about 5.0 mL. In other embodiments, the pre-sample volume can be, for example, a drop of bodily fluid, a few drops of bodily fluid, a combined volume of any number of lumen that form, for example, a flow path (or portion thereof) from the bodily fluid source to an initial collection chamber, portion, reservoir, etc. (e.g., a sequestration chamber).

[1041] On the other hand, the terms "sample," "second," and/or "subsequent" when used in the context of a volume of bodily fluid can refer to a volume, portion, or amount of bodily fluid that is either a random volume or a predetermined or desired volume of bodily fluid collected after transferring, diverting, sequestering, and/or isolating the pre-sample volume of bodily fluid. For example, in some embodiments, a desired sample volume of bodily fluid can

be about 10 mL to about 60 mL. In other embodiments, a desired sample volume of bodily fluid can be less than 10 mL or greater than 60 mL. In some embodiments, for example, a sample volume can be at least partially based on one or more tests, assays, analyses, and/or processes to be performed on the sample volume.

[1042] The embodiments described herein can be configured to selectively transfer bodily fluid to one or more fluid collection device(s). In some embodiments, a fluid collection device can include, but is not limited to, any suitable vessel, container, reservoir, bottle, adapter, dish, vial, syringe, device, diagnostic and/or testing machine, and/or the like. By way of specific example, in some instances, any of the embodiments and/or methods described herein can be used to transfer a sample volume into a sample reservoir such as any of those described in detail in U.S. Patent No. 8,197,420 entitled, "Systems and Methods for Parenterally Procuring Bodily-Fluid Samples with Reduced Contamination," filed December 13, 2007 ("the '420 Patent"), the disclosure of which is incorporated herein by reference in its entirety.

[1043] In some embodiments, a sample reservoir can be a sample or culture bottle such as, for example, an aerobic culture bottle or an anaerobic culture bottle. In this manner, the culture bottle can receive a bodily fluid sample, which can then be tested (e.g., via in vitro diagnostic (IVD) tests, and/or any other suitable test) for the presence of, for example, Gram-Positive bacteria, Gram-Negative bacteria, yeast, fungi, and/or any other organism. In some instances, the culture bottle can receive a bodily fluid sample and the culture medium (disposed therein) can be tested for the presence of any suitable organism. If such a test of the culture medium yields a positive result, the culture medium can be subsequently tested using a PCR-based system to identify a specific organism. Moreover, as described in further detail herein, in some instances, diverting a pre-sample or initial volume of bodily fluid can reduce and/or substantially eliminate contaminants in the bodily fluid sample that may otherwise lead to inaccurate test results.

[1044] Any of the sample containers, reservoirs, bottles, dishes, vials, etc., described herein can be devoid of contents prior to receiving a sample volume of bodily fluid or can include, for example, any suitable additive, culture medium, substances, enzymes, oils, fluids, and/or the like. For example, in some embodiments, a sample reservoir can include an aerobic or anaerobic culture medium (e.g., a nutrient rich and/or environmentally controlled medium to promote growth, and/or other suitable medium(s)), which occupies at least a portion of the inner volume defined by the sample reservoir. In some embodiments, a sample reservoir can include, for example, any suitable additive or the like such as, heparin, citrate, ethylenediaminetetraacetic acid (EDTA), oxalate, SPS, and/or the like, which similarly

occupies at least a portion of the inner volume defined by the sample reservoir. In other embodiments, a sample reservoir can be any suitable container used to collect a specimen.

[1045] While the term "culture medium" can be used to describe a substance configured to react with organisms in a bodily fluid (e.g., microorganisms such as bacteria) and the term "additive" can be used to describe a substance configured to react with portions of the bodily fluid (e.g., constituent cells of blood, serum, synovial fluid, etc.), it should be understood that a sample reservoir can include any suitable substance, liquid, solid, powder, lyophilized compound, gas, etc. Moreover, when referring to an "additive" within a sample reservoir, it should be understood that the additive could be a culture medium, such as an aerobic culture medium and/or an anaerobic culture medium contained in a culture bottle, an additive and/or any other suitable substance or combination of substances contained in a culture bottle and/or any other suitable reservoir such as those described above. That is to say, the embodiments described herein can be used with any suitable fluid reservoir or the like containing any suitable substance. Furthermore, any of the embodiments and/or methods described herein can be used to transfer a volume of bodily fluid to a reservoir (or the like) that does not contain a culture medium, additive, and/or any other substance prior to receiving a flow of bodily fluid.

[1046] While some of the embodiments are described herein as being used for procuring bodily fluid for one or more culture sample testing, it should be understood that the embodiments are not limited to such a use. Any of the embodiments and/or methods described herein can be used to transfer a flow of bodily fluid to any suitable device that is placed in fluid communication therewith. Thus, while specific examples are described herein, the devices, methods, and/or concepts are not intended to be limited to such specific examples.

[1047] The embodiments described herein and/or portions thereof can be formed or constructed of one or more biocompatible materials. In some embodiments, the biocompatible materials can be selected based on one or more properties of the constituent material such as, for example, stiffness, toughness, durometer, bioreactivity, etc. Examples of suitable biocompatible materials include metals, glasses, ceramics, or polymers. Examples of suitable metals include pharmaceutical grade stainless steel, gold, titanium, nickel, iron, platinum, tin, chromium, copper, and/or alloys thereof. A polymer material may be biodegradable or non-biodegradable. Examples of suitable biodegradable polymers include polylactides, polyglycolides, polylactide-co-glycolides (PLGA), polyanhydrides, polyorthoesters, polyetheresters, polycaprolactones, polyesteramides, poly(butyric acid), poly(valeric acid), polyurethanes, and/or blends and copolymers thereof. Examples of non-biodegradable polymers include nylons, polyesters, polycarbonates, polyacrylates, polymers of ethylene-vinyl

acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, and/or blends and copolymers thereof.

[1048] The embodiments described herein and/or portions thereof can include components formed of one or more parts, features, structures, etc. When referring to such components it should be understood that the components can be formed by a singular part having any number of sections, regions, portions, and/or characteristics, or can be formed by multiple parts or features. For example, when referring to a structure such as a wall or chamber, the structure can be considered as a single structure with multiple portions, or multiple, distinct substructures or the like coupled to form the structure. Thus, a monolithically constructed structure can include, for example, a set of substructures. Such a set of substructures may include multiple portions that are either continuous or discontinuous from each other. A set of substructures can also be fabricated from multiple items or components that are produced separately and are later joined together (e.g., via a weld, an adhesive, or any suitable method).

[1049] Referring now to the drawings, FIG. 1 is a schematic illustration of a fluid control device 100 according to an embodiment. Generally, the fluid control device 100 (also referred to herein as "control device" or "device") is configured to withdraw bodily fluid from a patient. A first portion or amount (e.g., an initial amount) of the withdrawn bodily fluid is sequestered from a second portion or amount (e.g., a subsequent amount) of the withdrawn bodily fluid which can be subsequently used for additional testing, discarded, and/or reinfused into the patient. In this manner, contaminants or the like can be sequestered within the first portion or amount, leaving the second portion or amount substantially free of contaminants. The second portion or amount of bodily fluid can then be used as a biological sample in one or more tests for the purpose of medical diagnosis and/or treatment (e.g., a blood culture test or the like), as described in more detail herein. The first portion or amount of bodily fluid can be discarded as waste or can be used in any suitable test that is less likely to produce false, inaccurate, distorted, inconsistent, and unreliable results as a result of potential contaminants contained therein. In other instances, the first portion or amount of bodily fluid can be infused back into the patient.

[1050] The control device 100 includes a housing 130 that has and/or forms an inlet 131, at least one outlet 136, and a sequestration chamber 134. The inlet 131 is configured to fluidically couple to a lumen-containing device, which in turn, can place the housing 130 in fluid communication with a bodily fluid source. For example, the housing 130 can be coupled to and/or can include a lumen-containing device that is in fluid communication with the inlet

131 and that is configured to be percutaneously disposed in a patient (e.g., a butterfly needle, intravenous (IV) catheter, peripherally inserted central catheter (PICC), syringe, sterile tubing, intermediary lumen-containing device, and/or bodily-fluid transfer device or the like). Thus, bodily fluid can be transferred from the patient and/or other bodily fluid source to the housing 130 via the inlet 131, as described in further detail herein. The outlet(s) 136 can be placed in fluid communication with a fluid collection device 180 (e.g., a fluid or sample reservoir, syringe, evacuated container, etc.). As such, the control device 100 can be used and/or manipulated to selectively transfer a volume of bodily fluid from a bodily fluid source, through the inlet 131, the housing 130, and the outlet(s) 136 to the fluid collection device 180, as described in further detail herein.

[1051] The housing 130 defines one or more fluid flow paths 133 between the inlet 131 and the sequestration chamber 134 and/or one or more fluid flow paths 154 between the inlet 131 and the outlet 136. The housing 130 of the device 100 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the housing 130 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 134. As described in further detail herein, the control device 100 and/or the housing 130 can be configured to transition between operating modes such that bodily fluid flows through at least one of the fluid flow paths 133 and/or 154. Moreover, the control device 100 and/or the housing 130 can be configured to transition automatically (e.g., based on pressure differential, time, electronically, saturation of a membrane, an absorbent and/or barrier material, etc.) or via intervention (e.g., user intervention, mechanical intervention, or the like).

[1052] The sequestration chamber 134 is at least temporarily placed in fluid communication with the inlet 131 via the fluid flow path(s) 133. As described in further detail herein, the sequestration chamber 134 is configured to (1) receive a flow and/or volume of bodily fluid from the inlet 131 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein. The sequestration chamber 134 can have any suitable arrangement such as, for example, those described herein with respect to specific embodiments. It should be understood, however, that the control device 100 and/or the housing 130 can have a sequestration chamber 134 in any suitable arrangement and is not intended to be limited to those shown and described herein. For example, in some embodiments, the sequestration chamber 134 can be at least partially formed by the housing 130. In other embodiments, the sequestration chamber 134 can be a reservoir placed and/or disposed within a portion of the housing 130. In other embodiments, the sequestration chamber

134 can be formed and/or defined by a portion of the fluid flow path 133. That is to say, the housing 130 can define one or more lumens and/or can include one or more lumen defining device(s) configured to receive a flow of bodily fluid from the inlet 131, thereby defining the fluid flow path 133. In such embodiments, at least a portion of the lumen and/or a portion of the lumen defining device(s) can form and/or can define the sequestration chamber 134.

[1053] The sequestration chamber 134 can have any suitable volume and/or fluid capacity. For example, in some embodiments, the sequestration chamber 134 can have a volume and/or fluid capacity between about 0.25 mL and about 5.0 mL. In some embodiments, the sequestration chamber 134 can have a volume measured in terms of an amount of bodily fluid (e.g., the initial or first amount of bodily fluid) configured to be transferred in the sequestration chamber 134. For example, in some embodiments, the sequestration chamber 134 can have a volume sufficient to receive an initial volume of bodily fluid as small as a microliter or less of bodily fluid (e.g., a volume as small as 20 drops of bodily fluid, 10 drops of bodily fluid, 5 drops of bodily fluid, a single drop of bodily fluid, or any suitable volume therebetween). In other embodiments, the sequestration chamber 134 can have a volume sufficient to receive an initial volume of bodily fluid up to, for example, about 5.0 mL, 10.0 mL, 15 mL, 20 mL, 30 mL, 40 mL, 50 mL, or more. In some embodiments, the sequestration chamber 134 can have a volume that is equal to a fraction of and/or a multiple of at least some of the volumes of one or more lumen(s) placing the sequestration chamber 134 in fluid communication with the bodily fluid source.

[1054] Although not shown in FIG. 1, in some embodiments, the sequestration chamber 134 can include any suitable arrangement, configuration, and/or feature, and/or can be formed of one or more materials configured to interact with a portion of the bodily fluid transferred into the sequestration chamber 134. For example, in some embodiments, the housing 130 can include an absorbent and/or hydrophilic material disposed within the sequestration chamber 134. Accordingly, when bodily fluid is transferred into the sequestration chamber 134, the absorbent and/or hydrophilic material can absorb, attract, retain, expand, and/or otherwise interact with at least a portion of the bodily fluid, which in turn, can sequester and/or retain at least an initial portion of the bodily fluid within the sequestration chamber 134, as described in further detail herein. In other embodiments, the sequestration chamber 134 can include and/or can be formed of an expandable or collapsible material configured to transition between a first state (e.g., while an initial portion of the bodily fluid is being transferred into the sequestration chamber 134) to a second state (e.g., after the initial portion of the bodily fluid is transferred into the sequestration chamber 134). In some embodiments, a force associated with and/or

resulting from such a material expanding or collapsing can be operable to transition the housing 130 and/or the device 100 from a first state, position, configuration, etc. to a second state, position, configuration, etc. In some embodiments, the sequestration chamber 134 and/or any other suitable portion of the housing 130 can include one or more chemicals, compounds, and/or the like configured to chemically interact with bodily fluid transferred through a portion of the housing 130, which can be operable to transition the control device 100 and/or the housing 130 between the first state and the second state (e.g., via a force or any other suitable means).

[1055] In some embodiments, the control device 100 and/or the housing 130 can include and/or define a flow controller 120 configured to selectively control a flow of fluids (e.g., gas or liquids) through a portion of the control device 100. For example, in some embodiments, the flow controller 120 can control a flow of bodily fluid through the control device 100 (or housing 130) and/or otherwise selectively control a flow of bodily fluid through at least one of the fluid flow paths 133 and/or 154. The flow controller 120 can be, for example, a valve, a membrane, a diaphragm, a restrictor, a vent, a selectively permeable member (e.g., a fluid impermeable barrier or seal that at least selectively allows the passage of air or gas therethrough), a port, a junction, an actuator, and/or the like, or any suitable combination thereof. In some embodiments, the flow controller 120 can be configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 134 and/or any other suitable portion of the housing 130. In this context, the flow of fluids, for example, can be a liquid such as water, oil, dampening fluid, bodily fluid, and/or any other suitable liquid, and/or can be a gas such as air, oxygen, carbon dioxide, helium, nitrogen, ethylene oxide, and/or any other suitable gas. For example, in some embodiments, a wall or structure of the housing 130 can define an opening, aperture, port, orifice, and/or the like that is in fluid communication with the sequestration chamber 134. In such embodiments, the flow controller 120 can be, for example, a semi-permeable member or membrane disposed in or about the opening to selectively allow a flow of air or gas through the opening while limiting or substantially preventing a flow of fluid (e.g., bodily fluid such as blood) through the opening.

[1056] In some embodiments, one or more flow controllers 120 or the like can be configured to facilitate air (or other fluid) displacement through one or more portions of the control device 100, which in some instances, can result in a pressure differential across one or more portions of the control device 100 or can result in and/or allow for a pressure equalization across one or more portions of the housing 130. In some embodiments, the control device 100 can be configured to selectively transfer a volume of bodily fluid to the sequestration chamber

134 or to the outlet 136 based at least in part on a pressure differential between two or more portions of the control device 100. In some embodiments, the pressure differential can result from fluidically coupling the outlet 136 to the fluid collection device 180, which can define and/or can be configured to produce a negative pressure (e.g., an evacuated reservoir, a syringe, a pressure charged canister, and/or other source or potential energy to create a vacuum or pressure differential). In other embodiments, the pressure differential can result from a change in volume and/or temperature. In still other embodiments, the pressure differential can result from at least a portion of the control device 100, the housing 130, and/or other portions of the flow path being evacuated and/or charged (e.g., the sequestration chamber 134 and/or any other suitable portion). In some embodiments, the pressure differential can be established automatically or via direct or indirect intervention (e.g., by the user).

[1057] Moreover, a flow of a fluid (e.g., gas and/or liquid) resulting from a pressure differential can be selectively controlled via one or more flow controllers 120 that can, for example, transition between one or more operating conditions to control the fluid flow. In some embodiments, for example, the flow controller 120 can be an actuator or the like configured to transition between one or more operating conditions or states to establish fluid communication between one or more portions of the control device 100 and/or configured to sequester one or more portions of the control device 100 (e.g., the sequestration chamber 134). In some embodiments, the flow controller 120 can be member or device formed of an absorbent material configured to selectively allow fluid flow therethrough. For example, such an absorbent material can be transitioned from a first state in which the material allows a flow of gas (e.g., air) therethrough but prevents a flow of liquid (e.g., bodily fluid) therethrough, to a second state in which the material substantially prevents a flow of gas and liquid therethrough. In other embodiments, the flow controller 120 can include one or more valves, membranes, diaphragms, and/or the like. In some embodiments, the flow controller 120 can include any suitable combination of devices, members, and/or features. It should be understood that the flow controllers included in the embodiments described herein are presented by way of example and not limitation. Thus, while specific flow controllers are described herein, it should be understood that fluid flow can be controlled through the control device 100 by any suitable means.

[1058] The outlet(s) 136 is/are in fluid communication with and/or is/are configured to be placed in fluid communication with the fluid flow paths 133 and/or 154. As shown in FIG. 1, the outlet 136 can be any suitable outlet, opening, port, stopcock, lock, seal, coupler, valve (e.g. one-way, check valve, duckbill valve, umbrella valve, and/or the like), etc. and is configured

to be fluidically coupled to the fluid collection device 180 (e.g., a fluid reservoir, culture sample bottle, syringe, container, vial, dish, receptacle, pump, adapter, and/or any other suitable collection or transfer device). In some embodiments, the outlet 136 can be monolithically formed with the fluid collection device 180. In other embodiments, the outlet 136 can be at least temporarily coupled to the fluid collection device 180 via an adhesive, a resistance fit, a mechanical fastener, a threaded coupling, a piercing or puncturing arrangement, any number of mating recesses, and/or any other suitable coupling or combination thereof. Similarly stated, the outlet 136 can be physically (e.g., mechanically) and/or fluidically coupled to the fluid collection device 180 such that an interior volume defined by the fluid collection device 180 is in fluid communication with the outlet 136. In still other embodiments, the outlet 136 can be operably coupled to the fluid collection device 180 via an intervening structure (not shown in FIG. 1), such as a flexible sterile tubing. In some embodiments, the arrangement of the outlet 136 can be such that the outlet 136 is physically and/or fluidically sealed prior to coupling to the fluid collection device 180. In some embodiments, the outlet 136 can be transitioned from a sealed configuration to an unsealed configuration in response to being coupled to the fluid collection device 180 and/or in response to a negative pressure differential between an environment within the outlet 136 and/or housing 130 and an environment within the fluid collection device 180.

[1059] The fluid collection device 180 can be any suitable device for at least temporarily containing a bodily fluid, such as, for example, any of those described in detail above. For example, in some embodiments, the fluid collection device 180 can be a single-use disposable collection tube(s), a syringe, a vacuum-based collection tube(s), an intermediary bodily-fluid transfer device, and/or the like. In some embodiments, the fluid collection device 180 can be substantially similar to or the same as known sample containers such as, for example, a Vacutainer® (manufactured by BD), a BacT/ALERT ® SN or BacT/ALERT ® FA (manufactured by Biomerieux, Inc.), and/or any suitable reservoir, vial, microvial, microliter vial, nanoliter vial, container, microcontainer, nanocontainer, and/or the like. In some embodiments, the fluid collection device 180 can be a sample reservoir that includes a vacuum seal that maintains negative pressure conditions (vacuum conditions) inside the sample reservoir, which in turn, can facilitate withdrawal of bodily fluid from the patient, through the control device 100, and into the sample reservoir, via a vacuum or suction force, as described in further detail herein. In embodiments in which the fluid collection device 180 is an evacuated container or the like, the user can couple the fluid collection device 180 to the outlet 136 to initiate a flow of bodily fluid from the patient such that a first or initial portion of the

bodily fluid is transferred into and sequestered by the sequestration chamber 134 and such that any subsequent portion or volume of bodily fluid bypasses and/or is otherwise diverted away from the sequestration chamber 134 and flows into the fluid collection device 180, as described in further detail herein.

[1060] Although the outlet 136 of the control device 100 and/or the housing 130 is described above as being fluidically coupled to and/or otherwise placed in fluid communication with the fluid collection device 180, in other embodiments, the control device 100 can be used in conjunction with any suitable bodily fluid collection device and/or system. For example, in some embodiments, the control device 100 described herein can be used in any suitable fluid transfer device such as those described in U.S. Patent Publication No. 2015/0342510 entitled, "Sterile Bodily-Fluid Collection Device and Methods," filed June 2, 2015 (referred to herein as the "'510 publication"), the disclosure of which is incorporated herein by reference in its entirety. More particularly, the control device 100 can be used in an "all-in-one" or pre-assembled device (e.g., such as those described in the '510 publication) to receive and sequester an initial volume of bodily fluid such that contaminants in subsequent volumes of bodily fluid are reduced and/or eliminated.

[1061] As described above, the device 100 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 100 to establish fluid communication between the inlet 131 and the bodily fluid source (e.g., a vein of a patient, cerebral spinal fluid (CSF) from the spinal cavity, urine collection, and/or the like). As a specific example, in some instances, the inlet 131 can be coupled to and/or can include a needle or the like that can be manipulated to puncture the skin of the patient and to insert at least a portion of the needle in the vein of the patient, thereby placing the inlet 131 in fluid communication with the bodily fluid source (e.g., the vein, an IV catheter, a PICC, etc.).

[1062] In some embodiments, once the inlet 131 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 136 can be fluidically coupled to the fluid collection device 180. As described above, in some embodiments, the fluid collection device 180 can be any suitable reservoir, container, and/or device configured to receive a volume of bodily fluid. For example, the fluid collection device 180 can be an evacuated reservoir or container that defines a negative pressure and/or can be a syringe that can be manipulated to produce a negative pressure. In some instances, coupling the outlet 136 to the fluid collection device 180 selectively exposes at least a portion of the fluid flow paths 133

and/or 154 to the negative pressure, thereby resulting in a negative pressure differential operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 131, and into the housing 130.

[1063] In some embodiments, the arrangement of the housing 130 is such that when a volume of bodily fluid is transferred to and/or through the inlet 131, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 131, through at least a portion of the fluid flow path 133, and into the sequestration chamber 134. That is to say, in some embodiments, the control device 100 and/or the housing 130 can be in first or initial state in which the initial portion or volume of bodily fluid can flow in or through at least a portion the fluid flow path 133 and into the sequestration chamber 134. For example, in some embodiments, the initial state of the control device 100 and/or the housing 130 can be one in which one or more flow controllers 120 (e.g., valves, membranes, diaphragms, restrictors, vents, air permeable and fluid impermeable barriers, ports, actuators, and/or the like, or a combination thereof) are in a first state in which the fluid flow path 133 is exposed to the negative pressure differential via the sequestration chamber 134. In other words, the negative pressure within or created by the fluid collection device 180 can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 134 that is operable in drawing an initial flow of bodily fluid into the sequestration chamber 134 when one or more flow controllers 120 is/are in a first or initial state.

[1064] For example, in some embodiments, the flow controller 120 can be an actuator or the like that includes a valve (e.g. one-way valve, check valve, duckbill valve, umbrella valve, and/or the like), a selectively permeable member (e.g., a fluid impermeable barrier or seal that allows at least selective passage of gas or air), a selectively permeable membrane, a diaphragm, and/or the like that is at least temporarily fluidically coupled to a flow path between the fluid collection device 180 and the sequestration chamber 134 (e.g., at least a portion of the fluid flow path 154). While in some embodiments the flow controller 120 examples noted above can be, for example, known off-the-shelf components that are used in medical devices to control the flow of fluids and air, in other embodiments, the flow controller 120 can be a custom, proprietary, and/or specifically tailored component integrated into the device 100. When the flow controller 120 is in the first or initial state, the flow controller 120 can allow a flow of fluid therethrough in response to the negative pressure of the fluid collection device 180. In some embodiments, the flow controller 120 or a portion or component thereof is configured to allow only a flow of air or gas through the flow controller 120 and is configured

to limit and/or substantially prevent a flow of liquid (e.g., bodily fluid) through the flow controller 120. As such, the fluid collection device 180 can produce a negative pressure differential within the sequestration chamber 134 that is operable to draw an initial portion and/or amount of bodily fluid into the sequestration chamber 134 when the flow controller 120 is in a first or initial state without allowing the initial portion of bodily fluid to flow into the fluid flow path 154 and/or otherwise out of the sequestration chamber 134.

[1065] Although not shown in FIG. 1, in some embodiments, the control device 100 and/or the housing 130 can include a member, device, mechanism, feature, etc. configured to modulate a magnitude of the negative pressure to which the sequestration chamber 134 is exposed. For example, in some embodiments, a housing can include a valve, a membrane, a porous material, a restrictor, an orifice, and/or any other suitable member, device, and/or feature configured to modulate pressure. In some embodiments, modulating and/or controlling a magnitude of the pressure to which the sequestration chamber 134 is exposed can, in turn, modulate a magnitude of pressure exerted on the bodily fluid and/or within a vein of a patient. In some instances, such pressure modulation can reduce, for example, hemolysis of a blood sample and/or a likelihood of collapsing a vein (e.g., which is particularly important in fragile patients needing microbial and/or other diagnostic testing associated with use of the control device 100). In addition, the modulation of the negative pressure can, for example, at least partially control a rate at which the control device 100 transitions between a first configuration or state and a second configuration or state. In some embodiments, modulating the negative pressure can act like a timer. For example, a time between the introduction of the negative pressure differential and the transitioning of the control device 100 from the first state to the second state can be known, predetermined, calculated, and/or controlled. As such, in some instances, modulating the negative pressure can at least partially control an amount or volume of bodily fluid transferred into the sequestration chamber 134 (i.e., can control a volume of the initial amount of bodily fluid).

[1066] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described above. For example, in some instances, the control device 100 and/or the housing 130 can remain in the first state until a predetermined and/or desired volume (e.g., the initial volume) of bodily fluid is transferred to the sequestration chamber 134. In some embodiments, the initial volume can be associated with and/or at least partially based on a volume of the sequestration chamber 134. In other embodiments, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that can be absorbed by an absorbent material, an expandable material, a hydrophilic material, a

wicking material, and/or other suitable material disposed in the sequestration chamber 134. In other embodiments, the initial volume of bodily fluid can be associated with and/or at least partially based on an amount or volume of bodily fluid that can be transferred into the sequestration chamber 134 in a predetermined time. In still other embodiments, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate a semi-permeable member or membrane otherwise configured to selectively expose the sequestration chamber 134 to the negative pressure of the fluid collection device 180 (i.e., the flow controller 120 such as an air permeable and liquid impermeable member or membrane). In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition one or more flow controllers 120 to a second state (e.g., a saturated or fully wetted state). In still other embodiments, the control device 100 and/or the housing 130 can be configured to transfer a volume of bodily fluid (e.g., the initial volume) into the sequestration chamber 134 until a pressure differential between the sequestration chamber 134 and the fluid flow path 133 and/or the bodily fluid source is brought into substantial equilibrium and/or is otherwise reduced below a desired threshold.

[1067] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 134, the initial volume is sequestered, segregated, retained, contained, isolated, etc. in the sequestration chamber 134. For example, in some embodiments, the transitioning of the one or more flow controllers 120 from a first state to a second state can be operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 134. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, other external sources of contamination, colonization of catheters and PICC lines that are used to collect samples, and/or the like can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 134 when the initial volume is sequestered therein.

[1068] With the initial volume transferred and/or diverted into the sequestration chamber 134, the device 100 can transition to the second state in which a subsequent volume(s) of bodily fluid can flow through at least a portion the fluid flow paths 133 and/or 154 from the inlet 131 to the outlet 136. In some embodiments, the control device 100 and/or the housing 130 can passively and/or automatically transition (e.g., without user intervention) from the first state to the second state once the initial volume of bodily fluid is sequestered in the sequestration chamber 134. For example, in some embodiments, filling the sequestration chamber 134 to capacity and/or fully saturating, wetting, and/or impregnating an absorbent or similar material

disposed between the sequestration chamber 134 and the fluid collection device 180 can be such that further transfer of bodily fluid into the sequestration chamber 134 is limited and/or substantially prevented due to a removal or diversion of the negative pressure. In other embodiments, the control device 100 and/or the housing 130 can be manually transitioned or transitioned in response to at least an indirect interaction by a user. For example, in some embodiments, a user can transition the control device 100 and/or the housing 130 from the first state to the second state by actuating an actuator or the like (e.g., actuating the flow controller 120 or a portion thereof). In still other embodiments, at least a portion of the initial volume of bodily fluid can transition the control device 100 and/or the housing 130 from the first state to the second state. For example, the control device 100 can include a flow controller 120 that is and/or that includes a bodily fluid activated switch, valve, port, and/or the like. In other embodiments, a volume of bodily fluid can move and/or displace one or more flow controller 120 (e.g., actuators or the like) that can, for example, open a port, flow path, and/or outlet. In still other embodiments, a user can manipulate such a flow controller 120 (e.g., switch, valve, port, actuator, etc.) to transition the control device 100 and/or the housing 130 from the first state to the second state.

[1069] With the fluid collection device 180 fluidically coupled to the outlet 136 and with the control device 100 and/or the housing 130 being in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 134), any subsequent volume(s) of the bodily fluid can flow from the inlet 131, through at least one of the fluid flow paths 133 and/or 154, through the outlet 136, and into the fluid collection device 180. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 134 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 100 and/or the housing 130 can be such that the control device 100 and/or the housing 130 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 134.

[1070] FIGS. 2-5 illustrate a fluid control device 200 according to an embodiment. The fluid control device 200 can be similar in at least form and/or function to the fluid control device 100 described above with reference to FIG. 1. Accordingly, portions of the fluid control device 200 that can be similar to portions of the fluid control device 100 are not described in further detail herein.

[1071] As shown in FIGS. 2-5, the fluid control device 200 (also referred to herein as "control device" or "device") includes a housing 230 having an inlet 231, an outlet 236, and an actuator 250. As described above with reference to the control device 100, the inlet 231 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, PICC line, or the like). The outlet 236 is configured to be fluidically coupled to a fluid collection device such as, for example, a sample reservoir, a syringe, and/or other intermediary bodily fluid transfer device or vessel (e.g., a transfer device similar to those described in the '510 publication), and/or the like.

[1072] As described above with reference to the housing 130, the housing 230 defines one or more fluid flow paths 233 between the inlet 231 and a sequestration chamber 234 and/or one or more fluid flow paths 254 between the inlet 231 and the outlet 236. The housing 230 of the device 200 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the housing 230 can be substantially similar in at least form and/or function to the housing 130 described above with reference to FIG. 1. The sequestration chamber 234 of the housing 230 is at least temporarily placed in fluid communication with the inlet 231 via the fluid flow path(s) 233. Moreover, the sequestration chamber 234 can be selectively placed in fluid communication with the fluid flow path 254 such that at least air or gas can be transferred therebetween, as described in further detail herein.

[1073] As described in further detail herein, the sequestration chamber 234 is configured to (1) receive a flow and/or volume of bodily fluid from the inlet 231 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein. The sequestration chamber 234 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 234 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 134. In the embodiment shown in FIGS. 2-5, the sequestration chamber 234 can be at least partially formed by the housing 230 that defines a lumen or flow path. In some embodiments, at least a portion of the fluid flow path 233 can extend through a portion of the housing 230 to form and/or define at least a portion of the sequestration chamber 234. As shown in FIGS. 2-5, the sequestration chamber 234 and/or a portion of the fluid flow path 233 forming the sequestration chamber 234 can have a serpentine configuration or the like. In other embodiments, the sequestration chamber 234 can have any suitable arrangement. For example, in some embodiments, a housing can include a sequestration chamber that is formed by a flexible tubing or the like that can be arranged in any suitable shape and/or configuration.

[1074] In some embodiments, the housing 230 and/or the sequestration chamber 234 can include, form, and/or define a flow controller 242. The flow controller 242 can be, for example, a valve, membrane, diaphragm, restrictor, vent, a selectively permeable member (e.g., a fluid impermeable barrier or seal that allows at least selective passage of gas or air such as, for example, a blood barrier and/or the like), port, etc. (collectively referred to herein as a "flow controller") configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 234 and/or any other suitable portion of the housing 230. More particularly, in the embodiment shown in FIGS. 2-5, the flow controller 242 is a selectively permeable fluid barrier (e.g., a blood barrier) that includes and/or is formed of a porous material configured to selectively allow a flow of gas therethrough but to prevent a flow of a liquid therethrough.

[1075] As shown, the flow controller 242 is positioned within the housing 230 to selectively establish fluid communication between the sequestration chamber 234 and the fluid flow path 254. Thus, with the flow controller 242 being configured as a semi-permeable member, the flow controller 242 can be configured to at least temporarily allow a gas or air to transfer between the fluid flow path 254 and the sequestration chamber 234 and can be configured to substantially prevent a flow of liquid between the fluid flow path 254 and the sequestration chamber 234, as described in further detail herein.

[1076] The outlet 236 of the housing 230 is in fluid communication with and/or is configured to be placed in fluid communication with the fluid flow paths 233 and/or 254. As shown in FIGS. 2-5, the outlet 236 can be any suitable outlet, opening, port, lock, seal, coupler, etc. and is configured to be fluidically coupled to a fluid collection device such as a sample reservoir, a syringe, container, and/or other sample vessel. In some embodiments, the outlet 236 can be monolithically formed with the fluid collection device or can be at least temporarily coupled to the fluid collection device, as described above with reference to the outlet 136 of the housing 130. The fluid collection device can be any suitable reservoir, container, and/or device for containing a bodily fluid, such as, for example, any of those described in detail above with reference to the fluid collection device 180. More particularly, in some embodiments, the outlet 236 can be configured to couple to an evacuated sample reservoir. As such, the user can couple the sample reservoir to the outlet 236 to initiate a flow of bodily fluid from the patient such that a first or initial portion of the bodily fluid is transferred into and sequestered by the sequestration chamber 234 and such that any subsequent portion or volume of bodily fluid bypasses and/or is otherwise diverted away from the sequestration chamber 234 and flows into the sample reservoir.

[1077] As shown in FIGS. 3-5, the housing 230 includes and/or is coupled to the actuator 250 configured to selectively control a flow of bodily fluid through the housing 230. More particularly, the actuator 250 is disposed, for example, between a portion of the fluid flow path 233 and a portion of the fluid flow path 254. While the actuator 250 is shown in FIGS. 3-5 as being positioned apart from, away from, and/or downstream of a junction between the fluid flow path 233 and the sequestration chamber 234, in other embodiments, the actuator 250 can be disposed at any suitable position within the housing 230. For example, in some embodiments, the actuator 250 can be positioned at and/or can form at least a portion of a junction between the fluid flow path 233, the sequestration chamber 234, and the fluid flow path 254.

[1078] The actuator 250 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the actuator 250 can be any suitable member or device configured to transition between a first state and a second state. In the embodiment shown in FIGS. 2-5, the actuator 250 is configured to isolate, sequester, separate, and/or otherwise prevent fluid communication between the fluid flow path 233 and the fluid flow path 254 when in the first state and is configured to place the fluid flow path 233 in fluid communication with the fluid flow path 254 when in the second state. In some embodiments, for example, the actuator 250 can be a valve, plunger, seal, membrane, flap, plate, and/or the like. As shown, for example, in FIG. 5, the actuator 250 can include one or more seals 265 configured to selectively establish fluid communication between the fluid flow channels 233 and 254 when the actuator 250 is transitioned from a first state to a second state (e.g., pressed, rotated, moved, activated, switched, slid, etc.).

[1079] Although the actuator 250 is particularly shown in FIGS. 2-5 and described above, in other embodiments, the control device 200 can include any suitable actuator or device configured to selectively establish fluid communication between the fluid flow path 233 and 254. Thus, while particularly shown in FIGS. 2-5, it should be understood that the control device 200 is presented by way of example only and not limitation. For example, while the actuator 250 is shown in FIGS. 2-5 as being disposed in a given position, in other embodiments, the actuator 250 can be placed at any suitable position along the housing 230. By way of example, in some embodiments, the actuator 250 can be disposed at the junction between the fluid flow path 233, the sequestration chamber 234, and the inlet 231. In such embodiments, a flow of bodily fluid can flow directly from the inlet 231 and into the sequestration chamber 234 when the actuator 250 is in the first state and can flow directly from the inlet 231 to the fluid flow path 254 when the actuator 250 is in the second state. In other words, the actuator

250 can form a portion of the sequestration chamber 234 such that when the actuator 250 is in the first state, bodily fluid flows from the inlet directly into the sequestration chamber 234. When the actuator 250 is actuated, placed, and/or transitioned to the second state, the actuator 250 can, for example, allow bodily fluid to flow directly from the inlet 231 to the fluid flow path 233. In such embodiments, the actuator 250 can prevent the formation of a junction between the inlet 231, the sequestration chamber 234, and the fluid flow path 233. Moreover, when in the second state, the actuator 250 can be operable in at least partially sequestering the sequestration chamber 234 from the inlet 231 and/or the fluid flow path 233.

[1080] In addition, the actuator 250 can be actuated and/or transitioned in any suitable manner. For example, in some embodiments, the actuator 250 can transition between the first and the second state in response to a manual actuation by the user (e.g., exerting a manual force on a button, slider, switch, rotational member, etc.). In other embodiments, the actuator 250 can be configured to automatically transition between the first state and the second state in response to a pressure differential (or lack thereof), a change in potential or kinetic energy, a change in composition or configuration (e.g., a portion of the actuator could at least partially dissolve or transform), and/or the like. In still other embodiments, the actuator 250 can be mechanically and/or electrically actuated or transitioned based on a predetermined time, volumetric flow rate, flow velocity, etc. While examples of actuators and/or ways in which an actuator can transition are provided herein, it should be understood that they have been presented by way of example only and not limitation. Thus, a control device 200 can include any suitable actuator configured to transition in any suitable manner.

[1081] As described above, the device 200 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 200 to establish fluid communication between the inlet 231 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 231 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 236 can be fluidically coupled to the fluid collection device. As described above, in the embodiment shown in FIGS. 2-5, the fluid collection device can be, for example, an evacuated reservoir or container that defines a negative pressure and/or can be any other suitable negative pressure source.

[1082] Coupling the outlet 236 to the fluid collection device selectively exposes at least a portion of the fluid flow path 254 to the negative pressure within the fluid collection device. As described above, the flow controller 242 is in fluid communication with the fluid flow path

254 and the sequestration chamber 234. Thus, coupling the outlet 236 to the fluid collection device exposes the sequestration chamber to the negative pressure of the fluid collection device, thereby resulting in a negative pressure differential operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 231, and into the housing 230. As described above with reference to the control device 100, the arrangement of the housing 230 is such that when a volume of bodily fluid is transferred to and/or through the inlet 231, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 231, through at least a portion of the fluid flow path 233, and into the sequestration chamber 234. That is to say, in some embodiments, the control device 200 and/or the housing 230 can be in first or initial state in which the initial portion or volume of bodily fluid can flow in or through at least a portion the fluid flow path 233 and into the sequestration chamber 234.

[1083] As described above, the housing 230 and/or the control device 200 can be in the initial state when the flow controller 242 and the actuator 250 are in a first state, position, configuration, etc. As such, the actuator 250 isolates, separates, segregates, sequesters and/or otherwise prevents direct fluid communication between the fluid flow paths 233 and 254. In addition, the inlet 231 is exposed to the negative pressure differential via the sequestration chamber 234. In other words, the negative pressure within the fluid collection device can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 234 that is operable in drawing an initial flow of bodily fluid from the inlet 233 into the sequestration chamber 234 when the housing 230 and/or control device 200 is in the first or initial state.

[1084] When the flow controller 242 is in the first or initial state, the flow controller 242 can allow a flow of fluid (e.g., a gas or air) therethrough in response to the negative pressure of the fluid collection device (e.g., a sample reservoir, a syringe, or other source of potential energy used to create negative pressure), as described above with reference to the housing 130. In some instances, it may be desirable to modulate and/or control a magnitude of the negative pressure differential. In the embodiment shown in FIGS. 2-5, for example, the housing 230 defines a restricted flow path 232 that places the flow controller 242 in fluid communication with the fluid flow path 254. More specifically, the restricted flow path 232 is a fluid flow path having a smaller diameter than at least the fluid flow path 254.

[1085] For example, in some embodiments, the restricted flow path 232 can have a diameter of about 0.0005", about 0.001", about 0.003", about 0.005", about 0.01", about 0.1", about 0.5" or more. In other embodiments, the restricted flow path 232 can have a diameter

less than 0.0005" or greater than 0.5". In some embodiments, the restricted flow path 232 can have a predetermined and/or desired length of about 0.01", about 0.05", about 0.1", about 0.15", about 0.2", about 0.5", or more. In other embodiments, the restricted flow path 232 can have a predetermined and/or desired length that is less than 0.01" or more than about 0.5". Moreover, in some embodiments, a restricted flow path 232 can have any suitable combination of diameter and length to allow for and/or to provide a desired flow characteristic through at least a portion of the control device 200.

[1086] In this embodiment, the restricted flow path 232 having a smaller diameter results in a lower magnitude of negative pressure being applied through the sequestration chamber than a magnitude of negative pressure when the restricted flow path has a larger diameter. In some instances, modulating a magnitude of negative pressure can control a rate at which bodily fluid is transferred into the sequestration chamber 234. For example, in some embodiments, a fluid collection device and/or other suitable negative pressure source may produce a negative pressure differential having a magnitude (e.g., a negative magnitude) of about 0.5 pounds per square inch (PSI), about 1.0 PSI, about 2.0 PSI, about 3.0 PSI, about 4.0 PSI, about 5.0 PSI, about 10 PSI, about 12.5 PSI, or about 14.7 PSI (e.g., at or substantially at atmospheric pressure at about sea level). In some embodiments, a fluid collection device such as an evacuated container or the like can have a predetermined negative pressure of about 12.0 PSI. Accordingly, by controlling the diameter and/or length of the restricted flow path 232, the amount of negative pressure to which the sequestration chamber 234 is exposed and/or the rate at which the negative pressure is applied can be controlled, reduced, and/or otherwise modulated. In some instances, the use of the restricted flow path 232 can result in a delay or ramp up of the negative pressure exerted on or in the sequestration chamber.

[1087] Moreover, in this embodiment, the restricted flow path 232 is, for example, a gas flow path configured to receive a flow of gas or air but not a flow of a liquid (e.g., bodily fluid). In some embodiments, the diameter of the restricted flow path 232 can be sufficiently small to limit and/or prevent a flow of a liquid therethrough. In addition, the arrangement of the restricted flow path 232 being disposed between the fluid flow path 254 and the flow controller 242 is such that a flow of bodily fluid and/or any other liquid is substantially prevented by the flow controller 242 (e.g., a selectively permeable barrier or seal).

[1088] Although the pressure modulation is described above as being based on a diameter of the restricted flow path 232 (i.e., a single restricted flow path), it should be understood that this is presented by way of example only and not limitation. Other means of modulating the magnitude of negative pressure to which the sequestration chamber is exposed can include, for

example, a porous material, a valve, a membrane, a diaphragm, a specific restriction, a vent, a deformable member or flow path, and/or any other suitable means. In other embodiments, a control device can include any suitable number of restricted flow paths, each of which can have substantially the same diameter or can have varied diameters. For example, in some embodiments, a control device can include up to 100 restricted flow paths or more. In such embodiments, each of the restricted flow paths can have a diameter of between about 0.0005" and about 0.1", between about 0.0005" and about 0.05", or between about 0.0005" and about 0.01". In some embodiments, multiple restricted flow paths can be configured to (1) selectively provide a flow path between the outlet 236 and the sequestration chamber 234 that exposes the sequestration chamber 234 to the negative pressure differential, and (2) act as a flow controller configured to selectively allow the passage of a gas and/or air while substantially preventing the passage of a liquid (e.g., bodily fluid).

[1089] In some embodiments, modulating and/or controlling a magnitude of the pressure to which the sequestration chamber 234 is exposed can, in turn, modulate a magnitude of pressure exerted on the bodily fluid and/or within a vein of a patient. In some instances, such pressure modulation can reduce, for example, hemolysis of a blood sample and/or a likelihood of collapsing a vein. In some instances, the ability to modulate and/or control an amount or magnitude of negative pressure can allow the control device 200 to be used across a large spectrum of patients that may have physiological challenges whereby negative pressure is often needed to facilitate collection of bodily fluid such as, for example, blood (i.e. pressure differential between atmospheric pressure and a patient's vascular pressure is not sufficient to facilitate consistent and sufficiently forceful flow) but not so much pressure that a rapid force flattens, collapses, caves-in, and/or otherwise inhibits patency and ability to collect blood.

[1090] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control device 100. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 242. In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition the flow controller 242 to a second state (e.g., a saturated or fully wetted state). In some embodiments, the flow controller 242 is placed in a sealed configuration when transitioned to the second state. That is to say, saturating and/or fully wetting the flow controller 242 (e.g., the semi-permeable material) places the flow controller 242 in a sealed configuration in which the flow controller 242 substantially prevents a flow of a liquid and a gas therethrough. Thus, transitioning the flow controller 242 to the second state sequesters,

blocks, isolates, separates, segregates, and/or otherwise prevents flow through the flow controller 242 between the restricted flow path 232 and the sequestration chamber 234.

[1091] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 234, the control device 200 and/or the housing 230 can be transitioned to its second state or operating mode to sequester, segregate, retain, contain, isolate, etc. the initial volume in the sequestration chamber 234. For example, as described above, the flow controller 242 is placed in the sealed configuration. In addition, the actuator 250 can be actuated to transition from its first state to its second state to establish fluid communication between the fluid flow paths 233 and 254. As such, the negative pressure otherwise exerted on or through the sequestration chamber 234 is now exerted on or through the fluid flow paths 233 and 254. In response, bodily fluid can flow from the inlet 231, through the fluid flow paths 233 and 254, through the outlet 236, and into the fluid collection device. In some embodiments, the transitioning of the flow controller 242 and the actuator 250 from their respective first states to their respective second states is operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 234. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 234 when the initial volume is sequestered therein.

[1092] With the fluid collection device fluidically coupled to the outlet 236 and with the control device 200 and/or the housing 230 being in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 234), any subsequent volume(s) of the bodily fluid can flow from the inlet 231, through the fluid flow paths 233 and 254, through the outlet 236, and into the fluid collection device. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 234 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 200 and/or the housing 230 can be such that the control device 200 and/or the housing 230 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 234.

[1093] While the control device 200 is described above with reference to FIGS. 2-5 as including the actuator 250 configured to be moved (e.g., via a force applied by a user) between the first state and the second state, in other embodiments, a control device can include any suitable member, device, mechanism, etc. configured to selectively establish fluid

communication between two or more fluid flow paths. For example, FIGS. 6-8 illustrate a fluid control device 300 according to an embodiment. The fluid control device 300 can be similar in at least form and/or function to the fluid control device 100 described above with reference to FIG. 1 and/or the fluid control device 200 described above with reference to FIGS. 2-5. Accordingly, portions of the fluid control device 300 that can be similar to portions of the fluid control devices 100 and/or 200 are not described in further detail herein.

[1094] As shown in FIGS. 6-8, the fluid control device 300 (also referred to herein as "control device" or "device") includes a housing 330 having an inlet 331 and an outlet 336, and including or being coupled to an actuator 350. As described above with reference to the control devices 100 and/or 200, the inlet 331 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like). The outlet 336 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 6-8).

[1095] As described above with reference to the housings 130 and/or 230, the housing 330 defines one or more fluid flow paths 333, 354A, and 354B configured to selectively place the inlet 331 in fluid communication with the sequestration chamber 334 and/or the outlet 336. The housing 330 of the device 300 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the housing 330 can be substantially similar in at least form and/or function to the housings 130 and/or 230 described above. In some embodiments, the housing 330 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 334. The sequestration chamber 334 of the housing 330 is at least temporarily placed in fluid communication with the inlet 331 via the fluid flow path(s) 333. Moreover, the sequestration chamber 334 can be selectively placed in fluid communication with the fluid flow path 354A such that at least air or gas can be transferred therebetween, as described in further detail herein.

[1096] As described in further detail herein, the sequestration chamber 334 is configured to (1) receive a flow and/or volume of bodily fluid from the inlet 331 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid therein. The sequestration chamber 334 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 334 can be substantially similar to the sequestration chamber 234 described above with reference to FIGS. 2-5 and thus, is not described in further detail herein. Likewise, the housing 330 and/or the sequestration chamber 334 include, form, and/or define a flow controller 342 that can be substantially similar to the flow controller 242 described above. As such, the flow controller 342 is positioned within the

housing 330 to selectively establish fluid communication between the sequestration chamber 334 and the fluid flow path 354A, as described in further detail herein.

[1097] The outlet 336 of the housing 330 is in fluid communication with and/or is configured to be placed in fluid communication with the fluid flow paths 333, 354A, and/or 354B. In addition, the outlet 336 is configured to be fluidically coupled to a fluid collection device such as, for example, a sample reservoir, container, vial, negative pressure source, syringe, and/or intermediate control and/or transfer device (not shown in FIGS. 6-8). The outlet 336 and the fluid collection device can each be substantially similar to the outlet 236 and fluid collection device, respectively, described above with reference to the control device 200. Thus, the outlet 336 and fluid collection device are not described in further detail herein.

[1098] As shown in FIGS. 6-8, the housing 330 includes and/or is coupled to the actuator 350, which is configured to selectively control a flow of bodily fluid through the housing 330. In some embodiments, the actuator 350 can be substantially similar in at least function to the actuator 250 described above with reference to FIGS. 2-5. In this embodiment, however, the actuator 350 is arranged as a plunger and includes a set of seals 365 disposed along an outer surface of the plunger. Moreover, the actuator 350 has a substantially annular shape and is configured to at least temporarily receive and/or otherwise be disposed about a portion of the flow controller 342, as shown in FIG. 8. As described above with reference to the actuator 250, the actuator 350 is configured to isolate, sequester, separate, and/or otherwise prevent fluid communication between the fluid flow path 333 and the fluid flow path 354B when in the first state and is configured to place the fluid flow path 333 in fluid communication with the fluid flow path 354B when in the second state.

[1099] As described above, the device 300 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 300 to establish fluid communication between the inlet 331 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 331 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 336 can be fluidically coupled to the fluid collection device. As described above, in the embodiment shown in FIGS. 6-8, the fluid collection device can be, for example, an evacuated reservoir, a syringe, and/or any container that defines a negative pressure.

[1100] Coupling the outlet 336 to the fluid collection device selectively exposes at least a portion of the fluid flow paths 354A and 354B to the negative pressure within and/or produced

by the fluid collection device. The arrangement of the actuator 350 when in its first state, configuration, and/or position is such that the actuator 350 isolates the fluid flow path 354B from the fluid flow path 333 and as such, the fluid flow path 333 is not exposed to the negative pressure differential produced by the fluid collection device. As described above, the flow controller 342 is in fluid communication with the fluid flow path 354A and the sequestration chamber 334. More particularly, the annular arrangement of the actuator 350 allows the flow controller 342 to be in fluid communication with the fluid flow path 354A (see e.g., FIG. 8). Thus, coupling the outlet 336 to the fluid collection device exposes the sequestration chamber 334 to the negative pressure of the fluid collection device, thereby resulting in a negative pressure differential operable in drawing bodily fluid from the bodily fluid source (e.g., the patient), through the inlet 331, and into the housing 330. As described above with reference to the control devices 100 and 200, the arrangement of the housing 330 is such that when a volume of bodily fluid is transferred to and/or through the inlet 331, an initial portion of the volume of bodily fluid (also referred to herein as an "initial volume" or a "first volume") flows from the inlet 331 and into the sequestration chamber 334. That is to say, in some embodiments, the housing 330 can be in first or initial state in which the initial portion or volume of bodily fluid can flow from the inlet 331 and into the sequestration chamber 334.

[1101] As described above, the housing 330 and/or the control device 300 can be in the initial state when the flow controller 342 and the actuator 350 are in a first state, position, configuration, etc. As such, the actuator 350 isolates, separates, segregates, sequesters and/or otherwise prevents direct fluid communication between the fluid flow paths 333 and 354B. In addition, the inlet 331 is exposed to the negative pressure differential via the sequestration chamber 334. In other words, the negative pressure within or produced by the fluid collection device can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 334 that is operable in drawing an initial flow of bodily fluid from the inlet 331 into the sequestration chamber 334 when the housing 330 and/or control device 300 is in the first or initial state. As described in detail above, in some instances, it may be desirable to modulate and/or control a magnitude of the negative pressure differential by any suitable means such as those described herein.

[1102] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control devices 100 and/or 200. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 342. In other words, in some embodiments, the initial volume of bodily

fluid can be a volume sufficient to transition the flow controller 342 to a second state (e.g., a saturated or fully wetted state). As described above with reference to the flow controller 242, the flow controller 342 is placed in a sealed configuration when transitioned to the second state. Thus, transitioning the flow controller 342 to the second state sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents flow through the flow controller 342.

[1103] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 334, the control device 300 and/or the housing 330 can be transitioned to its second state or operating mode to sequester, segregate, retain, contain, isolate, etc. the initial volume in the sequestration chamber 334. As described above, the flow controller 342 is placed in the sealed configuration and thus, substantially prevents a flow of fluid therethrough. In this embodiment, the arrangement of the actuator 350 is such that when the flow controller 342 is placed in the sealed configuration, at least a portion of the negative pressure otherwise being exerted through the flow controller 342 is instead exerted on the actuator 350, which in turn, is sufficient to transition the actuator 350 from its first state to its second state. For example, in some embodiments, the negative pressure is operable to move the actuator 350 from a first position (e.g., the first state) to a second position (e.g., the second state), thereby establishing fluid communication between the fluid flow paths 333 and 354B.

[1104] More particularly, moving the actuator 350 to its second position (or otherwise transitioning the actuator 350 to its second state), moves and/or transitions the seals 365 relative to the fluid flow paths 333 and 354B such that fluid communication is established therebetween. As such, the negative pressure otherwise exerted on or through the sequestration chamber 334 is now exerted on or through the fluid flow paths 333 and 354B. In response, bodily fluid can flow from the inlet 331, through the fluid flow paths 333 and 354B, through the outlet 336, and into the fluid collection device. In some embodiments, the transitioning of the flow controller 342 and the actuator 350 from their respective first states to their respective second states is operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 334. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 334 when the initial volume is sequestered therein.

[1105] With the fluid collection device fluidically coupled to the outlet 336 and with the control device 300 and/or the housing 330 being in the second state (e.g., the initial volume of bodily fluid is sequestered in or by the sequestration chamber 334), any subsequent volume(s)

of the bodily fluid can flow from the inlet 331, through the fluid flow paths 333 and 354B, through the outlet 336, and into the fluid collection device. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 334 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the housing 330 can be such that housing 330 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 334.

[1106] FIGS. 9 and 10 illustrate a fluid control device 400 according to an embodiment. The fluid control device 400 can be similar in at least form and/or function to the fluid control device 100 described above with reference to FIG. 1, the fluid control device 200 described above with reference to FIGS. 2-5, and/or the fluid control device 300 described above with reference to FIGS. 6-8. Accordingly, portions of the fluid control device 400 that can be similar to portions of the fluid control devices 100, 200, and/or 300 are not described in further detail herein.

[1107] As shown in FIGS. 9 and 10, the fluid control device 400 (also referred to herein as "control device" or "device") includes a housing 430 having an inlet 431 and an outlet 436, and having and/or being coupled to an actuator 450. As described above with reference to the control devices 100, 200, and/or 300, the inlet 431 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like). The outlet 436 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 9 and 10).

[1108] As described above, the housing 430 of the control device 400 is configured to (1) receive a flow and/or volume of bodily fluid via the inlet 431 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within the sequestration chamber 434. The housing 430 can be any suitable shape, size, and/or configuration. In some embodiments, the housing 430 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 434. For example, in the embodiment shown in FIGS. 9 and 10, the housing 430 is arranged (at least in part) as a syringe-like device or the like, as described in further detail herein.

[1109] The housing 430 defines fluid flow paths 433 and 454 that are selectively in fluid communication with the outlet 436 and that selectively receive a flow of fluid therethrough (e.g., a liquid and/or a gas). The outlet 436 of the housing 430 is in fluid communication with

and/or is configured to be placed in fluid communication with the fluid flow paths 433 and/or 454. In addition, the outlet 436 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 9 and 10). The outlet 436 and the fluid collection device can each be substantially similar to the outlet 236 and fluid collection device, respectively, described above with reference to the control device 200. Thus, the outlet 436 and fluid collection device are not described in further detail herein.

[1110] The housing 430 includes and/or is coupled to the actuator 450 configured to selectively control a flow of bodily fluid through the housing 430. In this embodiment, the actuator 450 includes a first plunger 460 and a second plunger 461 movably disposed within the housing 430 and configured to at least partially define the sequestration chamber 434. More specifically, the actuator 450 is configured to move between a first state in which the inlet 431 is placed in fluid communication with the sequestration chamber 434 (FIG. 9) and a second state in which the inlet 431 is placed in fluid communication with the outlet 436 via the fluid flow path 454 (FIG. 10). In this embodiment, when the actuator 450 and/or housing 430 is in the first state, the inlet 431 is in fluid communication with a portion of the housing 430 defined between the first plunger 460 and the second plunger 461.

[1111] When in the first state, the first plunger 460 is disposed in a position such that a dampening chamber 437 is defined by the housing 430 on a side of the first plunger 460 opposite the sequestration chamber 434. As shown, the dampening chamber 437 is configured to be placed in fluid communication with the fluid flow path 433 via a port 435. The port 435 can be an opening, a valve, a membrane, a diaphragm, and/or any other suitable flow controller or the like configured to at least selectively establish fluid communication between the fluid flow path 433 and the dampening chamber 437. Furthermore, when the actuator 450 and/or the housing 430 is in the first state, the dampening chamber 437 includes and/or contains a dampening fluid 456 such as a gas (compressed or uncompressed) and/or a liquid (e.g., water, oil, dampening fluid, and/or any other suitable liquid).

[1112] When the actuator 450 and/or housing 430 are in the first state, the second plunger 461 is disposed in a position within the housing 430 such that one or more seals 465 formed by or coupled to the second plunger 461 fluidically isolate, separate, and/or sequester the inlet 431 from the fluid flow path 454. In addition, the second plunger 461 and/or the seals 465 formed by or coupled thereto fluidically isolate the fluid flow path 454 from the sequestration chamber 434. Thus, when the actuator 450 and/or control device 400 are in the first state, the inlet 431 is in fluid communication with the sequestration chamber 434 and is fluidically isolated from the fluid flow paths 433 and 454 as well as the outlet 436 (see FIG. 9). As

described in further detail herein, the actuator 450 and/or the control device 400 can be configured to transition to the second state in which the sequestration chamber 434 is sequestered within the housing 430 and the inlet 431 is placed in fluid communication with the fluid flow path 454 (see FIG. 10).

[1113] As described above, the device 400 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 400 to establish fluid communication between the inlet 431 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 431 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 436 can be fluidically coupled to the fluid collection device. As described above, in the embodiment shown in FIGS. 9 and 10 the fluid collection device can be, for example, an evacuated reservoir or container that defines a negative pressure.

[1114] As shown in FIG. 9, the actuator 450 and/or the control device 400 can be in a first or initial state prior to coupling the outlet 436 to the fluid collection device. Thus, the fluid flow path 433 is in fluid communication with the dampening chamber 437 and the fluid flow path 454 is fluidically isolated from the inlet 431 and the sequestration chamber 434 (e.g., via the second plunger 461). As described above, coupling the outlet 436 to the fluid collection device exposes at least a portion of the fluid flow paths 433 and 454 to the negative pressure within the fluid collection device. When the actuator 450 and/or the control device 400 are in the first state, the second plunger 461 isolates the housing 430 and/or the sequestration chamber 434 from the negative pressure exerted via the fluid flow path 454. Conversely, the negative pressure exerted through the fluid flow path 433 can be operable in exerting at least a portion of the negative pressure on the dampening chamber 437 (e.g., via the port 435). In some embodiments, for example, the port 435 can be transitioned from a closed configuration to an open configuration in response to the negative pressure.

[1115] The negative pressure exerted through the fluid flow path 433 is operable in transitioning the actuator 450 from a first state to a second state. For example, in some embodiments, the negative pressure differential draws the dampening fluid 456 from the dampening chamber 437 and into the fluid flow path 433 or a secondary chamber or the like. Moreover, the negative pressure urges the first plunger 460 to transition and/or move relative to the housing 430 from a first configuration or position to a second configuration or position. In some embodiments, the transitioning and/or moving of the first plunger 460 can be such that a volume of the housing 430 defined between the first plunger 460 and the second plunger 461

is increased (i.e., a volume of the sequestration chamber 434 is increased). In some embodiments, the increase in the volume of the sequestration chamber 434 results in a negative pressure therein, which in turn, can be operable in drawing an initial volume of bodily fluid through the inlet 431 and into the sequestration chamber 434. In other words, the negative pressure of the fluid collection device indirectly results in a negative pressure differential between the inlet 431 and the sequestration chamber 434 that is operable in drawing the initial volume of bodily fluid into the sequestration chamber 434.

[1116] As shown in FIG. 10, movement of the first plunger 460 results in a similar movement of the second plunger 461. For example, in some embodiments, the arrangement of the actuator 450 is such that after the first plunger 460 has moved a predetermined amount (and/or after the volume of the sequestration chamber 434 has been increased a predetermined amount) and an initial volume of bodily fluid has been drawn into the sequestration chamber 434, the second plunger 461 is moved or transitioned from a first position and/or configuration to a second position and/or configuration. As such, the actuator 450 is placed in its second state in which the sequestration chamber 434 is sequestered from the inlet 431. In addition, the second plunger 461 and/or the seals 465 coupled thereto place the inlet 431 in fluid communication with the fluid flow path 454. Thus, the negative pressure otherwise exerted on or through the fluid flow path 433 is now exerted on or through the fluid flow path 454. In response, bodily fluid can flow from the inlet 431, through the fluid flow path 454, through the outlet 436, and into the fluid collection device.

[1117] In some embodiments, the transitioning of the actuator 450 from the first state to the second state is operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 434. As described in further detail herein, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 434 when the initial volume is sequestered therein. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 434 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the housing 430 can be such that housing 430 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 434.

[1118] As described above with reference to the control devices 100, 200, and/or 300, the control device 400 is configured to modulate an amount of negative pressure exerted on the

first plunger 460 when the actuator 450 is in the first state. Specifically, in this embodiment, the dampening fluid 456 disposed in the dampening chamber 437 reduces a magnitude of the negative pressure exerted on the first plunger 460. As such, the rate at which the actuator 450 and/or control device 400 is transitioned from the first state to the second state can be controlled. Moreover, in some instances, exposing the housing 430 to the full magnitude of the negative pressure may result transitioning the actuator 450 and/or the control device 400 from the first state to the second state prior to receiving the initial volume of bodily fluid in the sequestration chamber 434. Thus, modulating the magnitude of the pressure can ensure a desired volume of bodily fluid is transferred into the sequestration chamber 434. Although shown in FIGS. 9 and 10 as modulating the negative pressure via the dampening fluid 456, it should be understood that this is presented by way of example only and not limitation. Any other suitable means of dampening and/or modulating a magnitude of the negative pressure can be used to control the transitioning of the actuator 450 and/or housing 430.

[1119] Although the housing 430 is shown in FIGS. 9 and 10 and described above as including the plungers 460 and 461 and being in a syringe-like configuration, in other embodiments, a housing can include any other suitable means for controlling fluid flow therethrough. For example, FIG. 11 and 12 illustrate a fluid control device 500 according to an embodiment. The fluid control device 500 can be similar in at least form and/or function to any of the fluid control devices 100, 200, 300, and/or 400. Accordingly, portions of the fluid control device 500 that can be similar to portions of the fluid control devices 100, 200, 300, and/or 400 are not described in further detail herein. As shown in FIGS. 11 and 12, the fluid control device 500 (also referred to herein as "control device" or "device") includes a housing 530 having an inlet 531 and an outlet 536, and having and/or being coupled to an actuator 550. As described above with reference to the control devices 100, 200, 300, and/or 400, the inlet 531 is configured to be placed in fluid communication with a bodily fluid source to receive a fluid of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like). The outlet 536 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 11 and 12). The inlet 531, the outlet 536, and the fluid collection device can be substantially similar to those described above and thus, are not described in further detail herein.

[1120] As described above, the housing 530 of the control device 500 is configured to (1) receive a flow and/or volume of bodily fluid via the inlet 531 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within the sequestration chamber 534. The housing 530 can be any suitable shape, size, and/or

configuration. In some embodiments, the housing 530 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 534. For example, in the embodiment shown in FIGS. 11 and 12, the housing 530 can be arranged in a substantially similar manner as the housing 430 described above with reference to FIGS. 9 and 10. As described in further detail herein, the housing 530 can differ from the housing 430, by arranging the actuator 550 as, for example, a diaphragm rather than one or more plungers.

[1121] The housing 530 defines a set of fluid flow paths 533 and 554 in fluid communication with the outlet 536 and configured to selectively receive a flow of fluid therethrough (e.g., a liquid and/or a gas). The housing 530 includes and/or is coupled to the actuator 550 configured to selectively control a flow of bodily fluid through the housing 530. In this embodiment, the actuator 550 includes a diaphragm 576 movably disposed within the housing 530 and configured to at least partially define the sequestration chamber 534. More specifically, the actuator 550 is configured to move between a first state in which the inlet 531 is placed in fluid communication with the sequestration chamber 534 (FIG. 11) and a second state in which the inlet 531 is placed in fluid communication with the outlet 536 via the fluid flow path 554 (FIG. 12).

[1122] As shown in FIG. 11, when the actuator 550 and/or control device 500 is in the first state, the inlet 531 is in fluid communication with a portion of the housing 530 defined between the diaphragm 576 and one or more seals 565. Moreover, the diaphragm 576 is disposed in a first state such that a dampening chamber 537 is defined by the housing 530 on a side of the diaphragm 576 opposite the sequestration chamber 534, as described above with reference to the housing 430. As shown, the dampening chamber 537 is configured to be placed in fluid communication with the fluid flow path 533 via a port 535. The port 535 can be an opening, a valve, a membrane, a diaphragm, and/or any other suitable flow controller or the like configured to at least selectively establish fluid communication between the fluid flow path 533 and the dampening chamber 537. Furthermore, when the actuator 550 and/or the control device 500 is in the first state, the dampening chamber 537 includes and/or contains a dampening fluid such as a gas (compressed or uncompressed) and/or a liquid (e.g., water, oil, dampening fluid, and/or any other suitable liquid). As described above with reference to the control devices 400, the arrangement of the dampening chamber 537, the dampening fluid, and the port 535 can be configured to modulate an amount of negative pressure exerted on the diaphragm 576 when the actuator 550 is in the first state. Although shown in FIGS. 11 and 12 as modulating the negative pressure via the dampening fluid, it should be understood that this

is presented by way of example only and not limitation. Any other suitable means of dampening and/or modulating a magnitude of the negative pressure can be used to control the transitioning of the actuator 550 and/or the control device 500.

[1123] As described above with reference to the actuator 450, when the actuator 550 and/or the control device 500 are in the first state, the one or more seals 565 are disposed in a position within the housing 530 such that the one or more seals 565 fluidically isolate, separate, and/or sequester the inlet 531 from the fluid flow path 554. In addition, the one or more seals 565 fluidically isolate the fluid flow path 554 from the sequestration chamber 534. Thus, when the actuator 550 and/or the control device 500 are in the first state, the inlet 531 is in fluid communication with the sequestration chamber 534 and fluidically isolated from the fluid flow paths 533 and 554 as well as the outlet 536 (see FIG. 11). As described in further detail herein, the actuator 550 and/or the control device 500 housing 530 can be configured to transition to the second state in which the sequestration chamber 534 is sequestered within the housing 530 and the inlet 531 is placed in fluid communication with the fluid flow path 554 (see FIG. 12).

[1124] As described in detail above, the device 500 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, and/or the like. For example, in some instances, a user can place the inlet 531 in fluid communication with the bodily fluid source (e.g., the portion of the patient) and can fluidically couple the outlet 536 to the fluid collection device. As shown in FIG. 11, the actuator 550 and/or the device 500 can be in a first or initial state prior to coupling the outlet 536 to the fluid collection device. Thus, the fluid flow path 533 is in fluid communication with the dampening chamber 537 and the fluid flow path 554 is fluidically isolated from the inlet 531 and the sequestration chamber 534 (e.g., via the one or more seals 565), as described in detail above with reference to the control device 400 of FIGS. 9 and 10.

[1125] Coupling the outlet 536 to the fluid collection device selectively exposes at least a portion of the fluid flow paths 533 and 554 to the negative pressure within and/or produced by the fluid collection device. When the actuator 550 and/or the device 500 are in the first state, the one or more seals 565 isolate the housing 530 and/or the sequestration chamber 534 from the negative pressure exerted via the fluid flow path 554. Conversely, the negative pressure exerted through the fluid flow path 533 can be operable in exerting at least a portion of the negative pressure on the dampening chamber 537 (e.g., via the port 535). In some embodiments, for example, the port 535 can be transitioned from a closed configuration to an open configuration in response to the negative pressure. The negative pressure exerted through the fluid flow path 533 is operable in transitioning the actuator 550 from a first state to a second

state. For example, in some embodiments, the negative pressure differential draws the dampening fluid from the dampening chamber 537 and into the fluid flow path 533. Moreover, the negative pressure urges the diaphragm 576 to transition, flip, move, switch, deform, etc., from a first configuration or state (FIG. 11) to a second configuration or state (FIG. 12). As described above with reference to the actuator 450, the transitioning of the diaphragm 576 from the first state to the second state can be such that a volume of the housing 530 defined between the diaphragm 576 and the one or more seals 565 is increased (i.e., a volume of the sequestration chamber 534 is increased), which in turn, results in a negative pressure therein that can be operable in drawing an initial volume of bodily fluid through the inlet 531 and into the sequestration chamber 534.

[1126] As shown in FIG. 12, movement of the diaphragm 576 results in a similar movement of the one or more seals 565 such that the one or more seals 565 are disposed on the same side of the inlet 531 as the diaphragm 576. Thus, the sequestration chamber 534 is sequestered within the housing 530. In addition, moving the one or more seals 565 is such that fluid communication is established between the inlet 531 and the fluid flow path 554. Thus, the negative pressure otherwise exerted on or through the fluid flow path 533 is now exerted on or through the fluid flow path 554. In response, bodily fluid can flow from the inlet 531, through the fluid flow path 554, through the outlet 536, and into the fluid collection device, as described in detail above. In some embodiments, the transitioning of the actuator 550 from the first state to the second state is operable to sequester and/or retain the initial portion of the bodily fluid in the sequestration chamber 534, which can include contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 534 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 500 and/or the housing 530 can be such that the control device 500 and/or the housing 530 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 534.

[1127] FIGS. 13-15 illustrate a fluid control device 600 according to an embodiment. The fluid control device 600 can be similar in at least form and/or function to any of the fluid control devices 100, 200, 300, 400, and/or 500. Accordingly, portions of the fluid control device 600 that can be similar to portions of the fluid control devices 100, 200, 300, 400, and/or 500 are not described in further detail herein. As shown in FIGS. 13-15, the fluid control device 600

(also referred to herein as "control device" or "device") includes a housing 630 having an inlet 631 and an outlet 636, and having and/or being coupled to an actuator 650. As described above with reference to the control devices 100, 200, 300, 500, and/or 500, the inlet 631 is configured to be placed in fluid communication with a bodily fluid source to receive a fluid of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like). The outlet 636 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 13-15). The inlet 631, the outlet 636, and the fluid collection device can be substantially similar to those described above and thus, are not described in further detail herein.

[1128] As described above, the housing 630 of the control device 600 is configured to (1) receive a flow and/or volume of bodily fluid via the inlet 631 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within a sequestration chamber 634 included in and/or at least partially formed by the housing 630. The housing 630 can be any suitable shape, size, and/or configuration. In some embodiments, the housing 630 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 634. For example, in the embodiment shown in FIGS. 13-15, the housing 630 can be arranged in a substantially similar manner as the housing 530 described above with reference to FIGS. 11 and 12. That is to say, the housing 630 includes an actuator 650 that is arranged as a diaphragm.

[1129] The housing 630 defines a set of fluid flow paths 633 and 654 in fluid communication with the outlet 636 and configured to selectively receive a flow of fluid therethrough (e.g., a liquid and/or a gas). The housing 630 includes and/or is coupled to the actuator 650 configured to selectively control a flow of bodily fluid through the housing 630. In this embodiment, the actuator 650 includes a diaphragm 676 movably disposed within the housing 630 and configured to at least partially define the sequestration chamber 634. More specifically, the actuator 650 is configured to move between a first state in which the inlet 631 is placed in fluid communication with the sequestration chamber 634 and a second state in which the inlet 631 is placed in fluid communication with the outlet 636 via the fluid flow path 654, as described in detail above with reference to the control device 500.

[1130] As shown in FIGS. 14 and 15, when the actuator 650 and/or the device 600 is in the first state, the inlet 631 is in fluid communication with a portion of the housing 630 defined between the diaphragm 676 and one or more seals 665. Moreover, the diaphragm 676 is disposed in a first state such that a dampening chamber 637 is defined by the housing 630 on a side of the diaphragm 676 opposite the sequestration chamber 634, as described above with reference to the housing 530. As shown, the dampening chamber 637 is configured to be placed

in fluid communication with the fluid flow path 654 via a port 635 (such as those described above). Although not shown, when the actuator 650 and/or the device 600 is in the first state, the dampening chamber 637 includes and/or contains a dampening fluid such as a gas (compressed or uncompressed) and/or a liquid (e.g., water, oil, dampening fluid, and/or any other suitable liquid), that can be configured to modulate an amount of negative pressure exerted on the diaphragm, as described in detail above with reference to the control device 500. Although described as modulating the negative pressure via the dampening fluid, it should be understood that this is presented by way of example only and not limitation. Any other suitable means of dampening and/or modulating a magnitude of the negative pressure can be used to control the transitioning of the actuator 650 and/or device 600.

[1131] As described above with reference to the actuator 550, when the actuator 650 and/or the device 600 are in the first state, the seal 665 is disposed in a position within the housing 630 such that the seal 665 fluidically isolates, separates, and/or sequesters the inlet 631 from the fluid flow path 654. In addition, the seal 665 fluidically isolates the fluid flow path 654 from the sequestration chamber 634. Thus, when the actuator 650 and/or the device 600 are in the first state, the inlet 631 is in fluid communication with the sequestration chamber 634 and fluidically isolated from the fluid flow path 654 as well as the outlet 636. The actuator 650 and/or the device 600 can be configured to transition to the second state in which the sequestration chamber 634 is sequestered within the housing 630 and the inlet 631 is placed in fluid communication with the fluid flow path 654. Accordingly, the device 600 can be used to procure a bodily fluid sample having reduced contamination from microbes (e.g., dermally residing microbes and/or the like), in a substantially similar manner as the device 500 described above with reference to FIGS. 11 and 12. Thus, the functioning of the device 600 is not described in further detail herein.

[1132] FIGS. 16-18 illustrate a fluid control device 700 according to an embodiment. The fluid control device 700 can be similar in at least form and/or function to any of the fluid control devices 100, 200, 300, 400, 500, and/or 600. Accordingly, portions of the fluid control device 700 that can be similar to portions of the fluid control devices 100, 200, 300, 400, 500, and/or 600 are not described in further detail herein. As shown in FIGS. 16-18, the fluid control device 700 (also referred to herein as "control device" or "device") includes a housing 730 having an inlet 731 and an outlet 736, and having or being coupled to an actuator 750. As described above with reference to the control devices 100, 200, 300, 400, 500, and/or 600, the inlet 731 is configured to be placed in fluid communication with a bodily fluid source to receive a fluid of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the

like). The outlet 736 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 16-18). The inlet 731, the outlet 736, and the fluid collection device can be substantially similar to those described above and thus, are not described in further detail herein.

[1133] As described above, the housing 730 of the control device 700 is configured to (1) receive a flow and/or volume of bodily fluid via the inlet 731 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within the sequestration chamber 734. The housing 730 can be any suitable shape, size, and/or configuration. In some embodiments, the housing 730 can have a size that is at least partially based on a volume of bodily fluid at least temporarily stored, for example, in the sequestration chamber 734. For example, in the embodiment shown in FIGS. 16-18, the housing 730 can be arranged in a substantially similar manner as the housings 530 and/or 630. That is to say, the housing 530 includes and/or is coupled to the actuator 750 that is arranged as a diaphragm.

[1134] The housing 730 defines a set of fluid flow paths 733 and 754 in fluid communication with the outlet 736 (see e.g., FIGS. 17A and 17B) and configured to selectively receive a flow of fluid therethrough (e.g., a liquid and/or a gas). The housing 730 includes and/or is coupled to the actuator 750 configured to selectively control a flow of bodily fluid through the housing 730. In this embodiment, the actuator 750 includes a diaphragm 776 movably disposed within the housing 730 and configured to at least partially define the sequestration chamber 734. More specifically, the actuator 750 is configured to move between a first state in which the inlet 731 is placed in fluid communication with the sequestration chamber 734 and a second state in which the inlet 731 is placed in fluid communication with the outlet 736 via the fluid flow path 754, as described in detail above with reference to the control device 500.

[1135] In the embodiment shown in FIGS. 16-18, when the actuator 750 and/or the device 700 are in the first state, the inlet 731 is in fluid communication with the sequestration chamber 734 formed by a portion of the housing 730 defined between the diaphragm 776 and a flow controller 742 (e.g., a selectively permeable fluid barrier or seal, and/or any other flow controller such as any of those described above). Moreover, the diaphragm 776 is disposed in a first state such that the fluid flow path 733 is in fluid communication with the sequestration chamber 734. As described above with reference to the actuator 550, when in the actuator 750 and/or device 700 are in the first state, the diaphragm 776 and/or the seal 765 are disposed in a position within the housing 730 such that the diaphragm 776 and/or the seal 765 fluidically isolate, separate, and/or sequester the inlet 731 from the fluid flow path 754. In addition, the

diaphragm 776 and/or the seal 765 fluidically isolate the fluid flow path 754 from the sequestration chamber 734. Thus, when the actuator 750 and/or the device 700 are in the first state, the inlet 731 is in fluid communication with the sequestration chamber 734 and fluidically isolated from the fluid flow path 754.

[1136] As described above with reference to, for example, the control device 200, when the actuator 750 and/or the device 700 are in the first state, a negative pressure differential within the sequestration chamber 734 can result from the coupling of the fluid collection device to the outlet 736. More specifically, the fluid flow path 733 can be in fluid communication with the outlet 736 and the flow controller 742. When the flow controller 742 is in a first state, the flow controller 742 can allow a gas or air to pass therethrough. Thus, the negative pressure differential within the sequestration chamber 734 can result from the coupling of the fluid collection device to the outlet 736.

[1137] As shown in FIG. 18, the actuator 750 and/or the device 700 can be configured to transition to the second state in which the sequestration chamber 734 is sequestered within the housing 730 and the inlet 731 is placed in fluid communication with the fluid flow path 754, as described in detail above with reference to the control device 600. More particularly, an initial volume of bodily fluid can be transferred into the sequestration chamber 734, which in turn, can saturate, can wet, and/or otherwise can transition the flow controller 742 from the first or open state to a second or closed state. In some embodiments, the transitioning of the flow controller 742 from the first state to the second state is operable in isolating the fluid flow path 733 from the outlet 736. As such, a negative pressure exerted through the fluid flow path 754 can be operable in transitioning, switching, flipping, moving, deforming, and/or otherwise reconfiguring the diaphragm 776 such that the actuator 750 is placed in its second state. As such, the negative pressure of the fluid collection device can draw bodily fluid from the inlet 731, through the housing 730 (bypassing the sequestration chamber 734), through the fluid flow path 754 and the outlet 736, and into the fluid collection device, as described in detail above. Accordingly, the device 700 can be used to procure a bodily fluid sample having reduced contamination from microbes (e.g., dermally residing microbes and/or the like), in a manner substantially similar to one or more of the control devices 100, 200, 300, 400, 500, and/or 600 described in detail above. Thus, the functioning of the device 700 is not described in further detail herein.

[1138] In some embodiments, any of the control devices 100, 200, 300, 400, 500, 600, and/or 700 can be formed from any suitable components that can be manufactured, assembled, sterilized, and packaged as an assembly or integrated device. In such embodiments, a user can,

for example, open a packaging containing such an assembly or integrated device and can use the device as described above with reference to the control devices 100, 200, 300, 400, 500, 600, and/or 700. In some embodiments, any of the control devices can be monolithically formed in whole or at least in part.

[1139] In some embodiments any of the control devices can be physically coupled, attached, formed, and/or otherwise mated to a fluid collection device (e.g., a sample reservoir, a syringe, a blood culture bottle, a collection vial, a fluid transfer container, and/or any other suitable reservoir, collection device, and/or transfer device) during a manufacturing process. This can be done prior to sterilization so the collection pathway(s) and connection interface(s) (e.g., where the control device couples to the fluid collection device) maintain a closed-system, mechanical diversion device within a sterile environment that is not subject to touch-point contamination from external sources. In this manner, in order for a user to transfer a sample volume to the fluid collection device, the user would be forced first to sequester, segregate, and/or isolate at least a portion of the initial bodily fluid volume or flow. In some embodiments, the coupling, mating, and/or attachment of the fluid control device to the fluid collection device can be executed such that the control device can be removed (physically decoupled, removed with a specific "key," and/or any other approach used to separate the control device from the fluid collection device) after use to allow access to the fluid collection device, which can then be placed in an incubator and/or any other type of analytical machine, and accessed for analysis and/or otherwise further processed. In some embodiments, such decoupling may be blocked, limited, and/or substantially prevented prior to use and unblocked or allowed after use. In other embodiments, the fluid control device and the fluid collection device can be permanently coupled and/or monolithically formed (at least in part) to prevent such decoupling.

[1140] While described above as being coupled and/or assembled, for example, during manufacturing, in other embodiments, however, a control device can include one or more modular components that can be selected by a user based on a desired use, preference, patient, etc. In such embodiments, the user can couple one or more modular components (packaged together or packaged separately) to form the desired fluid control device. For example, FIGS. 19-25 illustrate a modular fluid control device 800 according to an embodiment. The fluid control device 800 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 800 can be similar to and/or substantially the same as corresponding portions of the fluid control device 200 described above with reference to FIGS. 2-5. Accordingly, such portions of the fluid control device 800 are not described in further detail herein.

[1141] The fluid control device 800 (also referred to herein as "control device" or "device") includes a housing 830 and an actuator 850. As described above, the control device 800 can be at least partially monolithically formed or can be otherwise preassembled during manufacturing. In other embodiments, the control device 800 can be at least partially modular such that a user can physically and fluidically couple the housing 830 and the actuator 850 to form the control device 800. The housing 830 of the device 800 can be any suitable shape, size, and/or configuration. For example, in the embodiment shown in FIGS. 19-25, the housing 830 can be, for example, relatively thin and substantially rectangular. In some embodiments, portions of the housing 830 can be substantially similar in at least form and/or function to the housing 230 described above with reference to FIGS. 2-5. Thus, while such portions are identified, similar components, features, and/or functions are not described in further detail herein.

[1142] As shown in FIGS. 19 and 20, the housing 830 forms and/or defines a sequestration chamber 834 that is in selective fluid communication with a first port 845 and a second port 846. The first port 845 and the second port 846 are configured to be at least fluidically coupled to a portion of the actuator 850 to allow for selective fluid flow between the housing 830 and the actuator 850. As described in further detail herein, the sequestration chamber 834 is configured (1) to receive a selective flow and/or volume of bodily fluid from a portion of the actuator 850 via the first port 845, and (2) to sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid (e.g., an initial or first flow and/or volume of bodily fluid or any portion thereof) within the sequestration chamber 834. The sequestration chamber 834 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 834 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 134. In the embodiment shown in FIGS. 19-25, the sequestration chamber 834 can be, for example, a fluid flow path that extends through and/or that is defined by at least a portion of the housing 830. In some embodiments, the sequestration chamber 834 can be substantially similar in at least form and/or function to the sequestration chamber 234 described above with reference to FIGS. 2-5 and thus, is not described in further detail herein.

[1143] As shown in FIG. 20, the housing 830 includes and/or defines a flow controller 842 and a restricted flow path 832. The flow controller 842 can be, for example, a valve, membrane, diaphragm, restrictor, vent, a selectively permeable member, port, etc. configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 834 and/or any other suitable portion of the housing 830. For example, the flow controller 842 can be a

selectively permeable fluid barrier (e.g., a blood barrier) that includes and/or is formed of a porous material configured to selectively allow a flow of gas therethrough but to prevent a flow of a liquid therethrough. In some embodiments, the flow controller 842 can be substantially similar to the flow controller 242 described in detail above with reference to FIGS. 2-5 and thus, is not described in further detail herein.

[1144] As shown, the restricted flow path 832 defined by the housing 830 is in fluid communication with the second port 846 and is positioned between the second port 846 and the flow controller 842 (or a portion of the housing 830 receiving or housing the flow controller 842). As described above with reference to the restricted flow path 232 shown in FIGS. 2-5, the restricted flow path 832 is a fluid flow path having a smaller diameter than, for example, one or more other flow paths defined by the housing 830 and/or actuator 850. For example, in some embodiments, the restricted flow path 832 can have a diameter between about 0.0005" to about 0.5" and can have a length between about 0.01" and about 0.5", as described above with reference to the restricted flow path 232. As described above, the smaller diameter of the restricted flow path 832 results in a lower magnitude of negative pressure being applied through the sequestration chamber 834 than a magnitude of negative pressure when the restricted flow path 832 has a larger diameter. In other words, the restricted flow path 832 can be configured to modulate an amount of negative pressure to which the sequestration chamber 834 is exposed. In some instances, modulating the amount of negative pressure can control a rate at which bodily fluid is transferred into the sequestration chamber 834. Moreover, in this embodiment, the restricted flow path 832 is, for example, a gas flow path configured to receive a flow of gas or air but not a flow of a liquid (e.g., bodily fluid), which can allow for a negative pressure differential sufficient to successfully collect the initial volume of bodily fluid and/or sufficient to transition at least a portion of the control device 800 to a second state, while limiting and/or substantially preventing a portion of the initial or first volume of bodily fluid from being drawn through the sequestration chamber 834 and the second port 846.

[1145] As shown in FIGS. 19-24, the actuator 850 includes a body 851 and an actuator rod 862. The body 851 of the actuator 850 includes an inlet 852 and an outlet 853. The inlet 852 and the outlet 853 can be substantially similar in at least form and/or function to the inlet 231 and the outlet 236, respectively, described above with reference to FIGS. 2-5. Thus, the inlet 852 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, PICC line, or the like). The outlet 853 is configured to be fluidically coupled to a fluid collection device 880 such as, for example, a sample reservoir, a syringe, and/or other

intermediary bodily fluid transfer device, adapter, or vessel (see e.g., FIG. 25) such as, for example, a transfer device similar to those described in the '510 publication.

[1146] As shown in FIG. 21, the body 851 of the actuator 850 includes and/or defines a first port 858 and a second port 859. The first port 858 is in fluid communication with the inlet 852 and the second port 859 is in fluid communication with the outlet 853. In addition, the first port 858 and the second port 859 are configured to be at least fluidically coupled to the first port 845 and the second port 846, respectively, of the housing 830. As described in further detail herein, the actuator 850 can be transitioned between a first operating mode or state and a second operating mode or state to selectively control fluid flow through the ports 858 and 859 of the actuator 850 and the ports 845 and 846 of the housing 830, which in turn, can selectively control a flow of bodily fluid into and/or out of the sequestration chamber 834 of the housing 830.

[1147] In some embodiments, the arrangement of the ports 858 and 859 of the actuator 850 and the ports 845 and 846 of the housing 830 can allow for and/or otherwise can provide a means of physically coupling the housing 830 to the actuator 850 as well as fluidically coupling the housing 830 to the actuator 850. For example, in some embodiments, the ports 858 and 859 of the actuator 850 and the ports 845 and 846 of the housing 830 can form a friction fit, a press fit, an interference fit, and/or the like. In other embodiments, the ports 858 and 859 of the actuator 850 can be coupled to the ports 845 and 846, respectively, of the housing 830 via an adhesive, a mechanical fastener, an elastomeric coupling, a gasket, an o-ring(s), and/or any other suitable coupling means. In still other embodiments, the ports 858 and 859 of the actuator 850 can be physically and fluidically coupled to the ports 845 and 846, respectively, of the housing 830 via an intervening structure such as, for example, one or more sterile, flexible tubing(s). As such, the device 800 can be and/or can have, for example, a modular configuration in which the housing 830 can be at least fluidically coupled to the actuator 850.

[1148] In some embodiments, such a modular arrangement can allow a user to select a housing (or actuator) with one or more desired characteristics based on, for example, the intended purpose and/or use of the assembled device. In other embodiments, the modular arrangement can allow and/or facilitate one or more components with desired characteristics to be coupled and/or assembled during manufacturing. For example, in some instances, it may be desirable to select a housing that includes and/or defines a sequestration chamber having a particular or desired volume. As a specific example, when the device is being used to procure bodily fluid from a pediatric patient and/or a very sick patient (for example), it may be desirable to select a housing that defines and/or includes a sequestration chamber with a smaller volume

than may otherwise be selected when the device is being used to procure bodily fluid from a seemingly healthy adult patient. Accordingly, such a modular arrangement can allow a user (e.g., a doctor, physician, nurse, technician, phlebotomist, etc.) to select a housing or an actuator having one or more desired characteristics based on, for example, the intended use of the device. In other instances, the modular arrangement can allow or facilitate assembly of a housing or an actuator having one or more desired characteristics during manufacturing without making significant changes to one or more manufacturing processes.

[1149] The actuator rod 862 of the actuator 850 is movably disposed within a portion of the body 851. The actuator rod 862 includes a first end portion 863 and a second end portion 864, at least one of which extends beyond the body 851 of the actuator 850 with the actuator rod 862 is disposed within the body 851 (see e.g., FIGS. 23 and 24). A portion of the actuator rod 862 includes and/or is coupled to a set of seals 865. The seals 865 can be, for example, o-rings, elastomeric over-molds, proud or raised dimensions or fittings, and/or the like. The arrangement of the actuator 862 and the body 851 of the actuator 850 can be such that an inner portion of the seals 865 forms a fluid tight seal with a surface of the actuator rod 862 and an outer portion of the seals 865 forms a fluid tight seal with an inner surface of the body 851. In other words, the seals 865 form one or more fluid tight seals between the actuator rod 862 and the inner surface of the body 851. As shown in FIGS. 23 and 24, the actuator rod 862 includes and/or is coupled to three seals 865 which form and/or define a first fluid flow path 833 within the body 851 of the actuator 850 and a second fluid flow path 854 within the body 851 of the actuator 850.

[1150] The actuator rod 862 is configured to be moved or transitioned relative to the body 851 between a first position or configuration and a second position or configuration. For example, in some instances, a force can be exerted on the first end portion 863 of the actuator rod 862 to place the actuator rod 862 in its first position and/or configuration, as shown in FIG. 23. The force exerted on the first end portion 863 of the actuator rod 862 can come from any suitable source. For example, a user can create the force with his or her hand or finger, a syringe, a positive or negative pressure source, and/or any other external energy source. When in the first position and/or configuration, the inlet 852 of the actuator 850 is in fluid communication with the first fluid flow path 833 and the outlet 853 of the actuator 850 is in fluid communication with the second fluid flow path 854. In some instances, a force can be exerted on the second end portion 864 of the actuator rod 862 to place the actuator rod 862 in its second position and/or configuration, as shown in FIG. 24. When in the second position and/or configuration, the inlet 852 and the outlet 853 of the actuator 850 are each in fluid

communication with the second fluid flow path 854 while the first fluid flow path is sequestered, isolated, and/or otherwise not in fluid communication with the inlet 852 and the outlet 853. Although not shown, the first port 858 of the actuator 850 is in fluid communication with the first fluid flow path 833 and the second port 859 of the actuator 850 is in fluid communication with the second fluid flow path 854. As such, moving and/or transitioning the actuator rod 862 (or the actuator 850 in general) between the first position and the second position can be operable in selectively controlling a flow of fluid (e.g., bodily fluid) between the inlet 852 of the actuator 850 and the housing 830, or between the inlet 852 of the actuator 850 and the outlet 853 of the actuator 850, as described in further detail herein.

[1151] As described above, the device 800 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, microbes external to the bodily fluid source, and/or the like. For example, in some instances, a user such as a doctor, physician, nurse, phlebotomist, technician, etc. can manipulate the device 800 to establish fluid communication between the inlet 852 and the bodily fluid source (e.g., a vein of a patient). Once the inlet 852 is placed in fluid communication with the bodily fluid source (e.g., the portion of the patient), the outlet 853 can be fluidically coupled to the fluid collection device 880. In the embodiment shown in FIGS. 19-25, the fluid collection device 880 can be, for example, a syringe (as shown in FIG. 25), and/or any other suitable container or device configured to define or produce a negative pressure or energy source.

[1152] As described in detail above with reference to, for example, the device 200, coupling the outlet 853 to the fluid collection device 880 selectively exposes at least a portion of the control device 800 to a negative pressure within and/or produced by the fluid collection device 880. More specifically, in the embodiment shown in FIGS. 19-25, coupling the outlet 853 to the fluid collection device 880 exposes the outlet 853 of the actuator 850 and the second fluid flow path 854 to the negative pressure within and/or produced by the fluid collection device 880. In addition, the second port 859 of the actuator 850 is in fluid communication with the second fluid flow path 854 and the second port 846 of the housing 830. The second port 846 of the housing 830, in turn, is in selective fluid communication with the sequestration chamber 834 via the flow controller 842 and the restricted flow path 832. For example, the device 800 and/or the flow controller 842 can be in a first operating state or mode in which the flow controller 842 allows a flow of gas (e.g., air) through the flow controller 842 while limiting and/or preventing a flow of liquid (e.g., bodily fluid such as blood) through the flow controller 842. Thus, coupling the fluid collection device 880 to the outlet 853 results in a

negative pressure differential between the fluid collection device 880 (and/or any suitable negative pressure source) and the sequestration chamber 834.

[1153] As described above, the control device 800 can be in a first or initial state when the flow controller 842 and/or the actuator 850 are in a first state, position, configuration, etc. As such, the actuator rod 862 can be in its first position and/or configuration in which the first fluid flow path 833 is in fluid communication with the inlet 852. In addition, the first port 858 of the actuator 850 and the first port 845 of the housing 830 establish fluid communication between the sequestration chamber 834 and the first fluid flow path 833. Thus, the negative pressure within the fluid collection device 880 can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 834 that is operable in drawing an initial flow, portion, amount, or volume of bodily fluid from the inlet 852, through the first fluid flow path 833, and into the sequestration chamber 834 when the actuator 850 and/or control device 800 is in the first or initial state (e.g., when the actuator rod 862 is in its first state, position, and/or configuration). In some instances, the arrangement of the flow controller 842 and/or the restricted flow path 832 can be configured to restrict, limit, control, and/or otherwise modulate an amount or magnitude of negative pressure exerted on or through the sequestration chamber 834, as described in detail above with reference to the device 200.

[1154] The initial portion and/or amount of bodily fluid can be any suitable volume of bodily fluid, as described in detail above with reference to the control device 100. For example, in some instances, the initial volume can be associated with and/or at least partially based on an amount or volume of bodily fluid that is sufficient to fully wet or saturate the flow controller 842. In other words, in some embodiments, the initial volume of bodily fluid can be a volume sufficient to transition the flow controller 842 from a first state to a second state (e.g., a saturated or fully wetted state). In some embodiments, the flow controller 842 is placed in a sealed configuration when transitioned to the second state. That is to say, saturating and/or fully wetting the flow controller 842 (e.g., the semi-permeable material) places the flow controller 842 in a sealed configuration in which the flow controller 842 substantially prevents a flow of a liquid and a gas therethrough. Thus, transitioning the flow controller 842 to the second state sequesters, blocks, isolates, separates, segregates, and/or otherwise prevents flow through the flow controller 842 between the restricted flow path 832 and the sequestration chamber 834.

[1155] After the initial volume of bodily fluid is transferred and/or diverted into the sequestration chamber 834, the control device 800 and/or the actuator 850 can be transitioned to its second state or operating mode to sequester, segregate, retain, contain, isolate, etc. the

initial volume in the sequestration chamber 834. For example, the actuator 850 can be actuated to transition from its first state to its second state, for example, by exerting a force on the second end portion 864 of the actuator rod 862. As such, the actuator rod 862 is moved and/or transitioned to its second state, position, and/or configuration in which the first fluid flow path 833 is sequestered and/or isolated from the inlet 852. With the flow controller 842 in the sealed configuration in response to the initial volume of bodily fluid being disposed in the sequestration chamber 834 and with the initial fluid flow path 833 sequestered and/or isolated from the inlet 852, the initial volume of bodily fluid is sequestered in the sequestration chamber 834. As described in detail above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 834 when the initial volume is sequestered therein.

[1156] As shown in FIG. 24, moving and/or transitioning the control device 800 and/or the actuator 850 to its second state or configuration establishes fluid communication between the inlet 852 and the outlet 853 via the second fluid flow path 854. As such, the negative pressure otherwise exerted on or through the sequestration chamber 834 is now exerted on or through the fluid flow path 854. In response, bodily fluid can flow from the inlet 852, through the fluid flow path 854, through the outlet 853, and into the fluid collection device 880. Thus, as described above, sequestering the initial volume of bodily fluid in the sequestration chamber 834 prior to collecting or procuring one or more sample volumes of bodily fluid reduces and/or substantially eliminates an amount of contaminants in the one or more sample volumes. Moreover, in some embodiments, the arrangement of the control device 800 can be such that the control device 800 cannot transition to the second state prior to collecting and sequestering the initial volume in the sequestration chamber 834, thereby reducing the likelihood of contaminants being transferred to the fluid collection device 880.

[1157] In some instances, it may be desirable to isolate the negative pressure source (e.g., the fluid collection device 880 from the inlet 853 such as, for example, if it is desirable to collect multiple samples of bodily fluid using multiple fluid collection device 880 (e.g., syringes). For example, in some instances, after filling the fluid collection device 880 the user can engage the actuator 850 and exert a force on the first end portion 863 of the actuator rod 862 to move and/or transition the actuator rod 862 from its second position and/or configuration toward its first position and/or configuration. As such, the second fluid flow path 854 no longer places the inlet 852 in fluid communication with the outlet 853. Moreover, the flow controller 842 can remain in the sealed state or configuration (e.g., fully saturated, wetted, and/or

otherwise preventing flow therethrough) such that the outlet 853 is substantially sequestered or isolated from the rest of the control device 800. In some instances, the user can then remove the filled fluid collection device 880 (e.g., syringe) and can couple a new fluid collection device 880 (e.g., syringe) to the outlet 853. With the new fluid collection device 880 coupled to the outlet 853, the user can, for example, exert a force on the second end portion 864 of the actuator rod 862 to move and/or transition the actuator rod 862 back to its second position, state, and/or configuration, as described above.

[1158] While the fluid collection device 880 coupled to the device 800 is shown in FIG. 25 as being a syringe, in other embodiments, a control device can be physically and/or fluidically coupled to any suitable collection device. For example, FIG. 26 illustrates a fluid control device 900. As described above with reference to the control device 800, the fluid control device 900 includes a housing 930 and an actuator 950, which can be arranged, for example, in a modular configuration or the like. The actuator 950 includes an inlet 952 configured to be placed in fluid communication with a bodily fluid source and an outlet 953 configured to be coupled to a fluid collection device 980. In the embodiment shown in FIG. 26, the fluid collection device 980 is a transfer adapter configured to be coupled to one or more reservoirs such as, for example, an evacuated container, a sample bottle, a culture bottle, etc. In such embodiments, the reservoir can be sealed prior to being coupled to the transfer adapter (i.e., the fluid collection device 980) and once coupled the seal can be punctured, displaced, deformed, and/or otherwise unsealed to expose the outlet 953 to the negative pressure within the reservoir. Thus, the fluid control device 900 can function in a substantially similar manner to the control device 800 described above with reference to FIGS. 19-25.

[1159] While the fluid control device 800 is shown as including the actuator rod 862 that includes the first end portion 863 and the second portion 864 on which a force can be exerted to transition the device 800 between its first and second configurations, states, and/or positions, in other embodiments, a control device can include an actuator having any suitable configuration. For example, the fluid control device 900 includes an actuator rod 962 having only a single end portion that extends beyond the body 951 of the actuator 950, as shown in FIG. 26. In such embodiments, the device 900 can be used to fill a fluid collection device such as, for example, a sample reservoir, container, bottle, etc. and if it is desirable for more than one sample to be collected, the user can, for example, decouple the inlet 952 from a lumen-containing device and/or any suitable device otherwise placing the inlet 952 in fluid communication with the bodily fluid source. Once decoupled, the user can couple the inlet of a new control device 900 to the lumen-containing device and/or the like and can collect one or

more additional samples in a manner similar to that described above with reference to the control device 800.

[1160] As described above, some fluid control device described herein can be and/or can have a modular configuration in which one or more components can be coupled to collectively form a fluid control device having a desired set of characteristics or the like. For example, the fluid control device 800 shown in FIGS. 19-25 includes the housing 830 and the actuator 850 in one modular arrangement. It should be understood, however, that a control device can have any suitable modular arrangement. For example, FIG. 27 illustrates a modular fluid control device 1000 according to an embodiment. The fluid control device (also referred to herein as "device") includes a housing 1030 forming and/or defining a sequestration chamber 1034, and an actuator 1050 forming and/or having an inlet 1052 and an outlet 1053. The device 1000 can be substantially similar to the control device 800 described in detail above but can be arranged such that housing 1030 is disposed in different position and/or orientation relative to the actuator 1050. In some embodiments, varying the arrangement may, for example, enhance usability, visibility, and/or the like and/or may otherwise allow for a more compact design.

[1161] As another example, FIG. 28 illustrates a modular fluid control device 1100 according to an embodiment. The fluid control device (also referred to herein as "device") includes a housing 1130 forming and/or defining a sequestration chamber 1134, and an actuator 1150 forming and/or having an inlet 1152 and an outlet 1153. The device 1100 can be substantially similar to the control device 800 described in detail above but can be arranged such that housing 1130 is disposed in different position and/or orientation relative to the actuator 1150. Moreover, as shown in FIG. 28, the actuator 1150 can be arranged such that the inlet 1152 and the outlet 1153 are disposed in substantially perpendicular positions relative to one another. As described above, in some embodiments, varying the arrangement may, for example, enhance usability, visibility, and/or the like and/or may otherwise allow for a more compact design. While examples of modular fluid control devices are shown herein, it should be understood that such embodiments are presented by way of example and not limitation. Thus, while specific arrangements and/or orientations may be described herein, the devices and/or concepts described herein are not intended to be limited to those shown herein.

[1162] While the housings 230, 330, 830, 930, 1030, and 1130 have been shown and described herein as including and/or defining a sequestration chamber that is arranged in a serpentine-like configuration, in other embodiments, a housing and/or any other suitable portion of a control device can include and/or can define a sequestration chamber having any suitable configuration. For example, FIGS. 29-34 illustrate a fluid control device 1200

according to an embodiment. The fluid control device 1200 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 1200 can be similar to and/or substantially the same as corresponding portions of the fluid control devices 200, 300, 800, 900, 1000, and/or 1100 described above. Accordingly, such portions of the fluid control device 1200 are not described in further detail herein.

[1163] The fluid control device 1200 (also referred to herein as "control device" or "device") includes a housing 1230 and an actuator 1250. As described above with reference to the control device 800, the control device 1200 can be arranged in a modular configuration such that the housing 1230 and the actuator 1250 can be physically and fluidically coupled to form the control device 1200. In other embodiments, the control device 1200 need not be modular. That is to say, in some embodiments, the control device 1200 can be assembled during manufacturing and delivered to a supplier and/or end user as an assembled device. In other embodiments, the control device can be monolithically formed and/or coupled to a fluid collection device in any suitable manner, as described in detail above.

[1164] The housing 1230 of the control device 1200 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the housing 1230 can be substantially similar in at least form and/or function to the housing 830 described in detail above. Accordingly, such similar portions of the housing 1230 are identified below but may not be described in further detail herein.

[1165] As shown in FIGS. 29-31, the housing 1230 forms and/or defines a sequestration chamber 1234 that is in selective fluid communication with a first port 1245 and a second port 1246. The second port 1246 is configured to receive, include, and/or define a flow controller 1242 (see e.g., FIG. 30) and a restricted flow path 1232 (see e.g., FIG. 31). Although shown as including the restricted flow path 1232, in other embodiments, a housing need not include or receive a restricted flow path (e.g., when excessive negative pressure being applied to the sequestration chamber 1234 is unlikely or otherwise not intended such as when a fluid collection device is a syringe or the like). The first port 1245 and the second port 1246 are configured to be at least fluidically coupled to a portion of the actuator 1250 to allow for selective fluid flow between the housing 1230 and the actuator 1250. As described in further detail herein, the sequestration chamber 1234 is configured (1) to receive a selective flow and/or volume of bodily fluid from a portion of the actuator 1250 via the first port 1245, and (2) to sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume

of bodily fluid (e.g., an initial or first flow and/or volume of bodily fluid or any portion thereof) within the sequestration chamber 1234.

[1166] The sequestration chamber 1234 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 1234 can have any suitable size, volume, and/or fluid capacity such as, for example, those described above with reference to the sequestration chamber 134. In the embodiment shown in FIGS. 29-34, the sequestration chamber 1234 can be, for example, a fluid flow path that extends through and/or that is defined by at least a portion of the housing 1230. In some embodiments, the sequestration chamber 1234 can be substantially similar in at least form and/or function to the sequestration chamber 834 described above with reference to FIGS. 19-25. The sequestration chamber 1234 and/or the housing 1230 can differ from the sequestration chamber 834 and/or the housing 830 by being arranged in a spiral configuration with the first port 1245 being in fluid communication with, for example, an inner portion of the spiraled sequestration chamber 1234 and the second port 1246 being in fluid communication with, for example, an outer portion of the spiraled sequestration chamber, as shown in FIG. 30. In some embodiments, the sequestration chamber 1234 can be, for example, a channel or the like formed in a portion of the housing 1230.

[1167] In some embodiments, the channel forming at least a portion of the sequestration chamber 1234 can have a relatively small cross-sectional shape and/or size that can reduce and/or substantially prevent a mixing of an initial volume of bodily fluid drawn into the sequestration chamber 1234 (channel) and a volume of air within the sequestration chamber 1234 (e.g., a volume of air that has not been vented or purged, as described in further detail herein). For example, in some instances, the relatively small cross-sectional shape and/or size of the sequestration chamber 1234 (channel), a surface tension associated with the bodily fluid flowing into the sequestration chamber 1234, and a contact angle between a surface of the housing 1230 forming the sequestration chamber 1234 and the bodily fluid flowing into the sequestration chamber 1234 can collectively limit and/or substantially prevent a mixing of the bodily fluid and a volume of air within the sequestration chamber 1234.

[1168] As shown in FIG. 30, the housing 1230 can include and/or can be coupled to a cover 1238 configured to enclose the channel, thereby forming the sequestration chamber 1234. The cover 1238 can be coupled to the housing 1230 in any suitable manner (e.g., via a friction fit, snap fit, interference fit, an adhesive, one or more mechanical fasteners, laser welding, ultrasonic welding, plasma techniques, annealing, heat boding and/or any other suitable coupling means or combination thereof). In other embodiments, the cover 1238 is

monolithically formed with and/or coupled to the housing 1230. Moreover, in some embodiments, the cover 1238 can be at least partially transparent to allow a user to visualize a flow of bodily fluid through the sequestration chamber 1234. In some embodiments, the arrangement of the housing 1230 and the cover 1238 can, for example, facilitate one or more manufacturing processes and/or can facilitate use of the control device 1200.

[1169] As shown in FIG. 30, the housing 1230 includes and/or defines a flow controller 1242 and a restricted flow path 1232. The flow controller 1242 can be, for example, a valve, membrane, diaphragm, restrictor, vent, a selectively permeable member, port, etc. configured to selectively control (at least in part) a flow of fluids into and/or out of the sequestration chamber 1234 and/or any other suitable portion of the housing 1230. For example, the flow controller 1242 can be a selectively permeable fluid barrier (e.g., a blood barrier) that includes and/or is formed of a porous material configured to selectively allow a flow of gas therethrough but to prevent a flow of a liquid therethrough. As such, the flow controller 1242 can be configured to vent and/or purge a volume of air within the sequestration chamber 1234 through the flow controller 1242 in response to a negative pressure differential within a portion of the control device 1200. Such a venting and/or purging of the volume of air within the sequestration chamber 1234 can result in a suction force and/or negative pressure differential being exerted and/or applied in or on the sequestration chamber 1234 that is operable to draw in the initial volume of bodily fluid. Moreover, the use of a selectively permeable fluid barrier can allow for the venting and/or purging of air without allowing a volume of bodily fluid to pass through the flow controller 1242. Accordingly, in some embodiments, the flow controller 1242 can be substantially similar to the flow controller 242 described in detail above with reference to FIGS. 2-5 and thus, is not described in further detail herein.

[1170] The actuator 1250 of the control device 1200 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the actuator 1250 can be substantially similar in at least form and/or function to the actuator 850 described in detail above. Accordingly, such similar portions of the actuator 1250 are identified below but may not be described in further detail herein.

[1171] As shown in FIGS. 32-34, the actuator 1250 includes a body 1251 and an actuator rod 1262. The body 1251 of the actuator 1250 includes an inlet 1252 and an outlet 1253. The inlet 1252 and the outlet 1253 can be substantially similar in at least form and/or function to the inlet 852 and the outlet 853, respectively, described above with reference to FIGS. 19-25. Thus, the inlet 1252 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as

a needle, IV catheter, PICC line, or the like). The outlet 1253 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 29-34) such as, for example, a sample reservoir, a syringe, and/or other intermediary bodily fluid transfer device, adapter, or vessel such as, for example, a transfer device similar to those described in the '510 publication. In some embodiments, such a transfer device can provide a negative pressure and/or can act as an external energy source to enable desired functionality and fluid flow path dynamics/characteristics of the control device 1200.

[1172] The body 1251 of the actuator 1250 includes and/or defines a first port 1258 and a second port 1259. The first port 1258 is in fluid communication with the inlet 1252 and the second port 1259 is in fluid communication with the outlet 1252. In addition, the first port 1258 and the second port 1259 are configured to be at least fluidically coupled to the first port 1245 and the second port 1246, respectively, of the housing 1230. In some embodiments, the arrangement of the ports 1258 and 1259 of the actuator 1250 and the ports 1245 and 1246 of the housing 1230 can allow for and/or otherwise can provide a means of physically coupling the housing 1230 to the actuator 1250 as well as fluidically coupling the housing 1230 to the actuator 1250. That is to say, in some embodiments, the arrangement of the ports 1258 and 1259 of the actuator 1250 and the ports 1245 and 1246 of the housing 1230 can allow for a modular configuration or arrangement as described above with reference to the control device 800. In other embodiments, the housing 1230 and/or actuator 1250 need not be modular.

[1173] In some embodiments, the body 1251 and the actuator rod 1262 collectively include and/or collectively form a lock configured to at least temporarily lock the actuator 1250. For example, in some embodiments, the body 1251 and the actuator rod 1262 can each define an opening 1257 in or through which a locking member can be disposed. In such embodiments, when the locking member (not shown in FIG. 32) is disposed in the openings 1257, the locking member can limit and/or substantially prevent the actuator rod 1262 from being moved relative to the body 1251. On the other hand, removing the locking member from the openings 1257 can allow the actuator rod 1262 to be moved relative to the body 1251. While described as forming a lock, in some embodiments, the body 1251 and the actuator rod 1262 collectively include and/or collectively form a feature and/or arrangement that can limit and/or substantially prevent the actuator rod 1262 from being pulled out of the body 1251. In such embodiments, the feature can be a snap, a lock, a catch, and/or any other suitable feature and/or arrangement.

[1174] As shown in FIGS. 33 and 34, a portion of the actuator rod 1262 includes and/or is coupled to a set of seals 1265. The seals 1265 can be, for example, o-rings, over-molded elastomeric material, raised protrusions, and/or the like. The arrangement of the actuator 1262

and the body 1251 of the actuator 1250 can be such that the seals 1265 form one or more fluid tight seals between the actuator rod 1262 and the inner surface of the body 1251, as described above with reference to the actuator 850. In the embodiment shown in FIGS. 33 and 34, the actuator rod 1262 includes and/or is coupled to three seals 1265 which form and/or define a first fluid flow path 1233 within the body 1251 of the actuator 1250 and a second fluid flow path 1254 within the body 1251 of the actuator 1250. In other embodiments, any number of seals may be used to achieve desired performance.

[1175] As described above with reference to the device 800, the device 1200 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, microbes external to the bodily fluid source, and/or the like. For example, the actuator rod 1262 is configured to be moved or transitioned relative to the body 1251 between a first position or configuration and a second position or configuration. In some embodiments, the transition of the actuator rod 1262 can be achieved by and/or can otherwise result from user interaction and manipulation of the actuator rod 1262, automatically in response to negative pressure and associated flow dynamics within the device 1200, and/or enacted by or in response to an external energy source which creates dynamics that result in the transitioning of the actuator rod 1262. As shown in FIG. 33, when in the first position and/or configuration, the inlet 1252 of the actuator 1250 is in fluid communication with the first fluid flow path 1233, which in turn, is in fluid communication with the first port 1258. The outlet 1253 of the actuator 1250 is in fluid communication with the second fluid flow path 1254, which in turn, is in fluid communication with the second port 1259. Thus, when in the actuator 1250 and/or actuator rod 1262 is in the first position and/or configuration (e.g., when the control device 1200 is in a first state or operating mode), the negative pressure within the fluid collection device (not shown in FIGS. 29-34) can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 1234 that is operable in drawing at least a portion of an initial flow, amount, or volume of bodily fluid from the inlet 1252, through the first fluid flow path 1233, and into the sequestration chamber 1234. Moreover, in some instances, the initial volume and/or flow of bodily fluid can be transferred into the sequestration chamber 1234 until, for example, the bodily fluid disposed within the sequestration chamber 1234 transitions the flow controller 1242 from an open or unsealed configuration or state (e.g., one in which a flow of gas or air can be drawn therethrough) to a sealed configuration or state (e.g., one in which a flow of gas and liquid cannot be drawn therethrough).

[1176] In some instances, a force can be exerted on the end portion 1263 of the actuator rod 1262 to place the actuator rod 1262 and/or actuator 1250 in its second position and/or configuration, as shown in FIG. 34. As described above, in some instances, prior to exerting the force on the end portion 1263 of the actuator rod 1262, the actuator 1250 may be transitioned from a locked configuration or state to an unlocked configuration or state. When the actuator rod 1262 and/or the actuator 1250 is placed in its second position and/or configuration (e.g., when the control device 1200 is transitioned to a second state or operating mode), the inlet 1252 and the outlet 1253 of the actuator 1250 are each in fluid communication with the second fluid flow path 1254 while the first fluid flow path 1233 is sequestered, isolated, and/or otherwise not in fluid communication with the inlet 1252 and the outlet 1253. As described in detail above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event or throughout the bodily fluid collection process, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 1234 when the initial volume is sequestered therein. As such, the negative pressure otherwise exerted on or through the sequestration chamber 1234 is now exerted on or through the second fluid flow path 1254. In response, bodily fluid can flow from the inlet 1252, through the second fluid flow path 1254, through the outlet 1253, and into the fluid collection device coupled to the outlet 1253. Accordingly, the device 1200 can function in a manner substantially similar to that of the device 800 and thus, the function of the device 1200 is not described in further detail herein.

[1177] FIGS. 35-40 illustrate a fluid control device 1300 according to an embodiment. The fluid control device 1300 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 1300 can be similar to and/or substantially the same as corresponding portions of the fluid control devices 200, 300, 800, 900, 1000, 1100, and/or 1200 described above. Accordingly, such portions of the fluid control device 1300 are not described in further detail herein.

[1178] The fluid control device 1300 (also referred to herein as "control device" or "device") includes a housing 1330 and an actuator 1350. As described above with reference to the control devices 800, the control device 1300 can be arranged in a modular configuration such that the housing 1330 and the actuator 1350 can be physically and fluidically coupled to form the control device 1300. In other embodiments, the control device 1300 need not be modular. That is to say, in some embodiments, the control device 1300 can be assembled during manufacturing and delivered to a supplier and/or end user as an assembled device. In

other embodiments, the device 1300 can be monolithically formed and/or collectively formed with, for example, a fluid collection device, as described above.

[1179] The housing 1330 of the control device 1300 can be any suitable shape, size, and/or configuration. As shown in FIGS. 35-37, the housing 1330 forms and/or defines a sequestration chamber 1334 that is in selective fluid communication with a first port 1345 and a second port 1346. The second port 1346 is configured to receive, include, and/or define a flow controller 1342 (see e.g., FIG. 36) and a restricted flow path 1332 (see e.g., FIG. 37). The first port 1345 and the second port 1346 are configured to be at least fluidically coupled to a portion of the actuator 1350 to allow for selective fluid flow between the housing 1330 and the actuator 1350. As described in further detail herein, the sequestration chamber 1334 is configured (1) to receive a selective flow and/or volume of bodily fluid from a portion of the actuator 1350 via the first port 1345, and (2) to sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid (e.g., at least a portion of an initial or first flow and/or volume of bodily fluid) within the sequestration chamber 1334. The sequestration chamber 1334 can have any suitable shape, size, and/or configuration. For example, in some embodiments, the sequestration chamber 1334 can be, for example, a channel or the like formed in a portion of the housing 1330 and the housing 1330 can include and/or can be coupled to a cover 1338 configured to enclose the channel, thereby forming the sequestration chamber 1334. In some embodiments, the housing 1330 can be substantially similar in at least form and/or function to the housing 1230 described in detail above with reference to FIGS. 29-34. Accordingly, the housing 1330 is not described in further detail herein.

[1180] The actuator 1350 of the control device 1300 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the actuator 1350 can be substantially similar in at least form and/or function to the actuators 850 and/or 1250 described in detail above. Accordingly, such similar portions of the actuator 1350 are identified below but may not be described in further detail herein.

[1181] As shown in FIGS. 38-40, the actuator 1350 includes a body 1351 and an actuator rod 1362. The body 1351 of the actuator 1350 includes an inlet 1352 and an outlet 1353. The inlet 1352 and the outlet 1353 can be substantially similar in at least form and/or function to the inlet 852 and the outlet 853, respectively, described above with reference to FIGS. 19-25. Thus, the inlet 1352 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, surgical tubing, other standard bodily-fluid transfer device, PICC line, or

the like). The outlet 1353 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 35-40) such as, for example, a sample reservoir, a syringe, and/or other intermediary bodily fluid transfer device, adapter, or vessel such as, for example, a transfer device similar to those described in the '510 publication.

[1182] The body 1351 of the actuator 1350 includes and/or defines a first port 1358 and a second port 1359. The first port 1358 is in fluid communication with the inlet 1352 and the second port 1359 is in fluid communication with the outlet 1353. In addition, the first port 1358 and the second port 1359 are configured to be at least fluidically coupled to the first port 1345 and the second port 1346, respectively, of the housing 1330. In some embodiments, the arrangement of the ports 1358 and 1359 of the actuator 1350 and the ports 1345 and 1346 of the housing 1330 can allow for and/or otherwise can provide a means of physically coupling the housing 1330 to the actuator 1350 as well as fluidically coupling the housing 1330 to the actuator 1350. That is to say, in some embodiments, the arrangement of the ports 1358 and 1359 of the actuator 1350 and the ports 1345 and 1346 of the housing 1330 can allow for a modular configuration or arrangement as described above with reference to the control device 800. In other embodiments, the housing 1330 and/or actuator 1350 need not be modular.

[1183] As shown in FIGS. 39 and 40, a portion of the actuator rod 1362 includes and/or is coupled to a set of seals 1365. The seals 1365 can be, for example, o-rings, elastomeric material, silicone or any other suitable material or configuration as described above with reference to the seals 1265. The arrangement of the actuator 1362 and the body 1351 of the actuator 1350 can be such that the seals 1365 form one or more fluid tight seals between the actuator rod 1362 and the inner surface of the body 1351, as described above with reference to the actuator 850. In the embodiment shown in FIGS. 33 and 34, the actuator rod 1362 includes and/or is coupled to three seals 1365 which form and/or define a first fluid flow path 1333 within the body 1351 of the actuator 1350 and a second fluid flow path 1354 within the body 1351 of the actuator 1350.

[1184] As described above with reference to the device 800, the device 1300 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, microbes external to the bodily fluid source, and/or the like. For example, the actuator rod 1362 is configured to be moved or transitioned relative to the body 1351 between a first position or configuration and a second position or configuration. As shown in FIG. 39, when in the first position and/or configuration, the inlet 1352 of the actuator 1350 is in fluid communication with the first fluid flow path 1333, which in turn, is in fluid communication with the first port 1358. The outlet 1353 of the actuator 1350 is in fluid

communication with the second fluid flow path 1354, which in turn, is in fluid communication with the second port 1359. Thus, when in the actuator 1350 and/or actuator rod 1362 is in the first position and/or configuration (e.g., when the control device 1300 is in a first state or operating mode), the negative pressure within the fluid collection device (not shown in FIGS. 35-40) can result in a negative pressure (or negative pressure differential) within at least a portion of the sequestration chamber 1334 that is operable in drawing at least a portion of an initial flow, amount, or volume of bodily fluid from the inlet 1352, through the first fluid flow path 1333, and into the sequestration chamber 1334. Moreover, in some instances, the initial volume and/or flow of bodily fluid can be transferred into the sequestration chamber 1334 until, for example, the bodily fluid disposed within the sequestration chamber 1334 transitions the flow controller 1342 from an open or unsealed configuration or state (e.g., one in which a flow of gas or air can be drawn therethrough) to a sealed configuration or state (e.g., one in which a flow of gas and liquid cannot be drawn therethrough).

[1185] In some instances, a force can be exerted on a first end portion 1363 of the actuator rod 1362 to place the actuator rod 1362 and/or actuator 1350 in its second position, state, operating mode, and/or configuration, as shown in FIG. 35. As described above, in some instances, prior to exerting the force on the first end portion 1363 of the actuator rod 1362, the actuator 1350 may be transitioned from a locked configuration or state to an unlocked configuration or state. In some embodiments, the transition of the actuator rod 1362 can be achieved by and/or can otherwise result from user interaction and manipulation of the actuator rod 1362, automatically in response to negative pressure and associated flow dynamics within the device 1300, and/or enacted by or in response to an external energy source which creates dynamics that result in the transitioning of the actuator rod 1362.

[1186] When the actuator rod 1362 and/or the actuator 1350 is placed in its second position and/or configuration (e.g., when the control device 1300 is transitioned to a second state or operating mode), the inlet 1352 and the outlet 1353 of the actuator 1350 are each in fluid communication with the second fluid flow path 1354 while the first fluid flow path 1333 is sequestered, isolated, and/or otherwise not in fluid communication with the inlet 1352 and the outlet 1353. As described in detail above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event or throughout the bodily-fluid collection process, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 1334 when the initial volume is sequestered therein. As such, the negative pressure otherwise exerted on or through the sequestration chamber 1334 is now exerted on or through the second fluid flow

path 1354. In response, bodily fluid can flow from the inlet 1352, through the second fluid flow path 1354, through the outlet 1353, and into the fluid collection device coupled to the outlet 1353. Accordingly, the device 1300 can function in a manner substantially similar to that of the device 800 and thus, the function of the device 1300 is not described in further detail herein.

[1187] In some instances, it may be desirable to isolate the negative pressure source (e.g., the fluid collection device from the inlet 1353 such as, for example, if it is desirable to collect multiple samples of bodily fluid using multiple fluid collection devices (e.g., syringes or the like). For example, in some instances, after filling the fluid collection device the user can engage the actuator 1350 and exert a force on a second end portion 1364 of the actuator rod 1362 to move and/or transition the actuator rod 1362 from its second position and/or configuration toward its first position and/or configuration. As such, the second fluid flow path 1354 no longer places the inlet 1352 in fluid communication with the outlet 1353. Moreover, the flow controller 1342 can remain in the sealed state or configuration (e.g., fully saturated, wetted, and/or otherwise preventing flow therethrough) such that the outlet 1353 is substantially sequestered or isolated from the rest of the control device 1300. In some instances, the user can then remove the filled fluid collection device and can couple a new fluid collection device to the outlet 1353. With the new fluid collection device coupled to the outlet 1353, the user can, for example, exert a force on the first end portion 1363 of the actuator rod 1362 to move and/or transition the actuator rod 1362 back to its second position, state, and/or configuration, as described above with reference to the actuator 850.

[1188] FIGS. 41-44 illustrate a fluid control device 1400 according to an embodiment. The fluid control device 1400 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 1400 can be similar to and/or substantially the same as corresponding portions of the fluid control devices 200, 300, 800, 900, 1000, 1100, 1200, and/or 1300 described above. Accordingly, such portions of the fluid control device 1400 are not described in further detail herein.

[1189] The fluid control device 1400 (also referred to herein as "control device" or "device") includes a housing 1430 and an actuator 1450. As described above with reference to the control device 800, the control device 1400 can be arranged in a modular configuration such that the housing 1430 and the actuator 1450 can be physically and fluidically coupled to form the control device 1400. In other embodiments, the control device 1400 need not be modular. That is to say, in some embodiments, the control device 1400 can be assembled during manufacturing and delivered to a supplier and/or end user as an assembled device. In

other embodiments, the device 1400 can be monolithically formed and/or collectively formed with, for example, a fluid collection device, as described above.

[1190] The housing 1430 of the control device 1400 can be any suitable shape, size, and/or configuration. The housing 1430 is configured to be in selective fluid communication with a portion of the actuator 1450 via a first port 1458 and a second port 1459. As shown in FIGS. 43 and 44, the housing 1430 includes a bladder 1478 that can be transitioned from a first configuration and/or state to a second configuration and/or state to form and/or define a sequestration chamber 1434. As described in further detail herein, the bladder 1478 is configured to transition from the first configuration and/or state (FIG. 43) to the second configuration and/or state (FIG. 44) to form and/or define the sequestration chamber 1434, which in turn, is configured to receive a selective flow and/or volume of bodily fluid from a portion of the actuator 1450 via the first port 1458. After the bladder 1478 is placed in the second configuration and/or state, the sequestration chamber 1434 can sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid (e.g., at least a portion of an initial or first flow and/or volume of bodily fluid) within the sequestration chamber 1434.

[1191] While the bladder 1478 is particularly shown in FIGS. 43 and 44, in other embodiments, the bladder 1478 can be any suitable shape, size, and/or configuration. Similarly, the bladder 1478 can be formed of any suitable material (e.g., any suitable biocompatible material such as those described herein and/or any other suitable material). In some embodiments, the bladder 1478 can be arranged and/or configured as, for example, a bellows, an expandable bag, a flexible pouch, and/or any other suitable reconfigurable container or the like. In addition, the sequestration chamber 1434 formed by the bladder 1478 can have any suitable shape, size, and/or configuration. In some embodiments, the housing 1430 can be substantially similar in at least form and/or function to the housing 1230 and/or 1330 described in detail above with reference to FIGS. 29-34 and FIGS. 35-40, respectively. Accordingly, the housing 1430 is not described in further detail herein.

[1192] The actuator 1450 of the control device 1400 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the actuator 1450 can be substantially similar in at least form and/or function to the actuators 850, 1250, and/or 1350 described in detail above. Accordingly, such similar portions of the actuator 1450 are identified below but may not be described in further detail herein.

[1193] As shown in FIGS. 41-44, the actuator 1450 includes a body 1451 and an actuator rod 1462. The body 1451 of the actuator 1450 includes an inlet 1452 and an outlet 1453. The

inlet 1452 and the outlet 1453 can be substantially similar in at least form and/or function to the inlet 1252 and the outlet 1253, respectively, described above with reference to FIGS. 29-34. Thus, the inlet 1452 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, surgical tubing, other standard bodily-fluid transfer device, PICC line, or the like). The outlet 1453 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 41-44) such as, for example, a sample reservoir, a syringe, and/or other intermediary bodily fluid transfer device, adapter, or vessel such as, for example, a transfer device similar to those described in the '510 publication.

[1194] The body 1451 of the actuator 1450 includes and/or defines the first port 1458 and the second port 1459. Although not shown, the first port 1458 is configured to be in fluid communication with the inlet 1452 and the second port 1459 is configured to be in fluid communication with the outlet 1453. In addition, the first port 1458 is configured to be in fluid communication with the housing 1430 and more particularly, an inner volume or an inlet side of the bladder 1478 that forms the sequestration chamber 1434. The second port 1459 is configured to be in fluid communication with a portion of the housing 1430 defined between an inner surface of the housing 1430 and an outer surface of the bladder 1478. In other words, the second port 1459 is in fluid communication with a portion of the housing 1430 that is isolated and/or sequestered from the inner volume of the bladder 1478 that forms the sequestration chamber 1434. In some embodiments, the arrangement of the ports 1458 and 1459 of the actuator 1450 can allow for and/or otherwise can provide a means of physically coupling the housing 1430 to the actuator 1450 as well as fluidically coupling the housing 1430 to the actuator 1450. That is to say, in some embodiments, the arrangement of the ports 1458 and 1459 of the actuator 1450 can allow for a modular configuration or arrangement as described above with reference to the control device 800. In other embodiments, the housing 1430 and/or actuator 1450 need not be modular.

[1195] Although not shown in FIGS. 41-44, a portion of the actuator rod 1462 includes and/or is coupled to a set of seals. The seals can be, for example, o-rings, elastomeric material, silicone or any other suitable material or configuration as described above with reference to the seals 1265 and/or 1365. The arrangement of the actuator rod 1462 and the body 1451 of the actuator 1450 can be such that the seals form one or more fluid tight seals between the actuator rod 1462 and the inner surface of the body 1451, as described above with reference to the actuators 850, 1250, and/or 1350. Moreover, as described above with reference to the actuators 1250 and/or 1350, the actuator rod 1462 can include and/or can be coupled to a set seals which

selectively form and/or define a first fluid flow path configured to place the inlet 1452 of the actuator 1450 in fluid communication with the first port 1458 (e.g., when in a first position, state, operating mode, and/or configuration) and a second fluid flow path configured to place the inlet 1452 in fluid communication with the outlet 1453 (e.g., when in a second position, state, operating mode, and/or configuration).

[1196] As described above with reference to the devices 800, 1200, and/or 1300, the device 1400 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, microbes external to the bodily fluid source, and/or the like. For example, as described above with reference to the devices 1200 and/or 1300, the actuator rod 1462 can be configured to be moved or transitioned relative to the body 1451 between a first position or configuration and a second position or configuration. When in the first position and/or configuration, the inlet 1452 of the actuator 1450 is in fluid communication with, for example, the first fluid flow path, which in turn, is in fluid communication with the first port 1458 (not shown in FIGS. 41-44). The outlet 1453 of the actuator 1450 is in fluid communication with the second fluid flow path 1454, which in turn, is in fluid communication with the second port 1459. Thus, when in the actuator 1450 and/or actuator rod 1462 is in the first position and/or configuration (e.g., when the control device 1400 is in a first state or operating mode), the negative pressure within the fluid collection device (not shown in FIGS. 41-44) can result in a negative pressure (or negative pressure differential) within the portion of the housing 1430 defined between the inner surface of the housing 1430 and the outer surface of the bladder 1478.

[1197] As shown in FIG. 43, the bladder 1478 can be in a first state and/or configuration prior to the fluid collection device being coupled to the outlet 1453. In some embodiments, for example, the bladder 1478 can have a flipped, inverted, collapsed, and/or empty configuration prior to coupling the fluid collection device to the outlet 1453. As shown in FIG. 44, the bladder 1478 can be configured to transition from the first state and/or configuration to a second state and/or configuration in response to the negative pressure differential resulting from the coupling of the fluid collection device to the outlet 1453. In other words, the negative pressure differential can be operable to transition the bladder 1478 from a collapsed or unexpanded configuration and/or state to an expanded configuration and/or state. For example, in some embodiments, the transitioning of the bladder 1478 can be similar to the transitioning and/or "flipping" of the diaphragm 576, described above with reference to FIGS. 11 and 12.

[1198] As described above, the bladder 1478 can be configured to transition from the first configuration and/or state to the second configuration and/or state to form and/or define the

sequestration chamber 1434. In some embodiments, the transitioning of the bladder 1478 results in an increase in an inner volume of the bladder 1478 (i.e., the sequestration chamber 1434). The increase in the inner volume can, in turn, result in a negative pressure differential between the sequestration chamber 1434 defined by the bladder 1478 and the inlet 1452 that is operable in drawing at least a portion of an initial flow, amount, or volume of bodily fluid from the inlet 1452, through the first port 1458, and into the sequestration chamber 1434. Moreover, in some instances, the initial volume and/or flow of bodily fluid can be transferred into the sequestration chamber 1434 until, for example, the bladder 1478 is fully expanded, and/or until the negative pressure differential is reduced and/or equalized.

[1199] Having transferred the initial volume of bodily fluid into the sequestration chamber 1434, a force can be exerted on a first end portion 1463 of the actuator rod 1462 to place the actuator rod 1462 and/or actuator 1450 in its second position, state, operating mode, and/or configuration, as described in detail above with reference to the devices 1200 and/or 1300. As described above, in some instances, prior to exerting the force on the first end portion 1463 of the actuator rod 1462, the actuator 1450 may be transitioned from a locked configuration or state to an unlocked configuration or state. In some embodiments, the transition of the actuator rod 1462 can be achieved by and/or can otherwise result from user interaction and manipulation of the actuator rod 1462, automatically in response to negative pressure and associated flow dynamics within the device 1400, and/or enacted by or in response to an external energy source which creates dynamics that result in the transitioning of the actuator rod 1462.

[1200] When the actuator rod 1462 and/or the actuator 1450 is placed in its second position and/or configuration (e.g., when the control device 1400 is transitioned to a second state or operating mode), the inlet 1452 and the outlet 1453 of the actuator 1450 are placed in fluid communication (e.g., via the second fluid flow path (not shown)) while the first fluid flow path (not shown) and/or the first port 1458 is sequestered, isolated, and/or otherwise not in fluid communication with the inlet 1452 and/or the outlet 1453. As described in detail above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event or throughout the bodily-fluid collection process, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 1434 when the initial volume is sequestered therein. As such, the negative pressure otherwise exerted on or through the housing 1430 is now exerted on or through the outlet 1453 and the inlet 1452 via, for example, the second fluid flow path (not shown). In response, bodily fluid can flow from the inlet 1452, through the body 1451 of the actuator 1450, through the outlet 1453, and into the fluid collection device coupled to the outlet

1453. Accordingly, the device 1400 can function in a manner substantially similar to that of the devices 800, 1200, and/or 1300 and thus, the function of the device 1400 is not described in further detail herein.

[1201] While the device 1400 is described above as including the housing 1430 and the actuator 1450, in other embodiments, a fluid control device can have, for example, at least a partially integrated design. For example, FIGS. 45-50 illustrate a fluid control device 1500 according to an embodiment. The fluid control device 1500 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 1500 can be similar to and/or substantially the same as corresponding portions of at least the fluid control device 1400 described above with reference to FIGS. 41-44. Accordingly, such portions of the fluid control device 1500 are not described in further detail herein.

[1202] The fluid control device 1500 (also referred to herein as "control device" or "device") includes an actuator 1550 having an actuator body 1551 and an actuator rod 1562. The actuator 1550 can be any suitable shape, size, and/or configuration. For example, in some embodiments, the actuator 1550 can be substantially similar in at least form and/or function to the actuators 850, 1250, 1350, and/or 1450 described in detail above. Accordingly, such similar portions of the actuator 1550 are identified below but may not be described in further detail herein.

[1203] As shown in FIGS. 45-50, the actuator 1550 includes an inlet 1552 and an outlet 1553, each of which is in fluid communication with the body 1551. The inlet 1552 and the outlet 1553 can be substantially similar in at least form and/or function to the inlet 1252 and the outlet 1253, respectively, described above with reference to FIGS. 29-34. Thus, the inlet 1552 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle, IV catheter, surgical tubing, other standard bodily-fluid transfer device, PICC line, or the like). The outlet 1553 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 45-50) such as, for example, a sample reservoir, a syringe, and/or other intermediary bodily fluid transfer device, adapter, or vessel such as, for example, a transfer device similar to those described in the '510 publication.

[1204] As shown in FIGS. 48-50, the actuator 1550 includes a bladder 1578 that can be transitioned from a first configuration and/or state (FIG. 48) to a second configuration and/or state (FIG. 49) to form and/or define a sequestration chamber 1534. As described in further detail herein, the bladder 1578 is configured to transition from the first configuration and/or

state (FIG. 48) to the second configuration and/or state (FIGS. 49 and 50) to form and/or define the sequestration chamber 1534, which in turn, is configured to receive a selective flow and/or volume of bodily fluid from the inlet 1552. After the bladder 1578 is placed in the second configuration and/or state, the sequestration chamber 1534 can sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid (e.g., at least a portion of an initial or first flow and/or volume of bodily fluid) within the sequestration chamber 1534. As such, the bladder 1578 can be substantially similar in at least form and/or function to the bladder 1478 described above with reference to FIGS. 41-44 and thus, is not described in further detail herein.

[1205] As shown in FIGS. 46 and 48-50, the body 1551 of the actuator 1550 includes and/or defines a port 1559 configured to be in fluid communication with the outlet 1553. In addition, the port 1559 defines a fluid flow path that is configured to be in fluid communication with a portion of the actuator 1550 defined between an inner surface of the body 1551 and an outer surface of the bladder 1578. In other words, the port 1559 is in fluid communication with a portion of the actuator 1550 that is isolated and/or sequestered from the inner volume of the bladder 1578 that forms and/or that is configured to form the sequestration chamber 1534.

[1206] As described above with reference to the devices 1200, 1300, and/or 1400, a portion of the actuator rod 1562 includes and/or is coupled to a set of seals 1565. The seals 1565 can be, for example, o-rings, elastomeric material, silicone or any other suitable material or configuration as described above with reference to the seals 1265 and/or 1365. The arrangement of the actuator rod 1562 and the body 1551 of the actuator 1550 can be such that the seals 1565 form one or more fluid tight seals between the actuator rod 1562 and the inner surface of the body 1551, as described above with reference to the actuators 850, 1250, and/or 1350. Moreover, as described above with reference to the actuators 1250 and/or 1350, the set seals 1565 can be arranged along the actuator rod 1562 to selectively form and/or define a fluid flow path 1554 that is sequestered from and/or fluidically isolated from the inlet 1552 when the actuator rod 1562 is in a first position and/or configuration and that is configured to place the inlet 1552 in fluid communication with the outlet 1553 when the actuator rod 1562 is in a second position and/or configuration.

[1207] As described above with reference to the devices 800, 1200, 1300, and/or 1400, the device 1500 can be used to procure a bodily fluid sample having reduced contamination from microbes such as, for example, dermally residing microbes, microbes external to the bodily fluid source, and/or the like. For example, as described above with reference to the devices 1200, 1300, and/or 1400, the actuator rod 1562 can be configured to be moved or transitioned

relative to the body 1551 between the first position or configuration and the second position or configuration. When in the first position and/or configuration, the inlet 1552 of the actuator 1550 is in fluid communication with a fluid flow path, which in turn, is in fluid communication with a portion of the body 1551 that is disposed on an inlet side of the bladder 1578. In other words, the fluid flow path establishes fluid communication between the inlet 1553 and the bladder 1578 and/or the sequestration chamber 1534 at least partially defined by the bladder 1578 when the bladder 1578 is transitioned to the second configuration and/or state. The outlet 1553 of the actuator 1550 is in fluid communication with the port 1559. Thus, when in the actuator 1550 and/or actuator rod 1562 is in the first position and/or configuration (e.g., when the control device 1500 is in a first state or operating mode), the negative pressure within the fluid collection device (not shown in FIGS. 45-50) can result in a negative pressure (or negative pressure differential) within the portion of the actuator body 1551 defined between the inner surface of the body 1551 and the outer surface of the bladder 1578, as described above with reference to the device 1400.

[1208] As shown in FIG. 48, the bladder 1578 can be in a first state and/or configuration prior to the fluid collection device being coupled to the outlet 1553. In some embodiments, for example, the bladder 1578 can have a flipped, inverted, collapsed, and/or empty configuration prior to coupling the fluid collection device to the outlet 1553. Moreover, when the actuator rod 1562 is in the first position and/or configuration, the fluid flow path 1554 is fluidically isolated from the inlet 1552. Accordingly, as shown in FIG. 49, the bladder 1578 can be configured to transition from the first state and/or configuration to a second state and/or configuration in response to the negative pressure differential resulting from the coupling of the fluid collection device to the outlet 1553. In other words, the negative pressure differential can be operable to transition the bladder 1578 from a collapsed or unexpanded configuration and/or state to an expanded configuration and/or state. For example, in some embodiments, the transitioning of the bladder 1578 can be similar to the transitioning and/or "flipping" of the diaphragm 576, described above with reference to FIGS. 11 and 12. In other embodiments, the bladder 1578 can be configured to transition between a first state and/or configuration to a second state and/or configuration in any suitable manner such as any of those described herein.

[1209] As described above, the bladder 1578 can be configured to transition from the first configuration and/or state to the second configuration and/or state to form and/or define the sequestration chamber 1534. In some embodiments, the transitioning of the bladder 1578 results in an increase in an inner volume of the bladder 1578 (i.e., the sequestration chamber 1534). The increase in the inner volume can, in turn, result in a negative pressure differential

between the sequestration chamber 1534 defined by the bladder 1578 and the inlet 1552 that is operable in drawing at least a portion of an initial flow, amount, or volume of bodily fluid from the inlet 1552 and a portion of the actuator body 1551, and into the sequestration chamber 1534. Moreover, in some instances, the initial volume and/or flow of bodily fluid can be transferred into the sequestration chamber 1534 until, for example, the bladder 1578 is fully expanded, and/or until the negative pressure differential is reduced and/or equalized.

[1210] Having transferred the initial volume of bodily fluid into the sequestration chamber 1534, a force can be exerted on a first end portion 1563 of the actuator rod 1562 to place the actuator rod 1562 and/or actuator 1550 in its second position, state, operating mode, and/or configuration, as described in detail above with reference to the devices 1200 and/or 1300. As described above, in some instances, prior to exerting the force on the first end portion 1563 of the actuator rod 1562, the actuator 1550 may be transitioned from a locked configuration or state to an unlocked configuration or state. In some embodiments, the transition of the actuator rod 1562 can be achieved by and/or can otherwise result from user interaction and manipulation of the actuator rod 1562, automatically in response to negative pressure and associated flow dynamics within the device 1500, and/or enacted by or in response to an external energy source which creates dynamics that result in the transitioning of the actuator rod 1562.

[1211] When the actuator rod 1562 and/or the actuator 1550 is placed in its second position and/or configuration (e.g., when the control device 1500 is transitioned to a second state or operating mode), the inlet 1552 and the outlet 1553 of the actuator 1550 are placed in fluid communication via the fluid flow path 1554 while the sequestration chamber 1534 is sequestered, isolated, and/or otherwise not in fluid communication with the inlet 1552 and/or the outlet 1553. As described in detail above, in some instances, contaminants such as, for example, dermally residing microbes or the like dislodged during the venipuncture event or throughout the bodily-fluid collection process, can be entrained and/or included in the initial volume of the bodily fluid and thus, are sequestered in the sequestration chamber 1534 when the initial volume is sequestered therein.

[1212] As described above with reference to the devices 1200 and/or 1300, transitioning the actuator rod 1562 to the second position and/or configuration is such that the fluid flow path 1554 places the inlet 1552 in fluid communication with the outlet 1553. For example, transitioning the actuator rod 1562 to the second position and/or configuration can move the seals 1565 relative to the inlet 1552 such that the fluid flow path 1554 is placed in fluid communication with both the inlet 1552 and the outlet 1553. As such, the negative pressure otherwise exerted on the outer surface of the bladder 1578 is now exerted on or through the

outlet 1553 and the inlet 1552 via the fluid flow path 1554. In response, bodily fluid can flow from the inlet 1552, through the fluid flow path 1554, through the outlet 1553, and into the fluid collection device coupled to the outlet 1553. Accordingly, the device 1500 can function in a manner substantially similar to that of the devices 800, 1200, 1300, and/or 1400 and thus, the function of the device 1500 is not described in further detail herein.

[1213] While the actuators 850, 1250, 1350, 1450, and 1550 have been described in detail above as being transitioned in response to an external force such as, for example, a force exerted by a user, in other embodiments, a fluid control device can include one or more actuators that can be transitioned in response to any suitable force, input, change of state or configuration, etc. For example, FIGS. 51 and 52 illustrate a portion of a fluid control device 1600 according to an embodiment. The fluid control device 1600 can be similar in at least form and/or function to the fluid control devices described herein. More specifically, portions of the fluid control device 1600 can be similar to and/or substantially the same as corresponding portions of at least the fluid control devices 500, 600, and/or 700 described above. Accordingly, such portions of the fluid control device 1600 are not described in further detail herein.

[1214] As shown in FIGS. 51 and 52, the fluid control device 1600 (also referred to herein as "control device" or "device") includes a housing 1630 having an inlet 1631 and an outlet 1636, and having and/or being coupled to an actuator 1650. As described in further detail herein, the housing 1630 defines a set of fluid flow paths 1633 and 1654 configured to establish fluid communication between one or more portions of the housing 1630 to selectively receive a flow of fluid therethrough (e.g., a liquid and/or a gas). The inlet 1631 is configured to be placed in fluid communication with a bodily fluid source to receive a flow of bodily fluid therefrom (e.g., via a lumen-containing device such as a needle or the like, as described in detail above). The outlet 1636 is configured to be fluidically coupled to a fluid collection device (not shown in FIGS. 51 and 52). The inlet 1631, the outlet 1636, and the fluid collection device can be substantially similar to those described above and thus, are not described in further detail herein.

[1215] The housing 1630 can be any suitable shape, size, and/or configuration. In some embodiments, the housing 1630 can have a size that is at least partially based on a volume of bodily fluid configured to be at least temporarily stored within one or more portions of the housing 1630. As described above, the housing 1630 of the control device 1600 is configured to (1) receive a flow and/or volume of bodily fluid via the inlet 1631 and (2) sequester (e.g., separate, segregate, contain, retain, isolate, etc.) the flow and/or volume of bodily fluid within a sequestration chamber 1634 included in and/or at least partially formed by the housing 1630.

In some embodiments, aspects of the housing 1630 can be substantially similar, for example, to aspects of the housings 630, 730, and/or 830. Accordingly, some portions and/or aspects of the housing 1630 are not described in further detail herein.

[1216] The housing 1630 includes and/or is coupled to the actuator 1650 configured to selectively control a flow of bodily fluid through the housing 1630. In this embodiment, the actuator 1650 includes a diaphragm 1676 and an actuator rod 1662 having a set of seals (e.g., seals 1665 and 1666). As described in further detail herein, the diaphragm 1676 and the actuator rod 1662 are configured to transition, move, and/or otherwise reconfigure within the housing 1630 in response to a negative pressure differential within at least a portion of the device. More specifically, the actuator 1650 is configured to move between a first state in which the inlet 1631 is placed in fluid communication with the sequestration chamber 1634 and a second state in which the inlet 1631 is placed in fluid communication with the outlet 1636 via the fluid flow path 1654, as described in detail above with reference to the control device 500.

[1217] In some embodiments, the diaphragm 1676 can be similar to, for example, the diaphragms 576, 676, and/or 776 described in detail above. Accordingly, the diaphragm 1676 can be at least partially disposed in a sequestration portion of the housing 1630 to define and/or to form at least a portion of the sequestration chamber 1634. As described in detail above, the diaphragm 1676 can be configured to transition, move, flip, and/or otherwise reconfigure from a first state to a second state in response to a negative pressure differential, which can be operable to draw an initial volume of bodily fluid into the sequestration chamber 1634 and/or to sequester the initial volume of bodily fluid in the sequestration chamber 1634 once disposed therein. Moreover, as shown in FIGS. 51 and 52, the diaphragm 1676 can include and/or can be coupled to a flow controller 1642. The flow controller 1642 can be any suitable flow controller such as any of those described herein. For example, in some embodiments, the flow controller 1642 can be a semi-permeable member or membrane such as an air permeable/liquid impermeable barrier (e.g., a blood barrier).

[1218] As described in detail above, the flow controller 1642 can be configured to transition from a first state in which the flow controller 1642 allows a flow of gas (e.g., air) to pass through the flow controller 1642 while preventing a flow of liquid (e.g., bodily fluid) to pass therethrough, to a second state in which the flow controller 1642 limits and/or substantially prevents a flow of gas and liquid to pass through the flow controller 1642. In some embodiments, the flow controller 1642 can be configured to transition from the first state to the second state in response to contact with, for example, the initial volume of bodily fluid

(e.g., at least a portion of the initial volume of bodily fluid can wet or saturate the flow controller 1642 to place the flow controller 1642 in the second state).

[1219] While the diaphragms 576, 676, and 776 are shown and described above as including a pin, rod, post, and/or the like that include and/or are coupled to one or more seals (e.g., the seals 565, 665, and 765, respectively), in the embodiment shown in FIGS. 51 and 52, the diaphragm 1676 includes a pin 1677 (e.g., a rod, an extension, a protrusion, a latch, a lock, and/or any other suitable feature, member, and/or mechanism) that does not include and/or is not coupled to a seal. For example, in this embodiment, the pin 1677 extends through a portion of the housing 1630 to selectively engage a portion of the actuator rod 1662, which in turn includes one or more seals (e.g., the seals 1665 and 1666), as described in further detail herein.

[1220] As shown in FIGS. 51 and 52, the actuator rod 1662 is movably disposed in, for example, an actuator portion 1639 of the housing 1630. The actuator rod 1662 includes a first seal 1665 and a second seal 1666 and is in contact with an energy storage member 1667 such as a spring or the like disposed within the actuator portion 1639 of the housing 1630. In the embodiment shown in FIGS. 51 and 52, the arrangement of the actuator 1650 can be such that a first end portion of the actuator rod 1662 is in selective contact with the pin 1677 of the diaphragm 1676 and a second end portion of the actuator rod 1662 (opposite the first end portion) is in contact with and/or otherwise is engaged with the energy storage member 1667.

[1221] As shown in FIG. 51, when the actuator 1650 is in a first state, the pin 1677 of the diaphragm 1676 can engage the actuator rod 1662 to maintain the actuator rod 1662 in a first or initial state and/or position in which the energy storage member 1667 has a relatively high potential energy (e.g., the energy storage member 1667 can be a spring maintained and/or held in a compressed state when in the first state). Furthermore, the first seal 1665 coupled to and/or disposed on the actuator 1662 is in a first or initial position in which the fluid flow path 1633 establishes fluid communication between the inlet 1631 and the sequestration chamber 1634 when the actuator 1650 is in the first state. As shown, the second seal 1666 coupled to and/or disposed on the actuator rod 1662 is likewise in a first or initial position in which the second seal 1666 is spaced apart from a seal surface 1640 formed by at least a portion of the actuator portion 1639 of the housing 1630.

[1222] In some embodiments, the separation of the second seal 1666 from the seal surface 1640 can be such that the fluid flow path 1654 places the outlet 1636 in fluid communication with the sequestration chamber 1634 via a restricted flow path 1632 (see FIG. 52). In some embodiments, the restricted flow path 1632 can be similar in at least form and/or function to any of the restricted flow paths described herein (e.g., the restricted flow paths 232, 832, 1232,

and/or 1332). As such, the restricted flow path 1632 can be configured to modulate a magnitude of a negative pressure differential applied on or in the sequestration chamber 1634 and/or a rate at which a negative pressure differential increases within the sequestration chamber 1634. In other embodiments, the outlet 1636 can be in fluid communication with the sequestration chamber 1634 via any suitable flow path, port, opening, valve, etc. In other words, in some embodiments, the control device 1600 need not include the restricted flow path 1632.

[1223] As shown in FIG. 51, when the actuator 1650 is in the first state, the actuator rod 1662 can be maintained in a first state or position in which the fluid flow path 1633 places the inlet 1631 in fluid communication with the sequestration chamber 1634, and the fluid flow path 1654 places the outlet 1636 in fluid communication with the sequestration chamber 1634 via the restricted flow path 1632. Accordingly, when a fluid collection device (such as those described herein) is coupled to the outlet 1636, a negative pressure defined in and/or otherwise produced by the fluid collection device can be operable to draw the initial volume of bodily fluid into the sequestration chamber 1634.

[1224] As described in detail above, the actuator 1650 can be transitioned to a second state and/or configuration in response to the initial volume being transferred into the sequestration chamber 1634. For example, in some embodiments, the initial volume of bodily fluid can be drawn into the sequestration chamber 1634 in response to a negative pressure being exerted through the flow controller 1642 (e.g., the selectively permeable membrane). In some instances, at least a portion of the bodily fluid drawn into the sequestration chamber 1634 can come into contact with the flow controller 1642, which in turn, can transition the flow controller 1642 from the first state to the second state (e.g., the flow controller 1642 limits and/or substantially prevents a flow of gas and liquid therethrough). As such, a negative pressure exerted on a surface of the diaphragm 1676 can build and can become sufficient to transition, move, and/or flip the diaphragm from a first state and/or configuration to a second state and/or configuration (see FIG. 52). In some embodiments, the transitioning of the diaphragm 1676 can correspond with and/or can be in response to the flow controller 1642 being transitioned from the first state to the second state (e.g., becoming fully wetted or the like, as described in detail above). In other embodiments, the diaphragm 1676 can transition before or after the flow controller 1642 has transitioned from the first state to the second state. In still other embodiments, the control device 1600 need not include the flow controller 1642 and the diaphragm 1676 can be configured to transition in response to being exposed to the negative pressure differential produced by the fluid collection device. In some such embodiments, the

diaphragm 1676 (and/or at least a portion thereof) can be configured to act in a similar manner to the flow controller 1642 by transitioning from the first state to the second state in a predictable and/or predetermined manner after being exposed to a predetermined negative pressure differential or a predetermined rate of change in negative pressure. Moreover, the transitioning of the diaphragm 1676 can be automatic (e.g., is not a result of user intervention).

[1225] As shown in FIG. 52, when the diaphragm 1676 is transitioned, moved, flipped, etc., the pin 1677 can be moved within the housing 1630 and relative to the actuator rod 1662. More particularly, the transitioning of the diaphragm 1676 can move the pin 1677 a sufficient amount that the pin 1677 is disengaged from the actuator rod 1662. As such, the energy storage member 1667 (e.g., spring) can be configured to release and/or convert at least a portion of its potential energy. As a specific example, in this embodiment, moving the pin 1677 can allow the spring 1667 to expand from a first or compressed state to a second or substantially uncompressed state. The transitioning of the energy storage member 1667 (e.g., spring) from the first state to the second state, in turn, moves the actuator rod 1662 within the actuator portion 1639 from a first state and/or position to a second state and/or position.

[1226] As shown in FIG. 52, when the actuator rod 1662 is in the second state and/or position, the first seal 1665 can be placed in a second or subsequent position in which the first seal 1665 sequesters the sequestration chamber 1634 from the inlet 1631. Similarly, the second seal 1666 can be placed in a second or subsequent position in which the second seal 1666 is pushed (e.g., by the energy storage member 1667) against the seal surface 1640, which in turn, sequesters the flow controller 1642 from the fluid flow path 1654. Furthermore, the placement of the first seal 1665 and the second seal 1666 when the actuator rod 1662 is in the second state and/or position is such that the fluid flow path 1633 is placed in fluid communication with the fluid flow path 1654. Thus, a negative pressure differential produced by the fluid collection device coupled to the outlet 1636 can be operable to draw a subsequent volume of bodily fluid from the inlet 1631, through the fluid flow path 1633 and 1654, through the outlet 1636, and into the fluid collection device. Moreover, the collecting and sequestering of the initial volume of bodily fluid can result in the subsequent volume(s) of bodily fluid being substantially free from contaminants, as described in detail above.

[1227] Referring now to FIG. 53, a flowchart is presented illustrating a method 10 of using a fluid control device to obtain a bodily fluid sample with reduced contamination according to an embodiment. The fluid control device can be similar to and/or substantially the same as any of the fluid control devices described in detail above. The method 10 includes establishing fluid communication between a bodily fluid source and an inlet of the fluid collection device,

at 11. For example, in some embodiments, a user can manipulate the fluid control device to physically and/or fluidically couple the inlet to a lumen-containing device (e.g., a needle, IV, PICC line, etc.) in fluid communication with a patient.

[1228] A fluid collection device is coupled to an outlet of the fluid control device, at 12. The coupling of the fluid collection device to the outlet is configured to produce a negative pressure differential within at least a portion of the fluid control device, as described in detail above. In some embodiments, for example, the fluid collection device can be a sample bottle or container that defines a negative pressure. In other embodiments, the fluid collection device can be a syringe or the like that can be manipulated to produce a negative pressure. Accordingly, a negative pressure differential can be produced within one or more portions of the fluid control device, as described above with reference to the control devices 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, and/or 1600.

[1229] An initial volume of bodily fluid is received from the inlet and into a sequestration portion of the fluid control device in response to the negative pressure differential, at 13. For example, in some embodiments, the sequestration portion can be similar to and/or substantially the same as the sequestration chamber 1234 described above with reference to FIGS. 29-34. In other embodiments, the sequestration portion can be similar to and/or substantially the same as the sequestration chamber 1634. In still other embodiments, the sequestration portion can be similar to and/or substantially the same as any of the sequestration chambers described herein. Furthermore, in some instances, the initial volume of bodily fluid can include contaminants entrained therein, which may otherwise result in false results during testing of a bodily fluid sample.

[1230] In response to contact with at least a portion of the initial volume of bodily fluid, a flow controller disposed in the sequestration portion is transitioned from a first state in which the flow controller allows a flow of a gas through the flow controller and prevents a flow of bodily fluid through the flow controller, to a second state in which the flow controller prevents a flow of gas and bodily fluid through the flow controller, at 14. For example, in some embodiments, the flow controller can be a selectively permeable member or membrane (e.g., a fluid or blood barrier and/or the like), as described above with reference to the flow controller 242. In other embodiments, the flow controller can be similar to and/or substantially the same as any of the flow controllers described herein. Thus, in some embodiments, the contact with at least the portion of the initial volume of bodily fluid can, for example, wet or saturate the flow controller such that the flow controller limits and/or substantially prevents a flow of gas and liquid (e.g., bodily fluid) therethrough. In other embodiments, the flow controller can be

a bladder and/or diaphragm that is configured to be transitioned in response to a negative pressure differential. For example, in such embodiments, a flow controller can be a substantially impermeable bladder or diaphragm that can transition from a first state to a second state when a negative pressure differential applied to a surface of the bladder and/or diaphragm exceeds a threshold amount of negative pressure.

[1231] The initial volume of bodily fluid is sequestered in the sequestration portion after the flow controller is transitioned to the second state, at 15. For example, in some embodiments, the fluid control device can include an actuator and/or any other suitable feature or mechanism configured to transition after the flow controller is placed in its second configuration to sequester the initial volume of bodily fluid. In some embodiments, the actuator can transition from a first state to a second state to automatically sequester the initial volume of bodily fluid in the sequestration portion, as described above with reference to, for example, the actuator 1650. In other embodiments, the actuator can transition from a first state to a second state in response to a force exerted by a user, as described above with reference to, for example, the actuator 850. In still other embodiments, the fluid control device can sequester the initial volume of bodily fluid in the sequestration portion in any suitable manner such as those described herein.

[1232] After sequestering the initial volume of bodily fluid, a subsequent volume of bodily fluid is transferred from the inlet, through the outlet, and into the fluid collection device, at 16. As described in detail above, in some instances, sequestering the initial volume of bodily fluid in the sequestration portion of the fluid control device can likewise sequester contaminants contained in the initial volume. Accordingly, contaminants in the subsequent volume of bodily fluid can be reduced or substantially eliminated.

[1233] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Where schematics and/or embodiments described above indicate certain components arranged in certain orientations or positions, the arrangement of components may be modified. While the embodiments have been particularly shown and described, it will be understood that various changes in form and details may be made. For example, while the control devices 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, and/or 1500 are described as transferring a bodily fluid into the device as a result of a negative pressure within a fluid collection device, in other embodiments, the devices described herein can be used with any suitable device configured to establish a pressure differential (e.g., a negative pressure differential). For example, in some embodiments, an outlet of a control device can be coupled

to a syringe or pump. In other embodiments, a control device can include a pre-charged sequestration chamber, a vented sequestration chamber, a manually activated device configured to produce a negative pressure, an energy source (e.g., a chemical energy source, a kinetic energy source, and/or the like), and/or any other suitable means of defining and/or forming a pressure differential within a portion of the control device. Moreover, as described above, the control devices can be coupled to such collection devices by a user (e.g., doctor, nurse, technician, physician, etc.) or can be coupled or assembled during manufacturing. In some embodiments, pre-assembling a control device and a collection device (e.g., a sample container or syringe) can, for example, force compliance with a sample procurement protocol that calls for the sequestration of an initial amount of bodily fluid prior to collecting a sample volume of bodily fluid.

[1234] While some of the embodiments described above include a flow controller and/or an actuator having a particular configuration and/or arrangement, in other embodiments, a fluid control device can include any suitable flow controller and/or actuator configured to selectively control a flow of bodily fluid through one or more portions of the fluid control device. For example, while some embodiments include an actuator such as a diaphragm or the like having one or more seals arranged as an O-ring or an elastomeric over-mold, which is/are moved with the diaphragm and relative to a portion of the device (e.g., the inlet, the outlet, or any other suitable portion) when the diaphragm is transitioned or flipped from a first state to a second state, in other embodiments, a fluid control device can include one or more seals having any suitable configuration. For example, in some embodiments, a fluid control device can include one or more seals arranged as an elastomeric sheet or the like that is/are fixedly coupled to a portion of the control device. In such embodiments, a portion of an actuator such as a pin or rod extending from a diaphragm (see e.g., FIGS. 11 and 12) can extend through an opening defined in the one or more elastomeric sheets, which in turn, form a substantially fluid tight seal with an outer surface of the pin or rod. As such, when the actuator (e.g., diaphragm) is transitioned from a first state to a second state, the portion of the actuator (e.g., the pin or rod) can move through one or more of the elastomeric sheets. In other words, the portion of the actuator moves relative to the one or more elastomeric sheets, which in turn, remain in a substantially fixed position relative to the portion of the control device. In some embodiments, the removal or the portion of the actuator can allow a flow of fluid through the opening defined by the one or more elastomeric sheets that was otherwise occluded by the portion of the actuator. Accordingly, the one or more elastomeric sheets can function in a similar manner as any of the seals described herein. Moreover, in some embodiments, such an arrangement may,

for example, reduce an amount of friction associated with forming the desired fluid tight seals, which in turn, may obviate the use of a lubricant otherwise used to facilitate the movement of the seals within the control device.

[1235] While the diaphragms (e.g., diaphragms 576, 676, and 776) are described herein as being configured to transition, move, flip, and/or otherwise reconfigure in response to an amount of negative pressure exerted on a surface of the diaphragm exceeding a threshold amount of negative pressure, in other embodiments, a fluid control device can include any suitable actuator or the like configured to transition, move, flip, and/or otherwise reconfigure in response to being exposed to a desired and/or predetermined amount of negative pressure. For example, in some embodiments, a fluid control device can include an actuator including and/or arranged as a movable member, plug, plunger, occlusion member, seal, and/or the like configured to selectively control a flow of fluid through at least a portion of the fluid control device. More particularly, the movable member or the like can be transitioned from a first state and/or position in which the movable member or the like is disposed in and/or otherwise occludes an opening, to a second state and/or position in which the movable member or the like is removed from the opening. In such embodiments, a negative pressure can be exerted through a portion of the device to transfer, for example, an initial volume of bodily fluid into a sequestration portion and/or chamber.

[1236] As described in detail above, in some embodiments, a device can include a flow controller such as a selectively permeable member or membrane, that can be configured to transition from a first state to a second state in response to being wetted (or otherwise transitioned) by the initial volume of bodily fluid. After transferring the initial volume of bodily fluid and after the flow controller is transitioned to its second state, an amount of negative pressure exerted on a surface of the movable member or the like may build until a magnitude of the negative pressure is sufficient to pull or move the movable member out of the opening, thereby allowing a flow of bodily fluid through the opening that was otherwise occluded by the movable member. In this manner, the movable member can function similar to any of the diaphragms described herein (e.g., the diaphragm 576, 676, and/or 776) that are configured to transition or flip from a first state to a second state. In such embodiments, the movable member can be, for example, an elastomeric plug, cork, plunger, and/or any other suitable member that can be moved or "popped" out of such an opening or portion of a flow path.

[1237] While some of the embodiments described above include a flow controller and/or actuator that selectively establishes fluid communication between a sequestration chamber and

a fluid collection device (e.g., a sample reservoir, a syringe, and/or any other suitable source of negative pressure) in other embodiments, a control device can be arranged to transfer a flow of bodily fluid in response to negative pressure differentials resulting from any suitable portion(s) of the device. For example, while the control device 200 is described above as including the flow controller 242 and the restricted flow path 232 that selectively place the sequestration chamber 234 in fluid communication with the sample reservoir until the flow controller 242 is transitioned to a sealed or closed state (e.g., until the flow controller 242 is sufficiently wetted), in other embodiments, a control device can include a sequestration chamber that is a pre-sealed evacuated and/or charged chamber such that establishing fluid communication between an inlet and the sequestration chamber results in a negative pressure differential that is sufficient to draw an initial volume of bodily fluid into the sequestration chamber. In such embodiments, the control device can be configured to transfer bodily fluid to the sequestration chamber until the pressure differential is sufficiently reduced and/or until pressures otherwise substantially equalize. Moreover, in some such embodiments, the sequestration chamber and/or the inlet can include a coupler, an actuator, a needle, a septum, a port, and/or any other suitable member that can establish fluid communication therebetween (e.g., that can transition the sequestration chamber from a sealed to an unsealed configuration).

[1238] While some of the embodiments described above include a flow controller and/or actuator that physically and/or mechanically sequesters one or more portions of a fluid control device, in other embodiments, a fluid control device need not physically and/or mechanically sequester one or more portions of the fluid control device. For example, in some embodiments, an actuator such as the actuator 1250 can be transitioned from a first state in which an initial volume of bodily fluid can flow from an inlet to a sequestration chamber or portion, to a second state in which (1) the sequestration chamber or portion is physically and/or mechanically sequestered and (2) the inlet is in fluid communication with an outlet of the fluid control device. In other embodiments, however, an actuator and/or any other suitable portion of a fluid control device can transition from a first state in which an initial volume of bodily fluid can flow from an inlet to a sequestration chamber or portion, to a second state in which the inlet is placed in fluid communication with the outlet without physically and/or mechanically sequestering (or isolating) the sequestration chamber or portion. When such a control device is in the second state, one or more features and/or geometries of the control device can result in a preferential flow of bodily fluid from the inlet to the outlet and the initial volume of bodily fluid can be retained in the sequestration chamber or portion without physically and/or mechanically being sequestered or isolated.

[1239] While the restricted flow path 232 is described above as modulating and/or controlling a magnitude of negative pressure applied on or through at least a portion of the device 200, in other embodiments, a control device can include any suitable feature, mechanism, and/or device configured to modulate, create, and/or otherwise control one or more pressure differentials through at least a portion of the control device. For example, in some embodiments, a user can transition and/or move an actuator to change (e.g., reduce or increase) the size of one or more portions of a fluid flow path or fluid flow interface within a portion of the control device to manually modulate and/or otherwise control an amount or magnitude of negative pressure within one or more portions of a control device.

[1240] Although various embodiments have been described as having particular features, concepts, and/or combinations of components, other embodiments are possible having any combination or sub-combination of any features, concepts, and/or components from any of the embodiments described herein. For example, as described above, the device 700 includes concepts, features, and/or elements of the devices 200 and 600. As another example, any of the embodiments described herein can include a lock or other suitable feature configured to at least temporarily maintain one or more components in a desired position, state, arrangement, and/or configuration. As another example, any of the embodiments described herein can include and/or can define a sequestration chamber and/or portion that is configured similar to, for example, the sequestration chamber 1234 described above with reference to FIG. 30. In other words, any of the fluid control devices described herein can include a sequestration chamber that is arranged and/or formed as a channel. In some embodiments, a channel forming at least a portion of a sequestration chamber can have a relatively small cross-sectional shape and/or size that can reduce and/or substantially prevent mixing of air and bodily fluid as the initial volume of bodily fluid is drawn into the channel, as described above with reference to the sequestration chamber 1234. Moreover, such a channel can have a spiral shape and/or configuration similar to the sequestration chamber 1234 described above and/or can have any other suitable shape and/or configuration.

[1241] As another example, any of the control devices described herein can include a flow controller arranged as a selectively permeable member or membrane as described above, for example, with reference to the flow controller 242. More particularly, while the control device 600 is not described as including a flow controller, in other embodiments, a portion of the diaphragm 676 can include and/or can form a flow controller formed, at least in part, of a selectively permeable material. In such embodiments, the flow controller can be configured to allow a volume of the sequestration chamber and/or portion 634 to be vented in response to

being exposed to the negative pressure differential (as described above). In other words, a volume of air can be drawn out of (e.g., vented from or purged from) the sequestration chamber 634 via the flow controller in response to the negative pressure differential within a portion of the fluid control device 600. In some instances, such an arrangement can allow for a reduction in a size and/or volume of the sequestration chamber 634 because a volume of air otherwise occupying a portion of the sequestration chamber 634 is vented or purged through the flow controller in response to the negative pressure differential.

[1242] By way of another example, any of the embodiments described herein can include any suitable actuator and/or flow controller configured to selectively control fluid flow through at least a portion of the device. Specifically, a flow controller or the like can be one or more of a selectively permeable material or membrane, a valve, a diaphragm, and/or any other suitable flow controller. While some of the embodiments have been described as including an actuator rod configured to be transitioned from a first configuration or position to a second configuration or position (e.g., the actuator rod 1262 of the actuator 1250), in other embodiments, any actuator described herein can include an actuator rod configured to transition from between a first position and second position to at least temporarily isolate an outlet of the device from one or more other portions of the device (e.g., as described above with reference to the actuators 850 and/or 1350). In some embodiments, such an actuator can be configured for use with a given and/or predetermined collection device such as, for example, a syringe. In other embodiments, such an actuator can be used with any suitable collection device.

[1243] In some embodiments, the specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. For example, while a portion of the actuator body 1551, sequestration chamber 1534, and/or the bladder 1578 are shown in FIGS. 45-50 as being substantially tubular having a round or substantially semi-circular end portion, in other embodiments, the portion of the actuator body 1551, sequestration chamber 1534, and/or bladder 1578 can have any suitable shape and/or size. In some embodiments, varying the size and/or shape of such components may reduce an overall size of the device 1500 and/or may increase the ergonomics of the device 1500 without changing the function of the device 1500. As a specific example, a housing, sequestration chamber, and/or bladder may have a substantially cylindrical shape with a relatively flat end portion or the like. Moreover, in some embodiments, a control device can include a bladder that is configured to "flip" similar to the diaphragms described above in response to being exposed to a negative pressure differential. In other embodiments, a bladder can be configured

to gradually transition (e.g., unroll, unfold, unfurl, and/or otherwise reconfigure) from the first state to the second state. In some instances, controlling a rate at which a bladder is transitioned may allow for a modulation and/or control of a negative pressure differential produced within the sequestration chamber.

[1244] In other embodiments, a device may include a bladder (similar in form and/or function to the bladders 1478 and/or 1578) disposed in a housing having a size, shape, and/or profile similar to the housings 1230 and/or 1330. In some such embodiments, the bladder can define a volume that is similar in shape and/or size the overall size, and/or shape of the housing (e.g., cylindrical with a relatively low profile or height). In some instances, such an arrangement can allow at least a portion of an initial volume of bodily fluid to remain in contact with a surface of the bladder (or diaphragm or other actuator), which can provide a visual indication to the user regarding the bodily fluid being transferred into the sequestration chamber. In other embodiments, a housing similar to the housing 1230 can define a spiral channel or any other suitable channel and can include a bladder disposed within at least a portion of that channel. In such embodiments, the bladder can function similarly to the bladder 1578 in which the bladder expands, opens, and/or otherwise increases in volume in response to being exposed to a negative pressure differential. In some embodiments, a bladder can define an enclosed volume configured to receive an initial volume of bodily fluid. In other embodiments, the bladder and a portion of the housing (e.g., a surface defining the sequestration chamber and/or channel) can collectively define the volume configured to receive the initial volume of bodily fluid. In this manner, a fluid control device can include a bladder configured to conform to any suitable shape, feature, channel, and/or configuration of a housing in which it is disposed. In some embodiments, the size and shape of the various components can be specifically selected for a desired rate and/or volume of bodily fluid flow into a fluid reservoir.

[1245] In some embodiments, the size and/or shape of the various components can be specifically selected for a desired or intended usage. For example, in some embodiments, a device such as those described herein can be configured for use with or on seemingly healthy adult patients. In such embodiments, the device can include a sequestration chamber that has a first volume (e.g., about 0.5 ml to about 5.0 ml). In other embodiments, a device such as those described herein can be configured for use with or on, for example, very sick patients and/or pediatric patients. In such embodiments, the device can include a sequestration chamber that has a second volume that is less than the first volume (e.g., less than about 0.5 ml). Thus, it should be understood that the size, shape, and/or arrangement of the embodiments and/or

components thereof can be adapted for a given use unless the context explicitly states otherwise.

[1246] Although not shown, any of the devices described herein can include an opening, port, coupler, septum, Luer-Lok, gasket, valve, threaded connecter, standard fluidic interface, etc. (referred to for simplicity as a "port") in fluid communication with the sequestration chamber. In some such embodiments, the port can be configured to couple to any suitable device, reservoir, pressure source, etc. For example, in some embodiments, the port can be configured to couple to a reservoir, which in turn, can allow a greater volume of bodily fluid to be diverted and/or transferred into the sequestration chamber. In other embodiments, the port can be coupled to a negative pressure source such as an evacuated container, a pump, a syringe, and/or the like to collect a portion of or the full volume of bodily fluid in the sequestration chamber, channel, reservoir, etc. and use that volume of bodily fluid (e.g., the pre-sample volume) for additional clinical and/or in vitro diagnostic testing purposes. In other embodiments, the port can be configured to receive a probe, sampling tool, testing device, and/or the like that can be used to perform one or more tests (e.g., tests not sensitive to potential contamination) on the initial volume while the initial volume is disposed or sequestered in the sequestration chamber. In still other embodiments, the port can be coupled to any suitable pressure source or infusion device configured to infuse the initial volume of bodily fluid sequestered in the sequestration chamber back into the patient and/or bodily fluid source (e.g., in the case of pediatric patients, very sick patients, patients having a low blood volume, and/or the like). In other embodiments, the sequestration channel, chamber, and/or reservoir can be configured with the addition of other diagnostic testing components integrated into the chamber (e.g., a paper test) such that the initial bodily fluid is used for that test.

[1247] In still other embodiments, the sequestration chamber, channel, and/or reservoir can be designed, sized, and configured to be removable and compatible with testing equipment and/or specifically accessible for other types of bodily fluid tests commonly performed on patients with suspected conditions. By way of example, a patient with suspected sepsis commonly has blood samples collected for lactate testing, procalcitonin testing, and blood culture testing. All of the fluid control devices described herein can be configured such that the sequestration chamber, channel, reservoir, etc. can be removed (e.g., after receiving the initial volume of bodily fluid) and the bodily fluid contained therein can be used for these additional testing purposes before or after the subsequent sample is collected for microbial testing.

[1248] Although not shown, in some embodiments, a fluid control device can include one or more lumen, channels, flow paths, etc. configured to selectively allow for a "bypass" flow of bodily fluid, where an initial amount or volume of bodily fluid can flow from the inlet, through the lumen, cannel, flow path, etc. to bypass the sequestration chamber, and into the collection device. In some embodiments, the fluid control device can include an actuator having, for example, at least three states – a first in which bodily fluid can flow from the inlet to the sequestration chamber, a second in which bodily fluid can flow from the inlet to the outlet after the initial volume is sequestered in the sequestration chamber, and a third in which bodily fluid can flow from the inlet, through the bypass flow path, and to the outlet. In other embodiments, the control device can include a first actuator configured to transition the device between a first and second state, as described in detail above with reference to specific embodiments, and can include a second actuator configured to transition the device to a bypass configuration or the like. In still other embodiments, the control device can include any suitable device, feature, component, mechanism, actuator, controller, etc. configured to selectively place the fluid control device in a bypass configuration or state.

[1249] Any of the embodiments described herein can be used in conjunction with any suitable fluid transfer, fluid collection, and/or fluid storage device such as, for example, the fluid reservoirs described in the '420 patent. In some instances, any of the embodiments described herein can be used in conjunction with any suitable transfer adapter, fluid transfer device, fluid collection device, and/or fluid storage devices such as, for example, the devices described in the '510 Publication and/or any of the devices described in U.S. Patent Publication No. 2015/0246352 entitled, "Apparatus and Methods for Disinfection of a Specimen Container," filed March 3, 2015; U.S. Patent No. 8,535,241 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed October 12, 2012; U.S. Patent No. 9,060,724 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed May 29, 2013; U.S. Patent No. 9,155,495 entitled, "Syringe-Based Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed December 2, 2013; U.S. Patent Publication No. 2016/0361006 entitled, "Devices and Methods for Syringe Based Fluid Transfer for Bodily-Fluid Sampling," filed June 13, 2016; U.S. Patent Publication No. 2018/0140240 entitled, "Systems and Methods for Sample Collection with Reduced Hemolysis," filed November 20, 2017; and/or U.S. Patent Publication No. 2017/0065733 entitled, "Apparatus and Methods for Maintaining Sterility of a Specimen Container," filed September 6, 2016, the disclosures of each of which are incorporated herein by reference in their entireties.

[1250] In some embodiments, a method of using a fluid control device such as those described herein can include the ordered steps of establishing fluid communication between a bodily fluid source (e.g., a vein of a patient or the like) and an inlet of a fluid control device. An outlet of the fluid control device is then placed in fluid communication with and/or otherwise engages a negative pressure source. Such a negative pressure source can be a sample reservoir, a syringe, an evacuated container, an intermediate transfer device, and/or the like. The fluid control device can be in a first state or operating mode when the outlet is coupled to the negative pressure source and, as such, a negative pressure differential is applied through the fluid control device that draws an initial volume of bodily fluid into a sequestration chamber of the fluid control device. For example, a negative pressure within a sample reservoir can be operable in drawing an initial volume of bodily fluid from a patient and into the sequestration chamber. Once the initial volume of bodily fluid is disposed in the sequestration chamber, the fluid control device is transitioned, either automatically or via user intervention, from the first state or operating mode to a second state or operating mode such that (1) the initial volume is sequestered in the sequestration chamber and (2) the fluid communication is established between the inlet and the outlet. The sequestration of the initial volume can be such that contaminants entrained in the flow of the initial volume are likewise sequestered within the sequestration chamber. With the initial volume of bodily fluid sequestered in the sequestration chamber and with fluid communication established between the inlet and the outlet, subsequent volumes of bodily fluid that are substantially free of contamination can be collected in one or more sample reservoirs.

[1251] While the method of using the fluid control device is explicitly described as including the recited ordered steps, in other embodiments, the ordering of certain events and/or procedures in any of the methods or processes described herein may be modified and such modifications are in accordance with the variations of the invention. Additionally, certain events and/or procedures may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above. Certain steps may be partially completed or may be omitted before proceeding to subsequent steps. For example, while the devices are described herein as transitioning from a first state to a second state in a discrete operation or the like, it should be understood that the devices described herein can be configured to automatically and/or passively transition from the first state to the second state and that such a transitioning may occur over a period of time. In other words, the transitioning from the first state to the second state may, in some instances, be relatively gradual such that as a last portion of the initial volume of bodily fluid is being transferred into the sequestration chamber, the

housing begins to transition from the first state to the second state. In some instances, the rate of change when transitioning from the first state to the second state can be selectively controlled to achieve one or more desired characteristics associated with the transition. Moreover, in some such instances, the inflow of the last portion of the initial volume can limit and/or substantially prevent bodily fluid already disposed in the sequestration chamber from escaping therefrom. Accordingly, while the transitioning from the first state to the second state may occur over a given amount of time, the sequestration chamber can nonetheless sequester the volume of bodily fluid disposed therein.

What is claimed:

1. A system, comprising:

a housing having an inlet and an outlet, the inlet configured to be placed in fluid communication with a bodily fluid source, the housing forming a sequestration portion configured to receive an initial volume of bodily fluid from the bodily fluid source;

a flow controller at least partially disposed in the sequestration portion of the housing and configured to transition from a first state to a second state; and

a fluid collection device configured to be fluidically coupled to the outlet to produce a negative pressure differential within at least a portion of the housing, the negative pressure differential produced by the fluid collection device operable to draw the initial volume of bodily fluid into the sequestration portion when the flow controller is in the first state, the negative pressure differential produced by the fluid collection device operable to draw the sample volume of bodily fluid through the outlet and into the fluid collection device when the flow controller is in the second state.

2. The system of claim 1, wherein the flow controller is configured to transition from the first state to the second state automatically.

3. The system of claim 1, wherein the flow controller is configured to transition from the first state to the second state in response to contact with a portion of the initial volume of bodily fluid disposed in the sequestration portion.

4. The system of claim 1, wherein the flow controller includes a selectively permeable material.

5. The system of claim 4, wherein prior to being placed in the second state, the flow controller is configured to allow a flow of a gas through the flow controller and to prevent a flow of bodily fluid through the flow controller.

6. The system of claim 5, wherein the flow controller is configured to prevent a flow of gas and bodily fluid through the flow controller when in the second state.

7. The system of claim 6, wherein the flow controller is configured to be placed in the second state in response to a portion of the initial volume of bodily fluid saturating the selectively permeable material.

8. The system of claim 1, wherein the flow controller is configured to modulate a magnitude of negative pressure exerted on the sequestration portion of the housing prior to the flow controller transitioning to the second state.

9. The system of claim 1, wherein the fluid collection device is a sample reservoir that defines a negative pressure operable to produce the negative pressure differential within at least the portion of the housing when fluidically coupled to the outlet.

10. The system of claim 1, wherein the fluid collection device is a syringe configured to be manipulated by a user after being fluidically coupled to the outlet to produce the negative pressure differential within at least the portion of the housing.

11. The system of claim 1, wherein the housing defines a first fluid flow path and a second fluid flow path, the negative pressure differential is operable to draw the initial volume of bodily fluid through the first fluid flow path from the inlet to the sequestration portion when the flow controller is in the first state, the negative pressure differential is operable to draw the sample volume of bodily fluid through the second fluid flow path from the inlet to the outlet when the flow controller is in the second state.

12. The system of claim 11, further comprising:

an actuator coupled to the housing, the actuator having a first actuator state in which the negative pressure differential is applied to the first fluid flow path and a second actuator state in which the negative pressure differential is applied to the second fluid flow path.

13. The system of claim 12, wherein the actuator is in the first actuator state when the flow controller is in the first state, the actuator is configured to be transitioned from the first actuator state to the second actuator state after the flow controller is transitioned to the second state.

14. The system of claim 13, wherein the negative pressure differential automatically transitions the actuator from the first actuator state to the second actuator state after the flow controller is transitioned to the second state.

15. An apparatus, comprising:

a housing having an inlet configured to be placed in fluid communication with a bodily fluid source and an outlet configured be placed in fluid communication with a fluid collection device, the housing forming a sequestration portion configured to receive an initial volume of bodily fluid from the bodily fluid source; and

an actuator coupled to the housing, the actuator having a first configuration in which a first fluid flow path places the inlet in fluid communication with the sequestration portion and a second configuration in which a second fluid flow path places the inlet in fluid communication with the outlet,

wherein the fluid collection device is configured to be placed in fluid communication with the outlet to produce a negative pressure differential (1) within the first fluid flow path operable to draw the initial volume of bodily fluid into the sequestration portion when the actuator is in the first configuration, and (2) within the second fluid flow path operable to draw a sample volume of bodily fluid into the fluid collection device when the actuator is in the second configuration.

16. The apparatus of claim 15, wherein the initial volume of bodily fluid is sequestered in the sequestration portion when the actuator is in the second configuration.

17. The apparatus of claim 15, wherein sequestering the initial volume in the sequestration portion reduces contamination in the sample volume.

18. The apparatus of claim 15, wherein the fluid collection device is a sample reservoir that defines a negative pressure operable to produce the negative pressure differential within the first fluid flow path and the second fluid flow path.

19. The apparatus of claim 15, wherein the fluid collection device is a syringe configured to be manipulated by a user after being placed in fluid communication with the outlet to produce the negative pressure differential within the first fluid flow path and the second fluid flow path.

20. The apparatus of claim 15, wherein the actuator is configured to transition from the first configuration to the second configuration in response to a force applied by a user on a portion of the actuator.

21. The apparatus of claim 15, wherein the actuator includes at least one seal configured to define a portion of the first fluid flow path when the actuator is in the first configuration, the at least one seal is configured to define a portion of the second fluid flow path when the actuator is in the second configuration.

22. The apparatus of claim 15, wherein the actuator includes a diaphragm configured to transition from a first state to a second state when a negative pressure differential within a portion of the first fluid flow path is greater than a threshold amount of negative pressure.

23. The apparatus of claim 22, wherein the diaphragm is coupled to at least one seal configured to define a portion of the first fluid flow path when the diaphragm is in the first state and configured to define a portion of the second fluid flow path when the diaphragm is in the second state.

24. The apparatus of claim 15, further comprising:

a flow controller at least partially disposed in the sequestration portion of the housing, the flow controller is configured to establish selective fluid communication between the sequestration portion and the actuator.

25. The apparatus of claim 24, wherein the flow controller includes a selectively permeable material.

26. The apparatus of claim 25, wherein the flow controller is configured to transition from a first state in which the selective permeable material allows a flow of a gas through the flow controller and prevents a flow of bodily fluid through the flow controller, to a second state in which the selectively permeable material prevents a flow of gas and bodily fluid through the flow controller.

27. The apparatus of claim 26, wherein the flow controller is configured to be placed in the second state in response to at least a portion of the initial volume of bodily fluid saturating the selectively permeable material.

28. The apparatus of claim 26, wherein the actuator is configured to be transitioned to the second configuration after the flow controller is transitioned to the second state.

29. A method of using a fluid control device to obtain a bodily fluid sample with reduced contamination, the method comprising:

establishing fluid communication between a bodily fluid source and an inlet of the fluid control device;

coupling a fluid collection device to an outlet of the fluid control device, the coupling of the fluid collection device to the outlet configured to produce a negative pressure differential within at least a portion of the fluid control device;

receiving an initial volume of bodily fluid from the inlet and into a sequestration portion of the fluid control device in response to the negative pressure differential;

transitioning, in response to contact with at least a portion of the initial volume of bodily fluid, a flow controller disposed in the sequestration portion from a first state in which the flow controller allows a flow of a gas through the flow controller and prevents a flow of bodily fluid through the flow controller, to a second state in which the flow controller prevents a flow of gas and bodily fluid through the flow controller;

sequestering the initial volume of bodily fluid in the sequestration portion after the flow controller is transitioned to the second state; and

transferring a subsequent volume of bodily fluid from the inlet, through the outlet, and into the fluid collection device.

30. The method of claim 29, wherein the flow controller includes a selectively permeable material.

31. The method of claim 29, wherein the flow controller is configured to be placed in the second state in response to at least a portion of the initial volume of bodily fluid saturating the selectively permeable material.

32. The method of claim 29, wherein the flow controller is configured to automatically transition from the first state to the second state in response to contact with at least the portion of the initial volume of bodily fluid.

33. The method of claim 29, wherein the coupling the fluid collection device to the outlet includes coupling a fluid reservoir to the outlet to produce the negative pressure differential within at least the portion of the fluid control device, the fluid reservoir defining a negative pressure prior to the fluid reservoir being coupled to the outlet.

34. The method of claim 29, wherein coupling the fluid collection device to the outlet includes coupling a syringe to the outlet, the method further comprising:

manipulating the syringe, after coupling the syringe to the outlet, to produce the negative pressure differential within at least the portion of the fluid control device.

35. The method of claim 29, further comprising:

transitioning an actuator of the fluid control device from a first configuration to a second configuration after transitioning the flow controller from the first state to the second state, the actuator defining at least a portion of a first fluid flow path between the inlet and the sequestration portion when in the first configuration, the actuator defining at least a portion of a second fluid flow path between the inlet and the outlet when in the second configuration.

36. The method of claim 29, wherein the sequestering of the initial volume of bodily fluid sequesters contaminants within the sequestration portion such that the subsequent volume of bodily fluid is substantially free of contaminants.

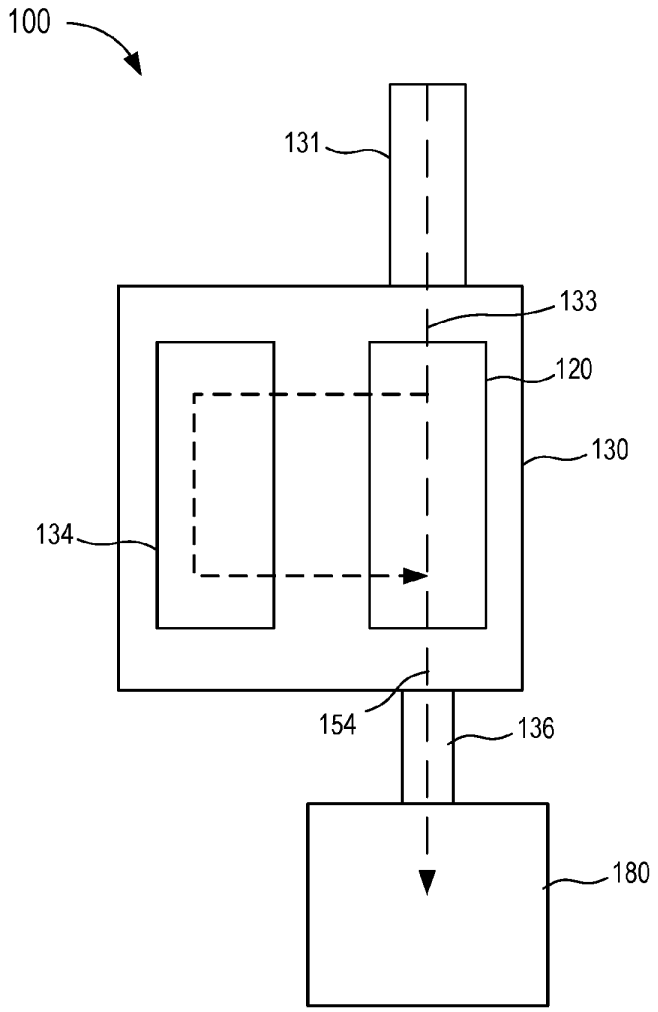


FIG. 1

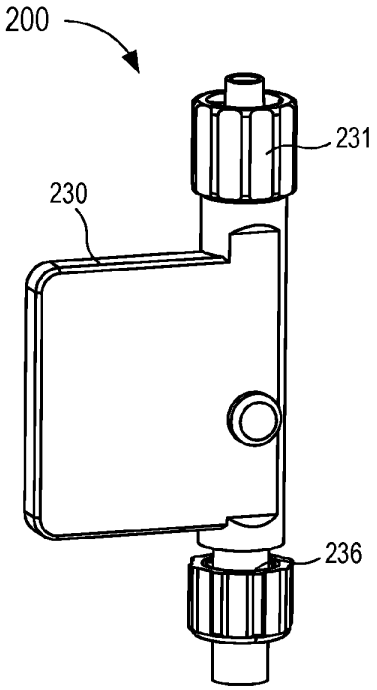


FIG. 2

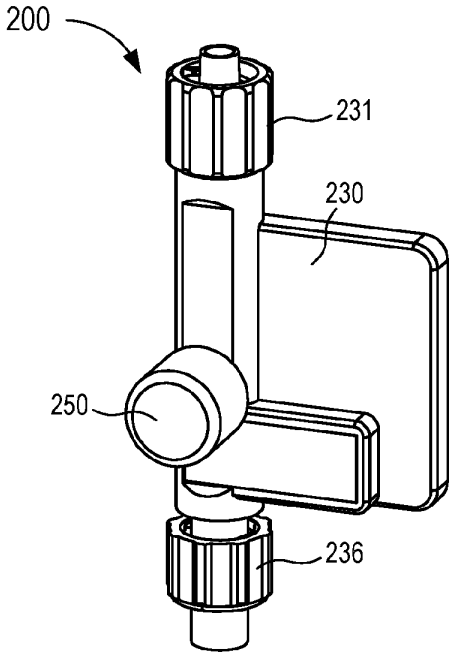


FIG. 3

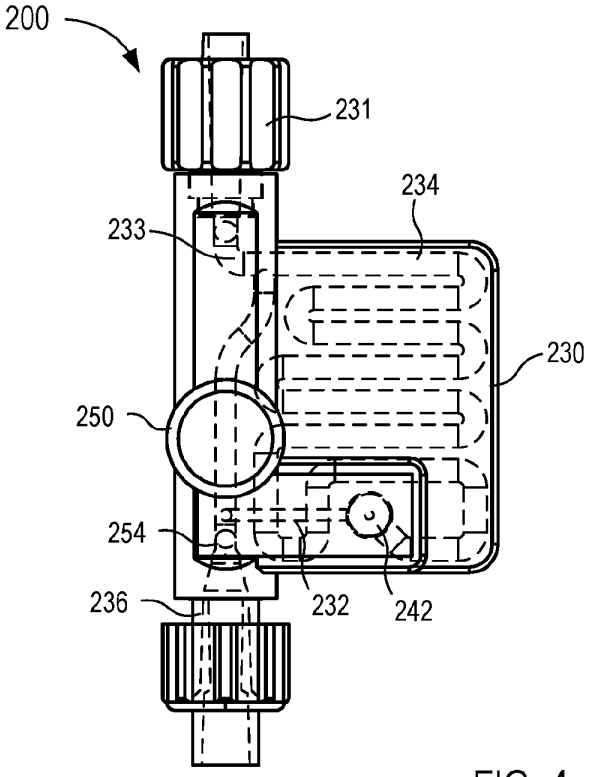


FIG. 4

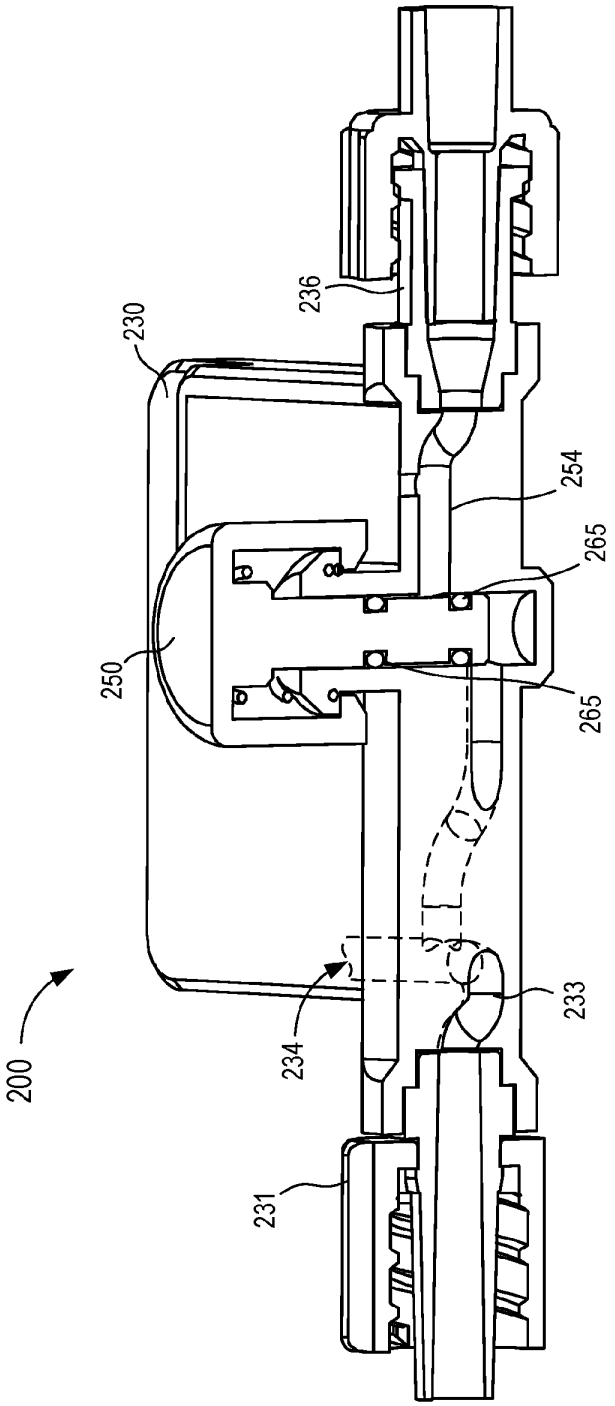


FIG. 5

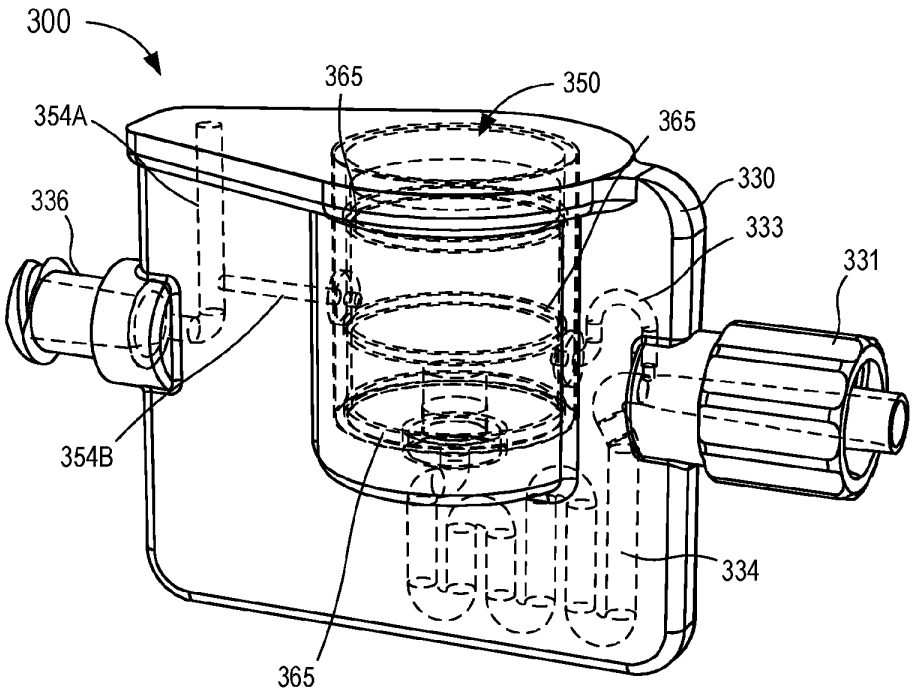

300
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354A
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330
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354B
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365

FIG. 6

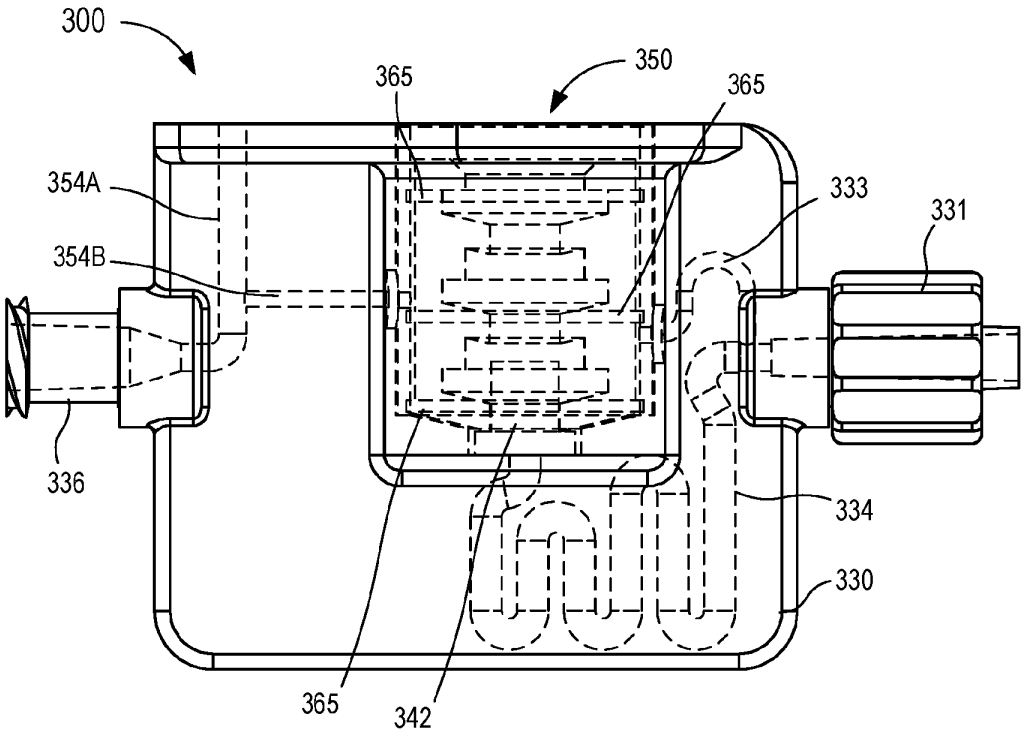

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FIG. 7

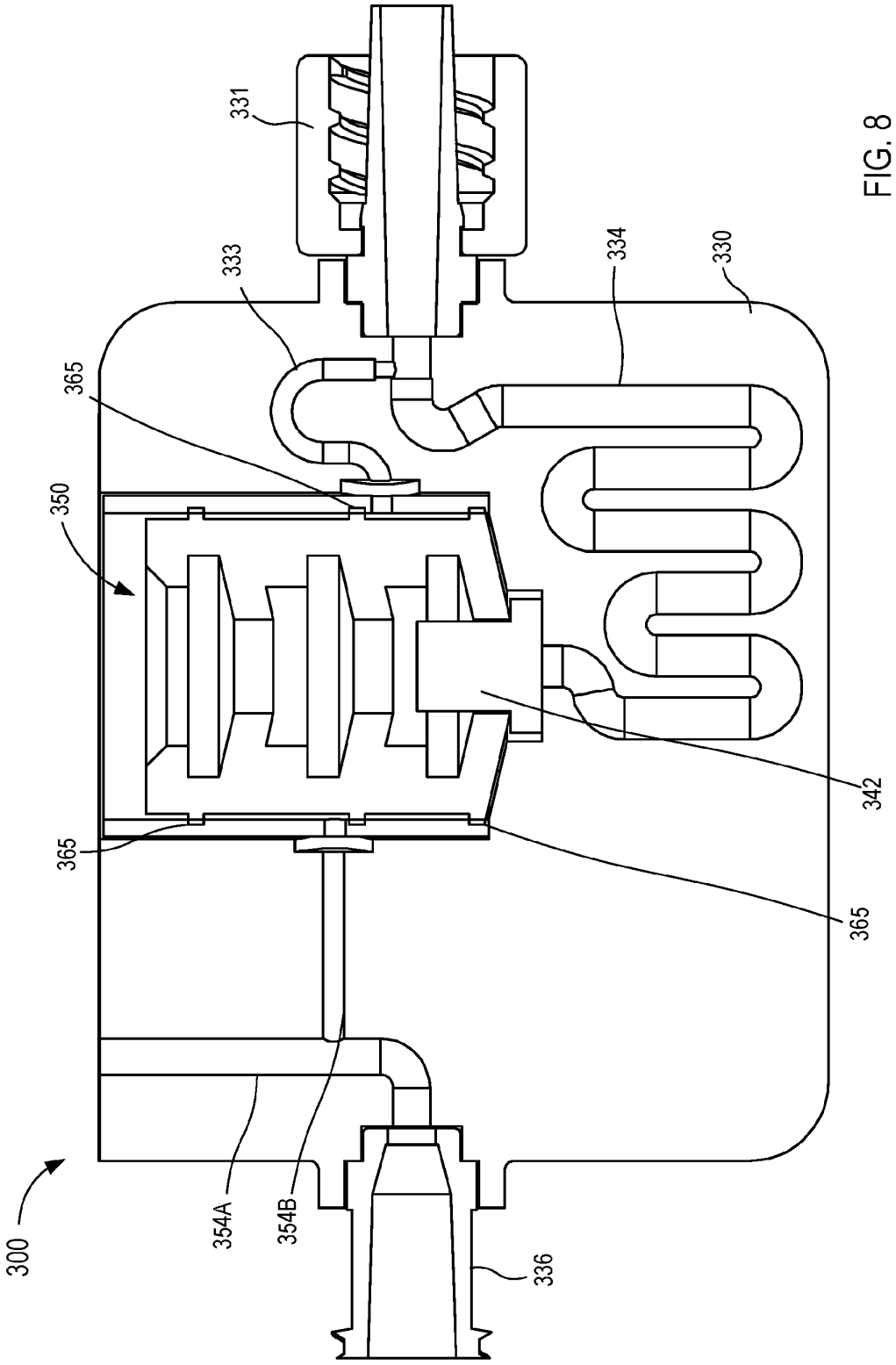


FIG. 8

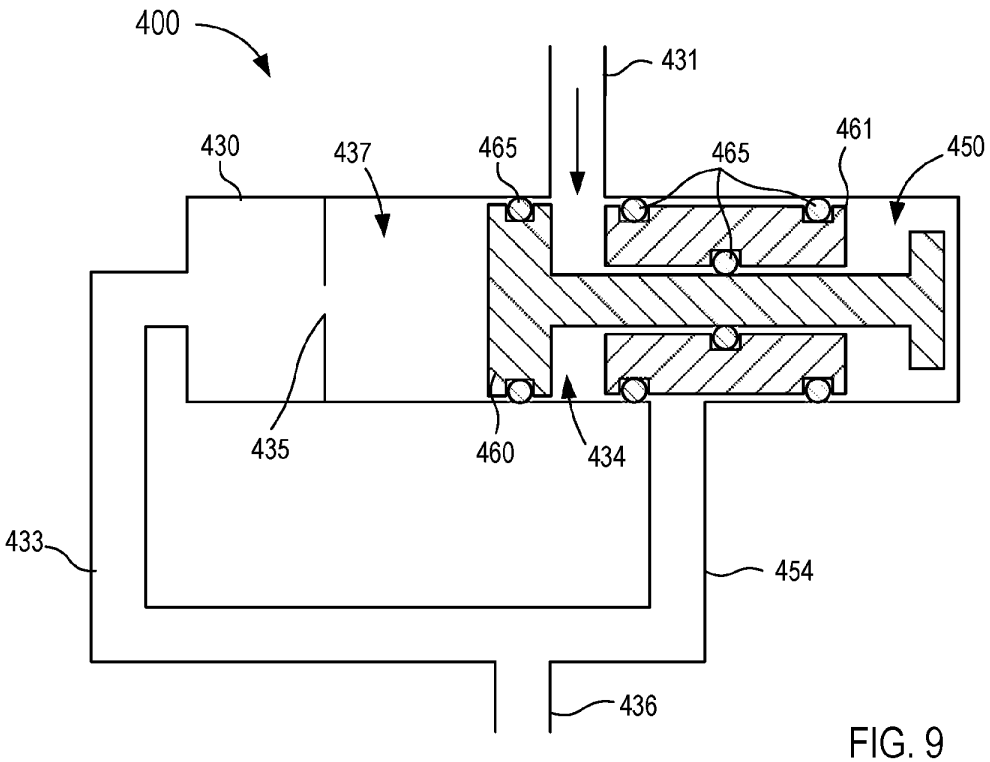

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FIG. 9

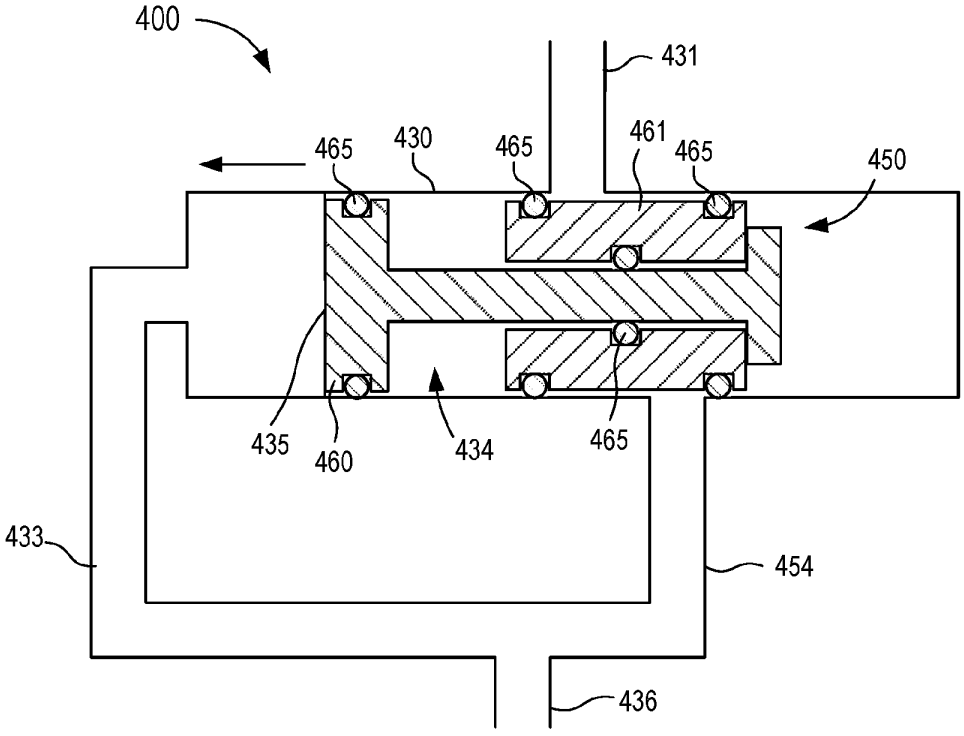

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FIG. 10

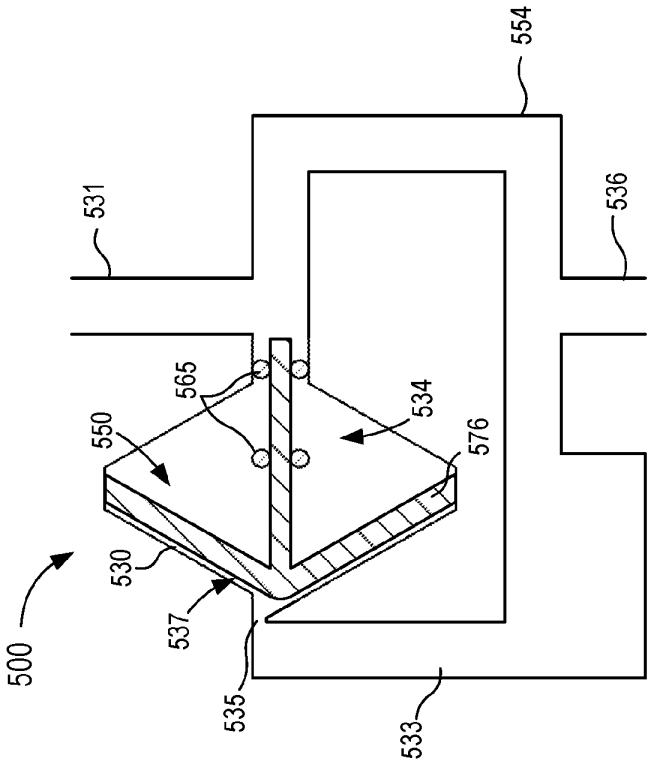

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FIG. 12

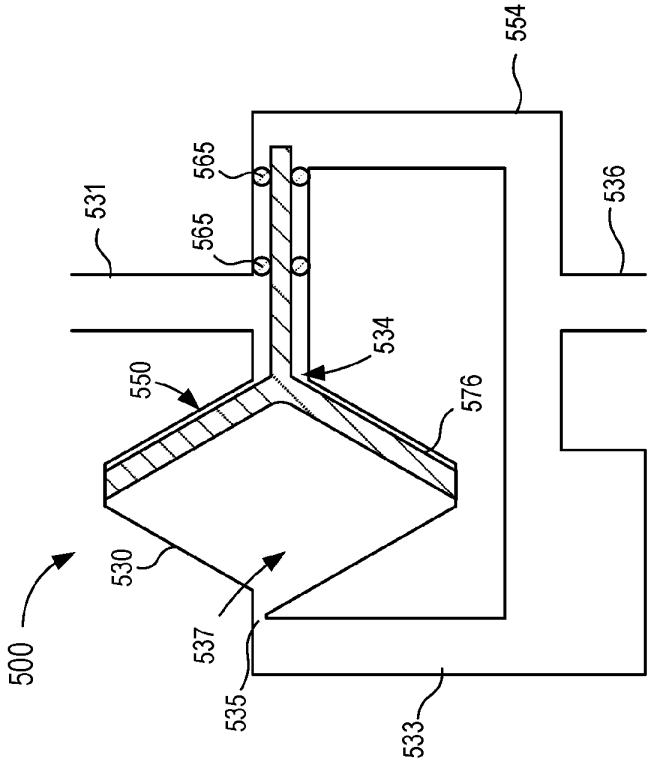

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FIG. 11

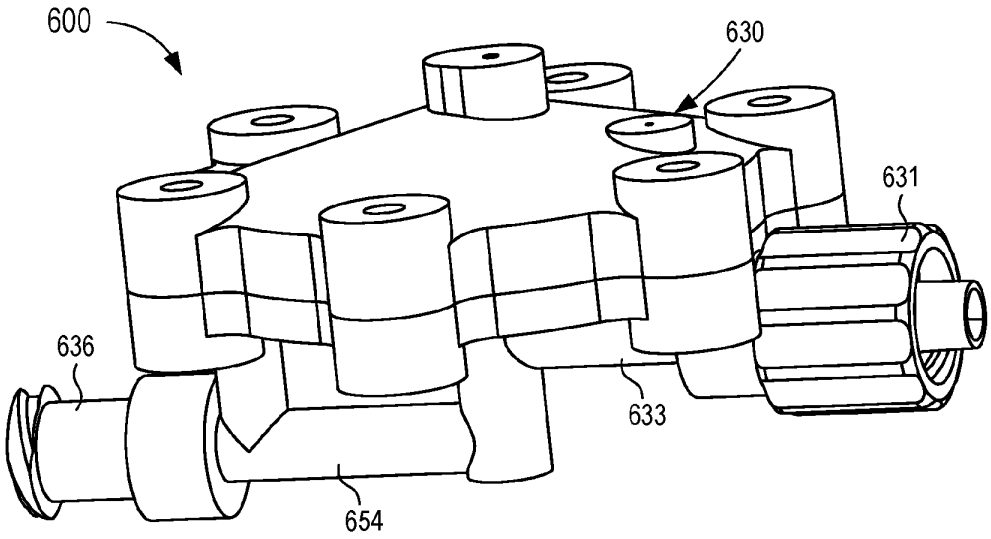

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FIG. 13

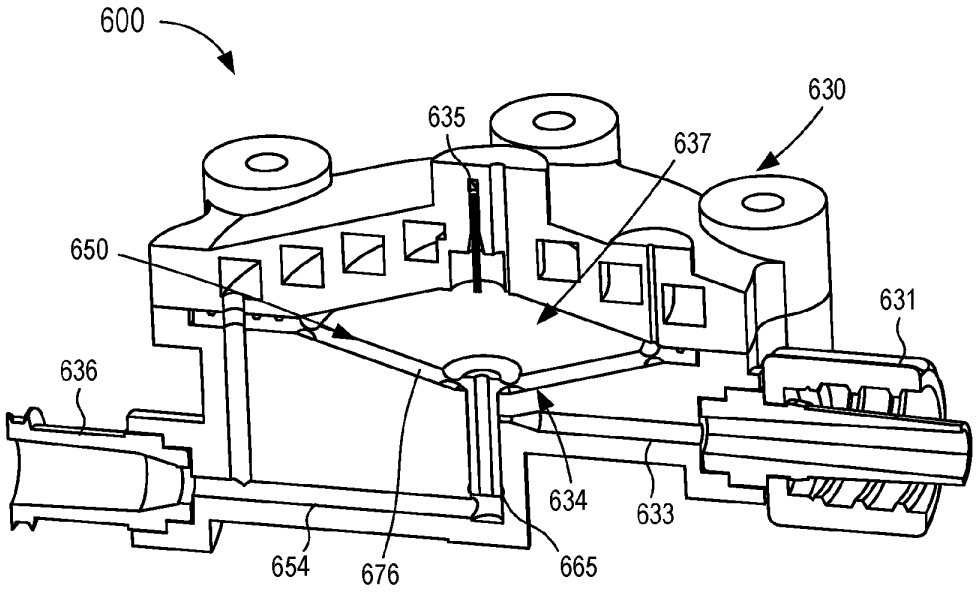

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FIG. 14

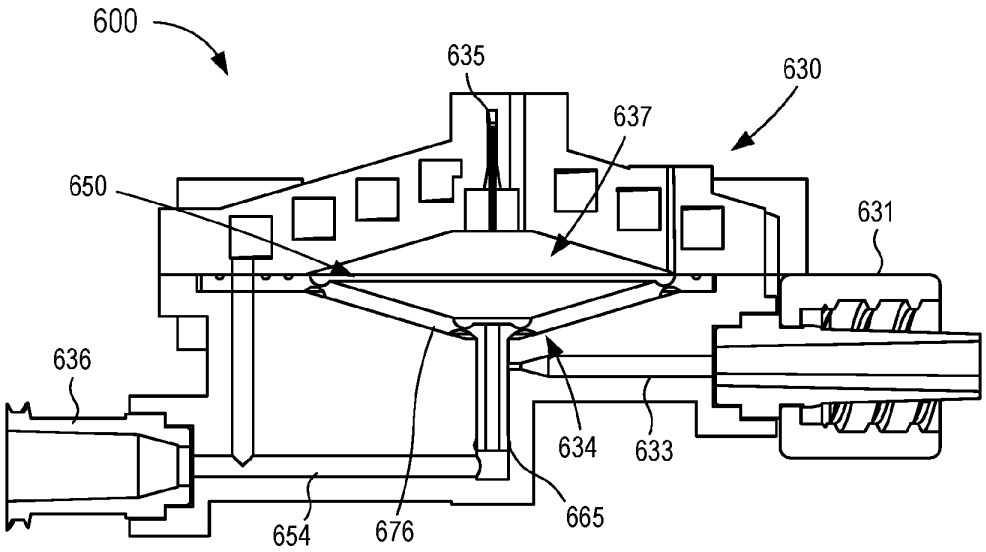


FIG. 15A

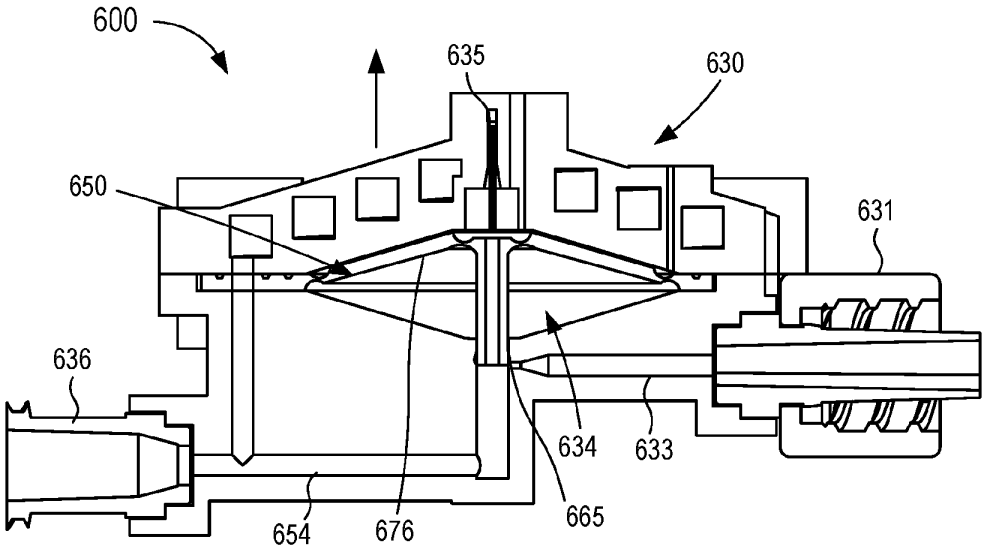


FIG. 15B

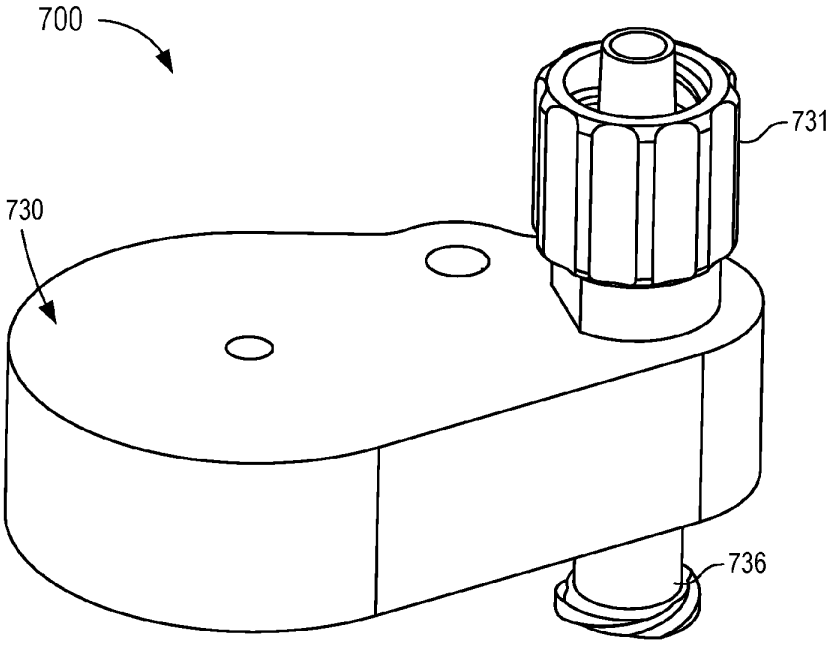


FIG. 16

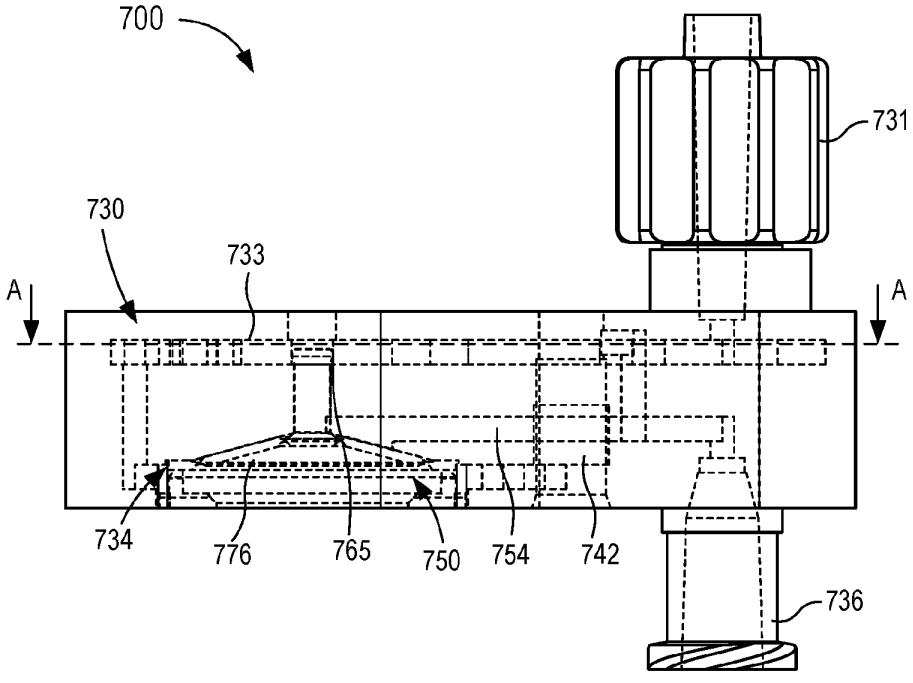


FIG. 17A

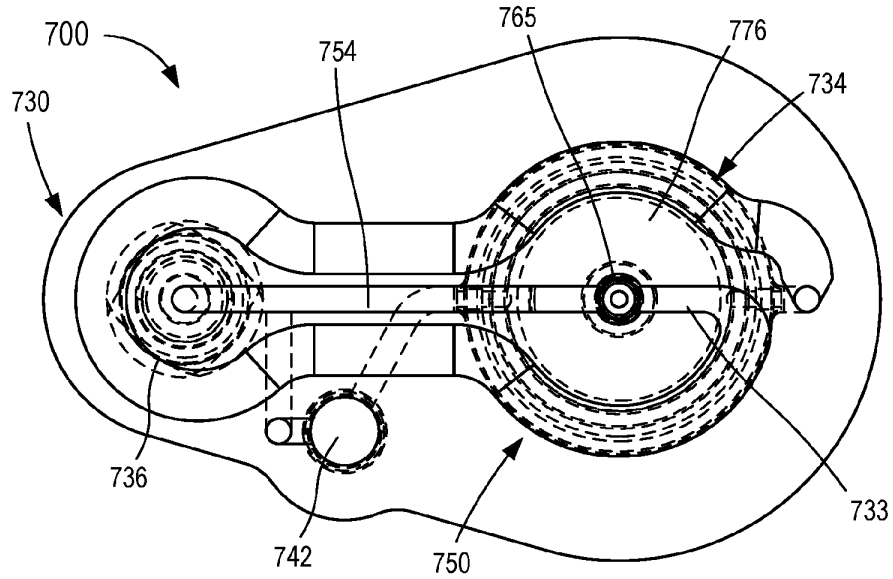


FIG. 17B

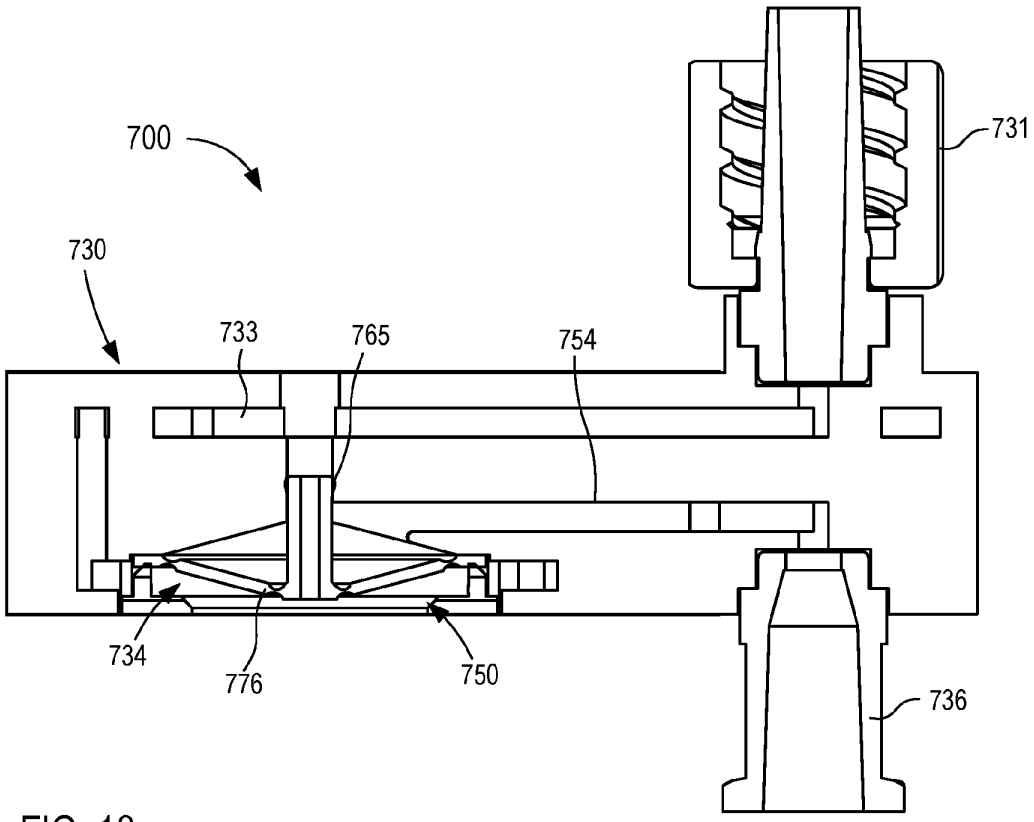


FIG. 18

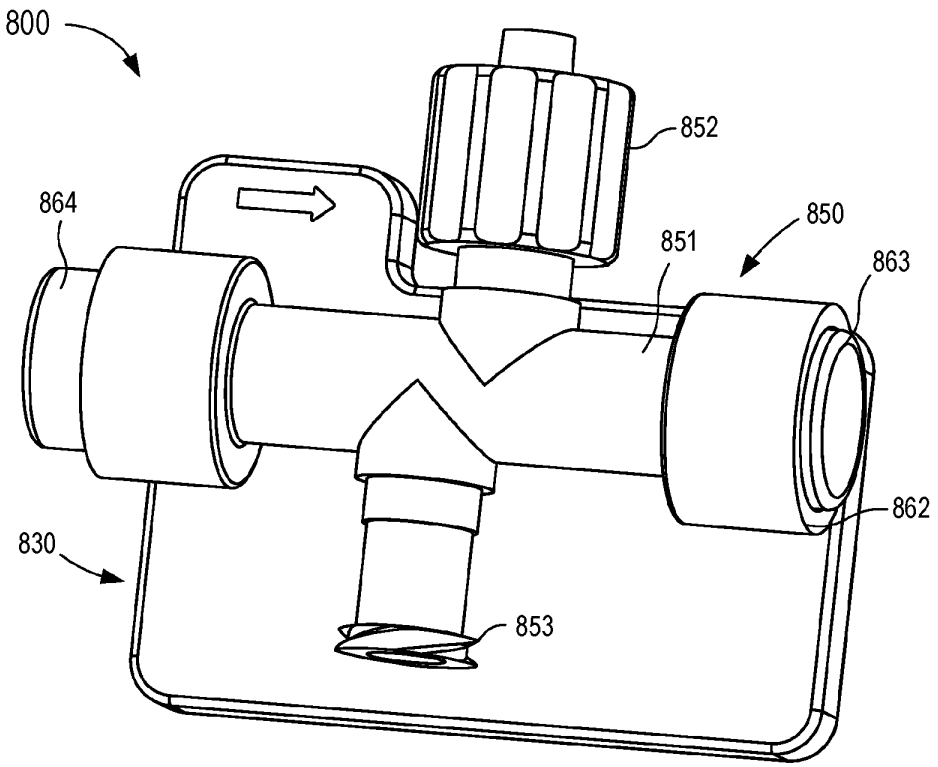


FIG. 19

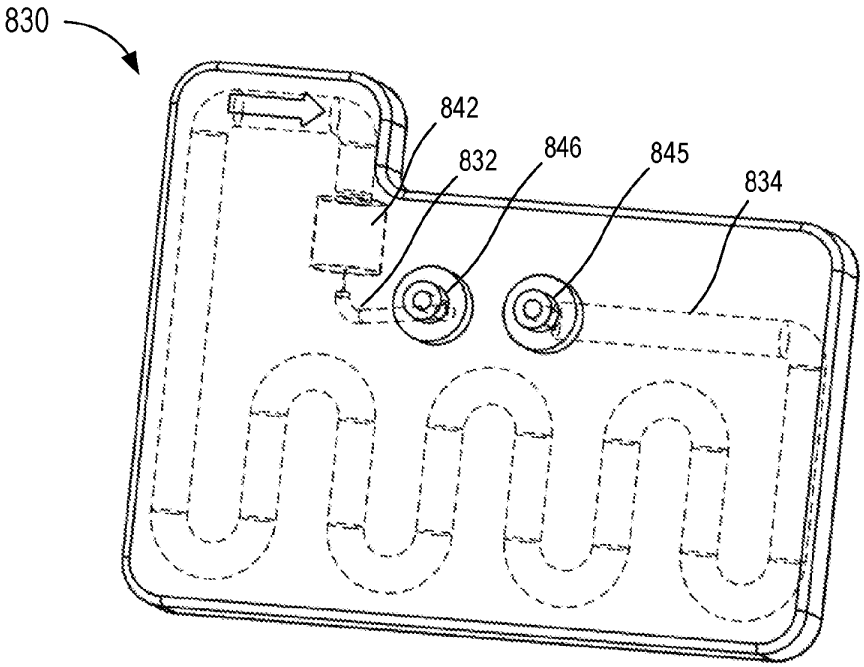


FIG. 20

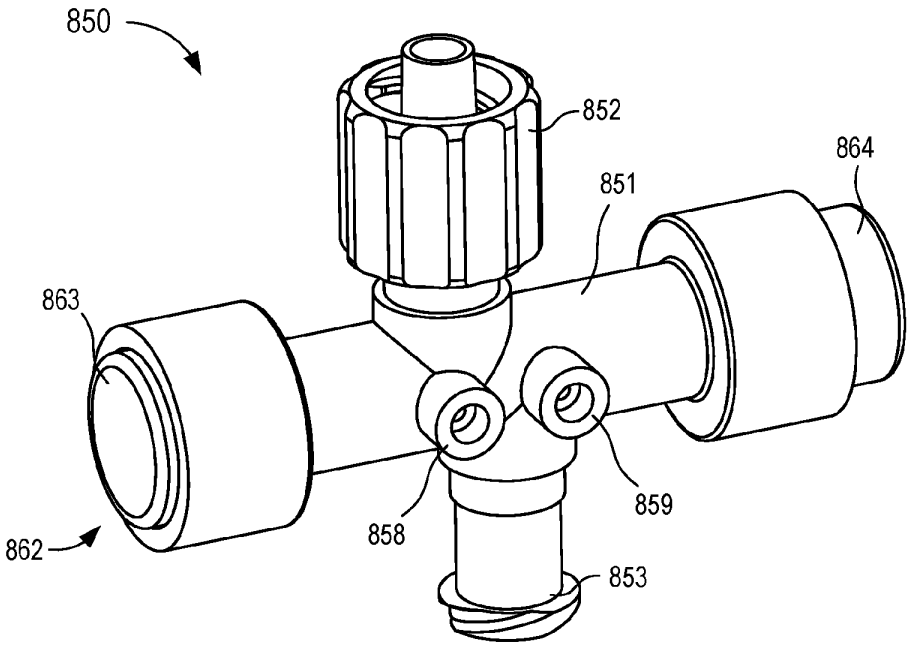


FIG. 21

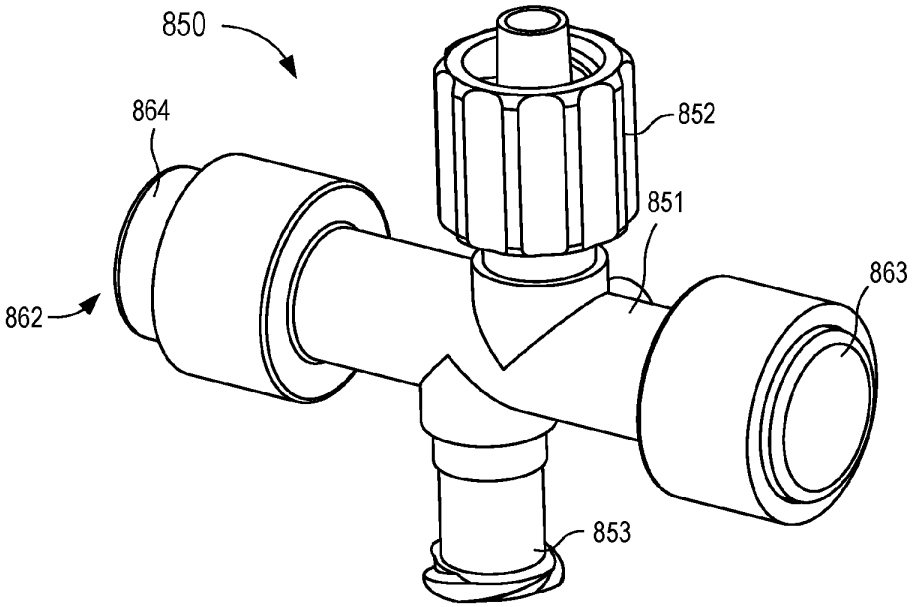


FIG. 22

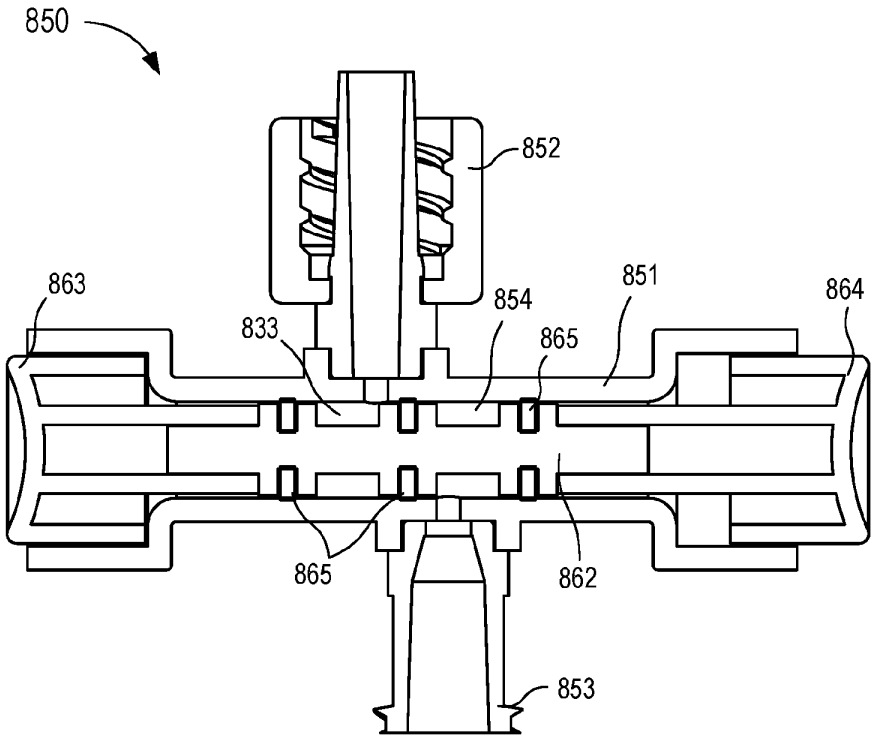

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FIG. 23

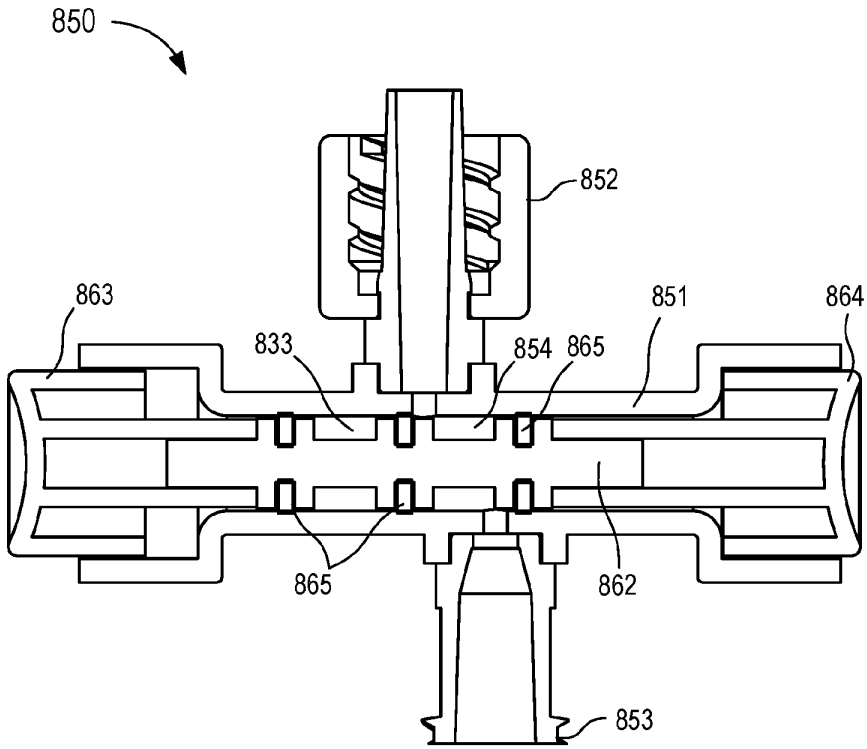

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FIG. 24

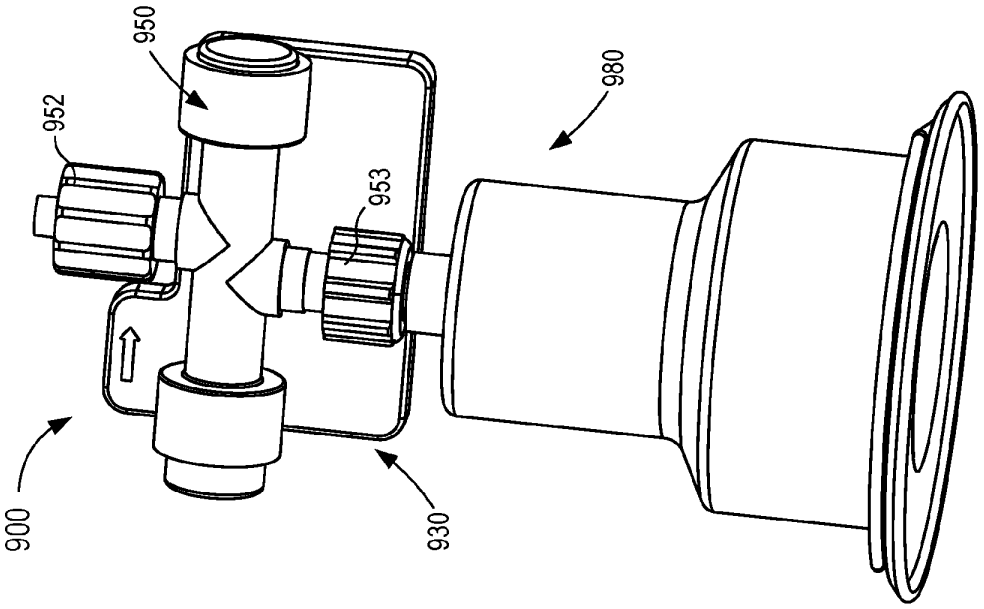


FIG. 26

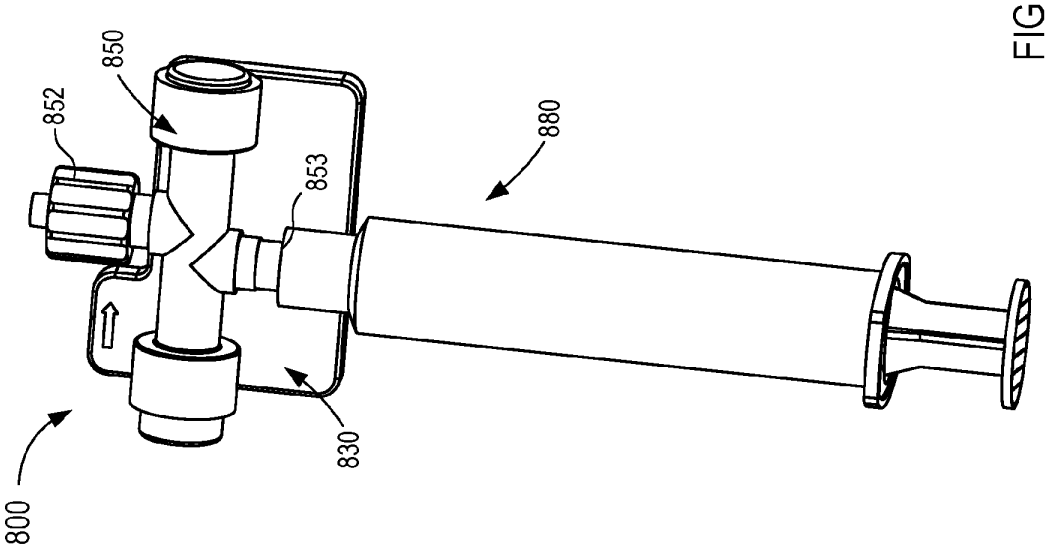


FIG. 25

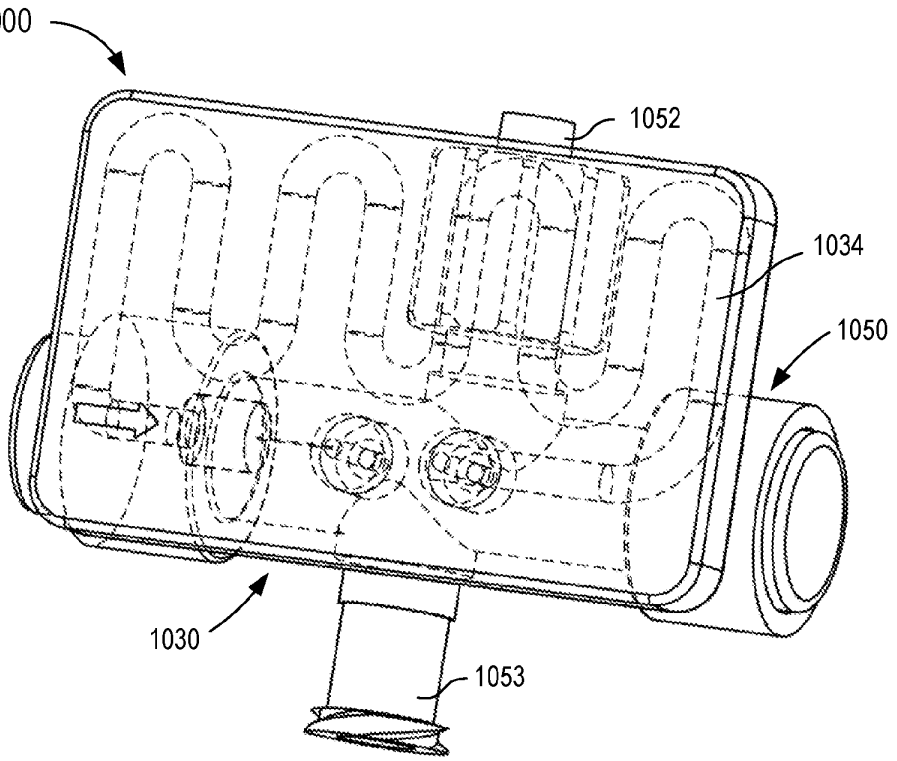


FIG. 27

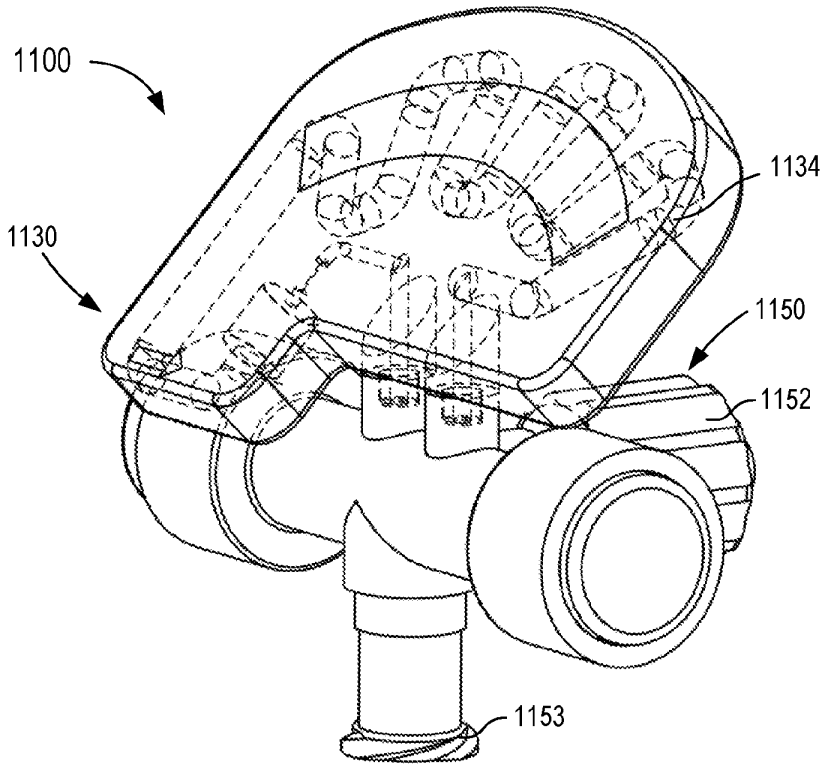


FIG. 28

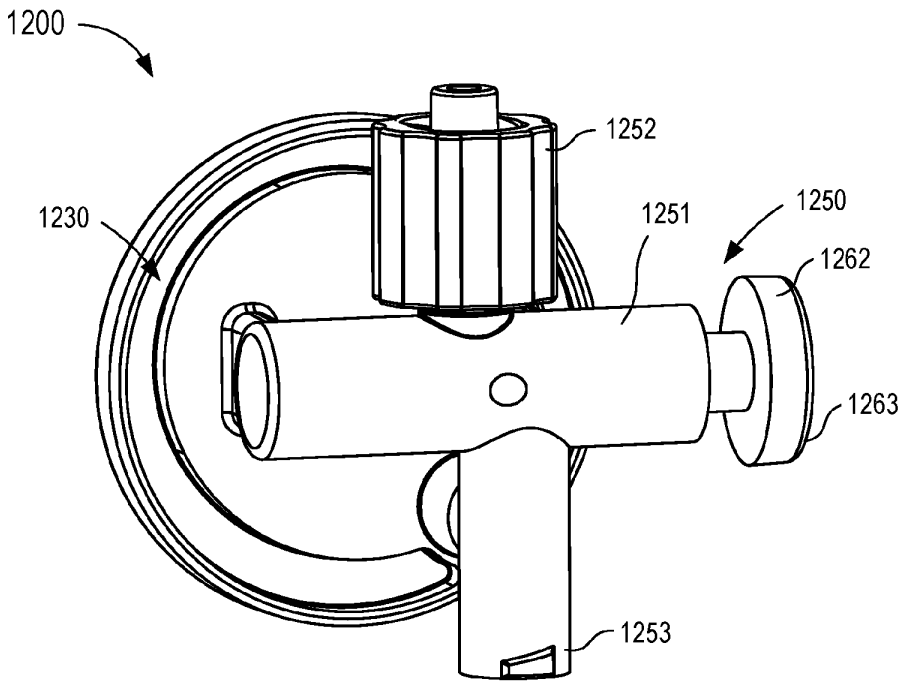

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FIG. 29

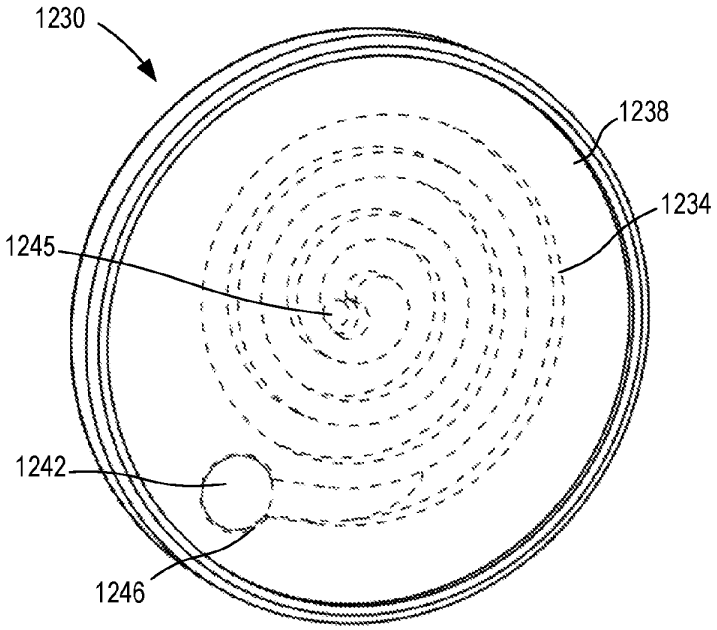

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FIG. 30

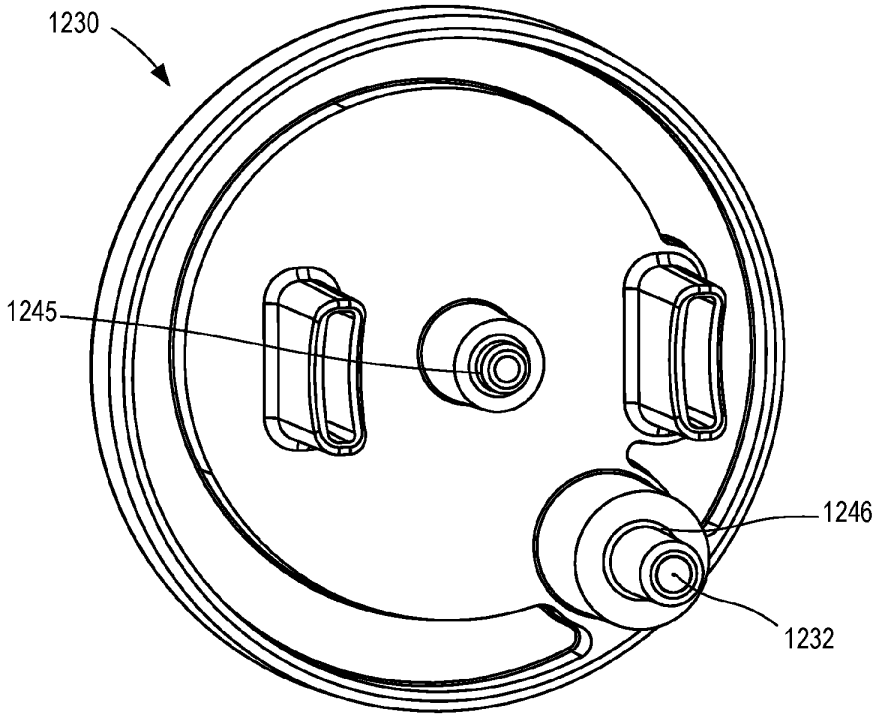

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FIG. 31

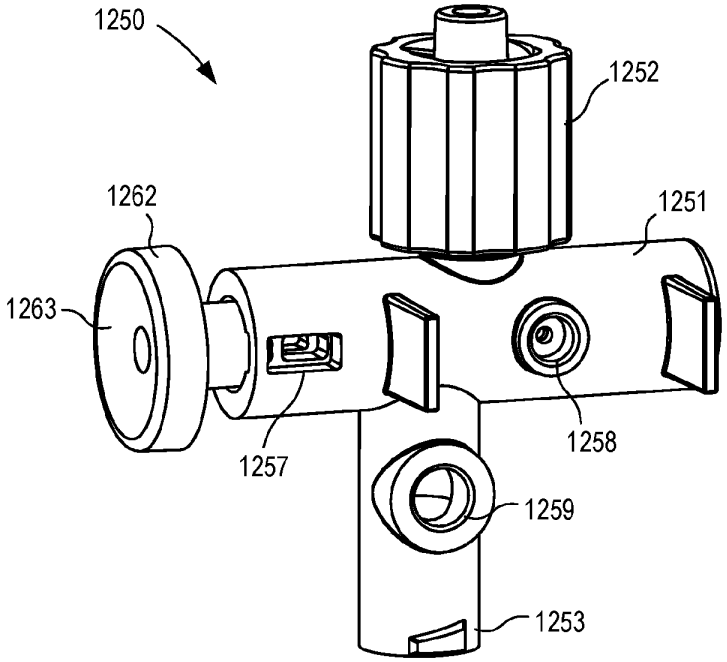

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FIG. 32

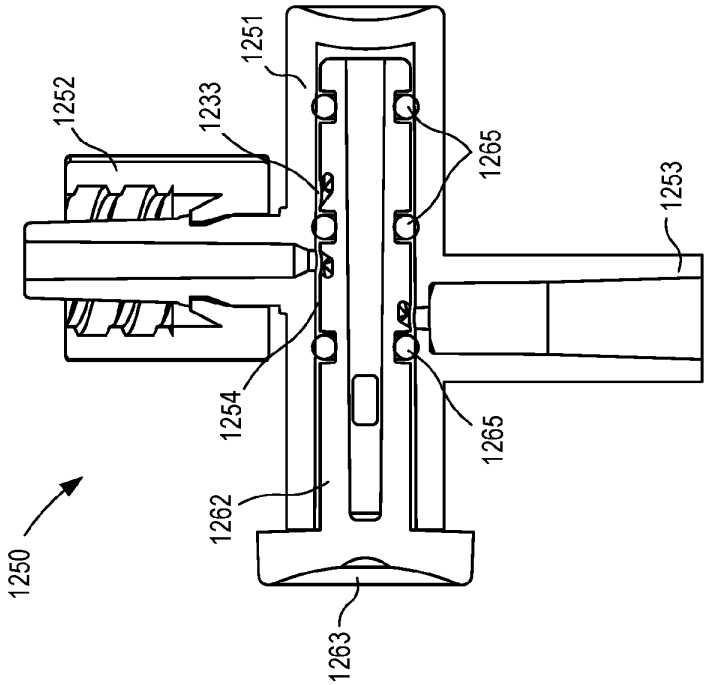

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FIG. 34

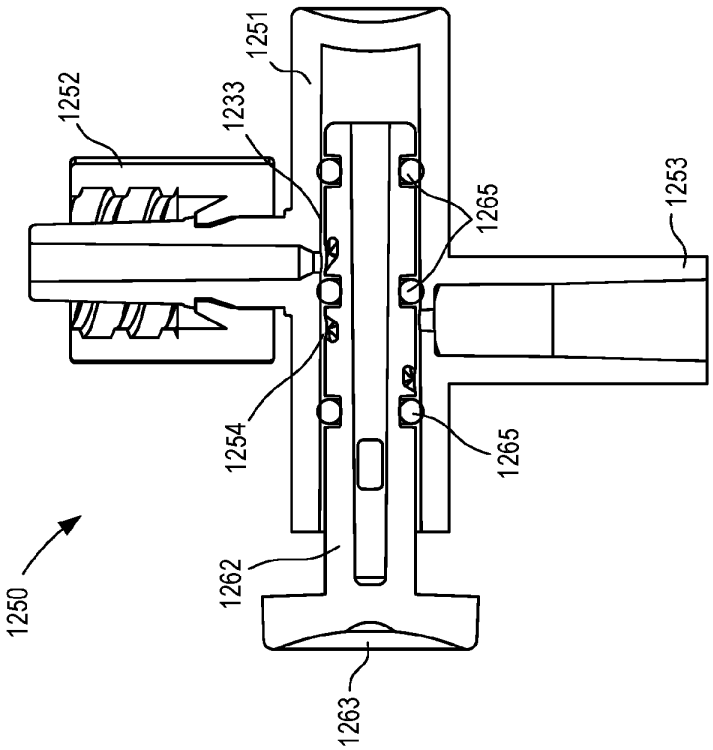

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FIG. 33

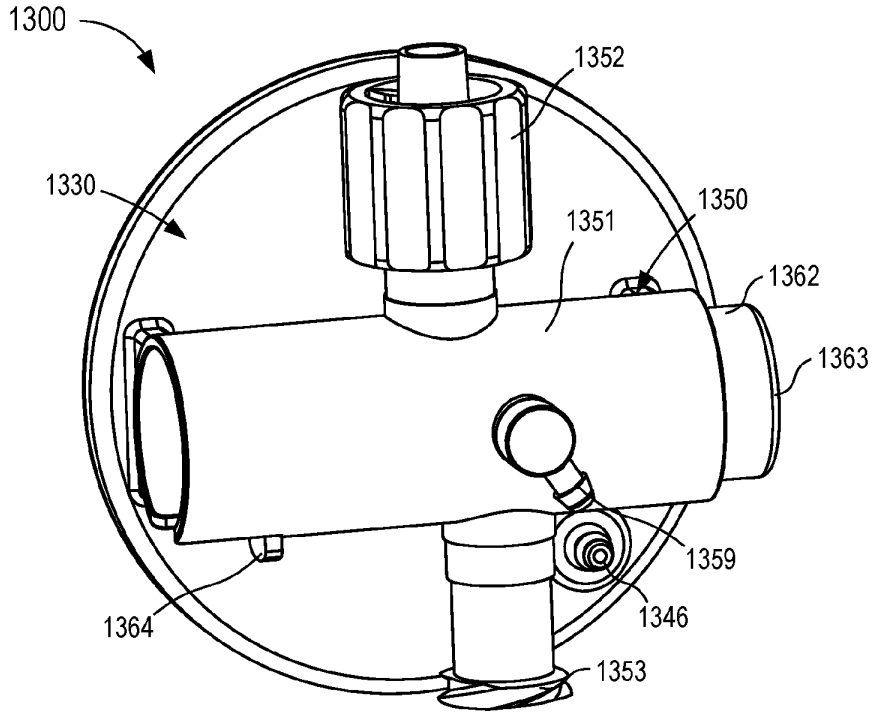

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FIG. 35

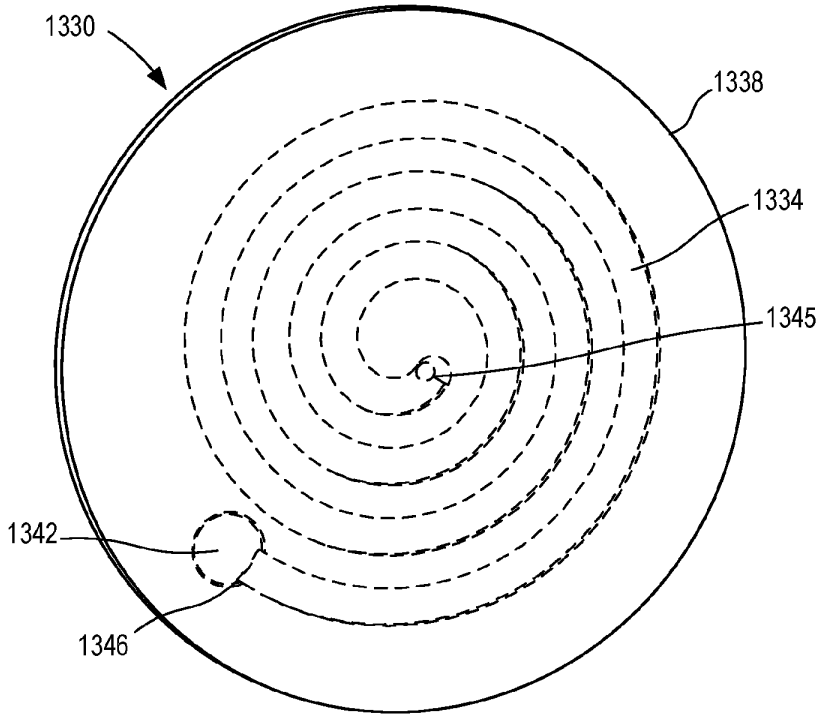

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FIG. 36

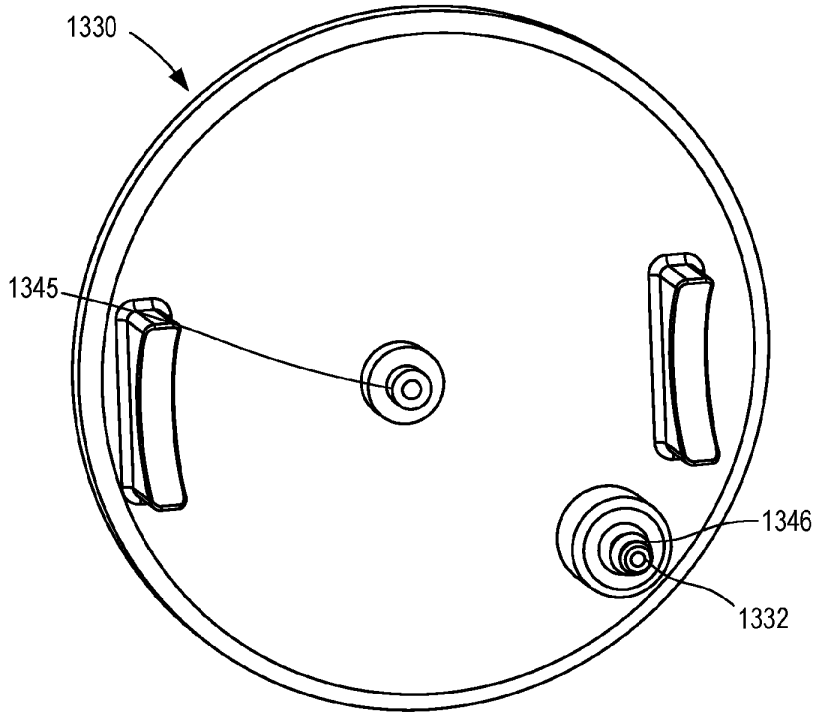


FIG. 37

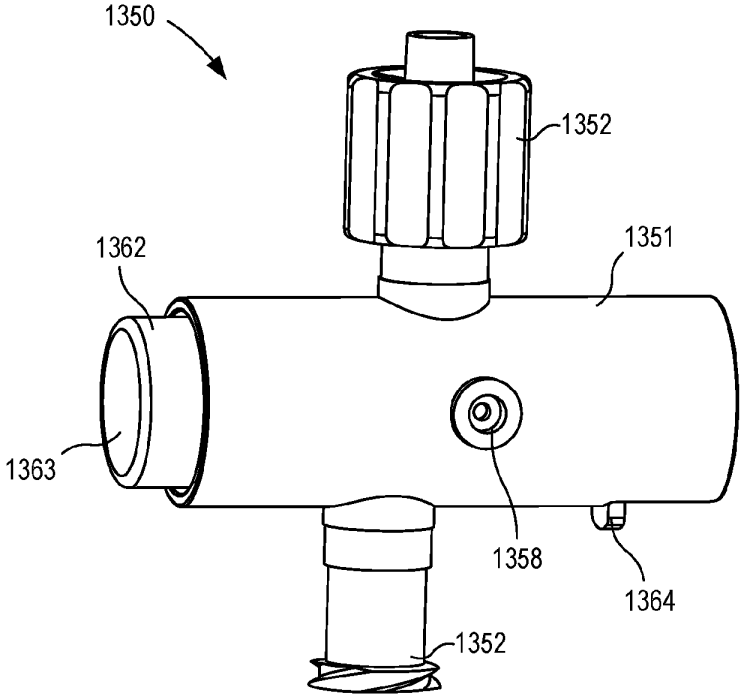


FIG. 38

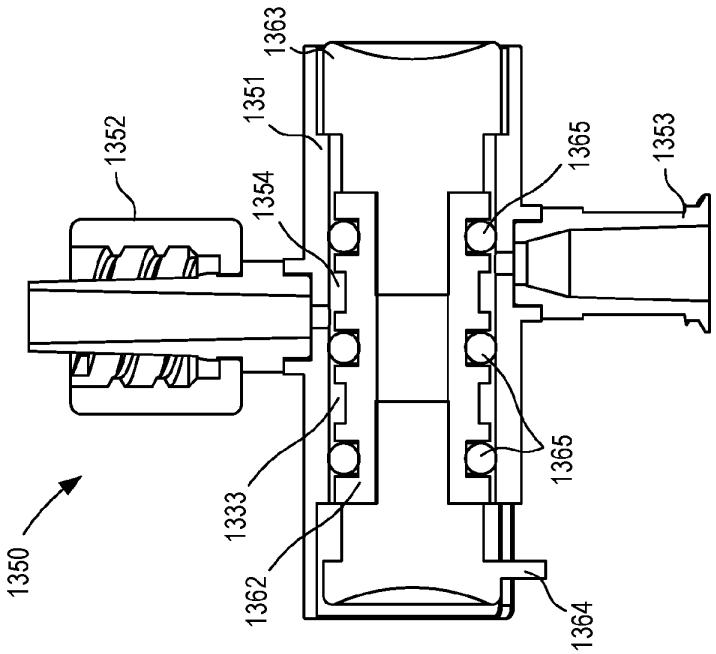

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FIG. 40

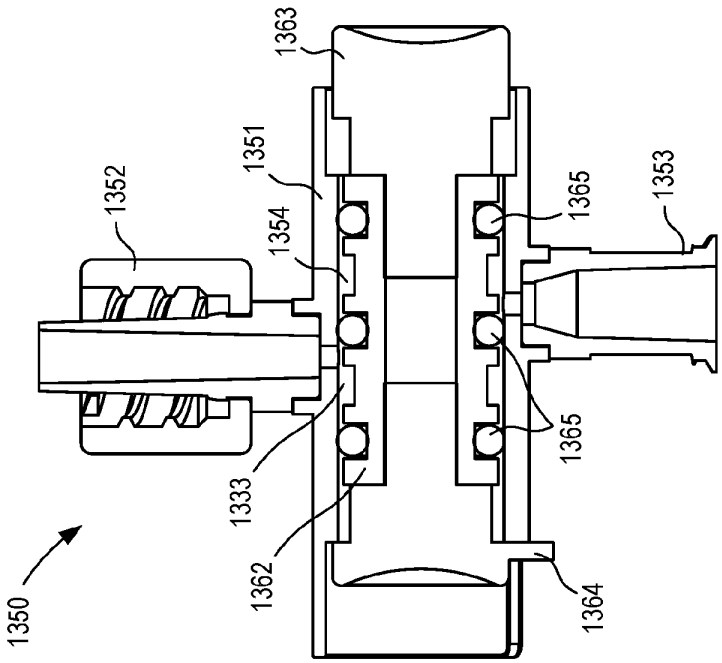

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FIG. 39

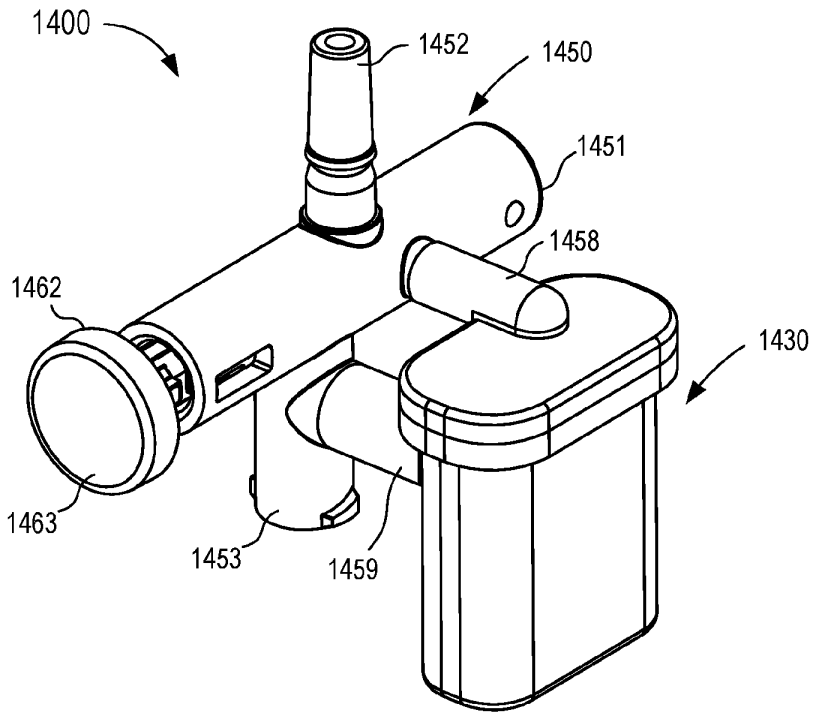

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FIG. 41

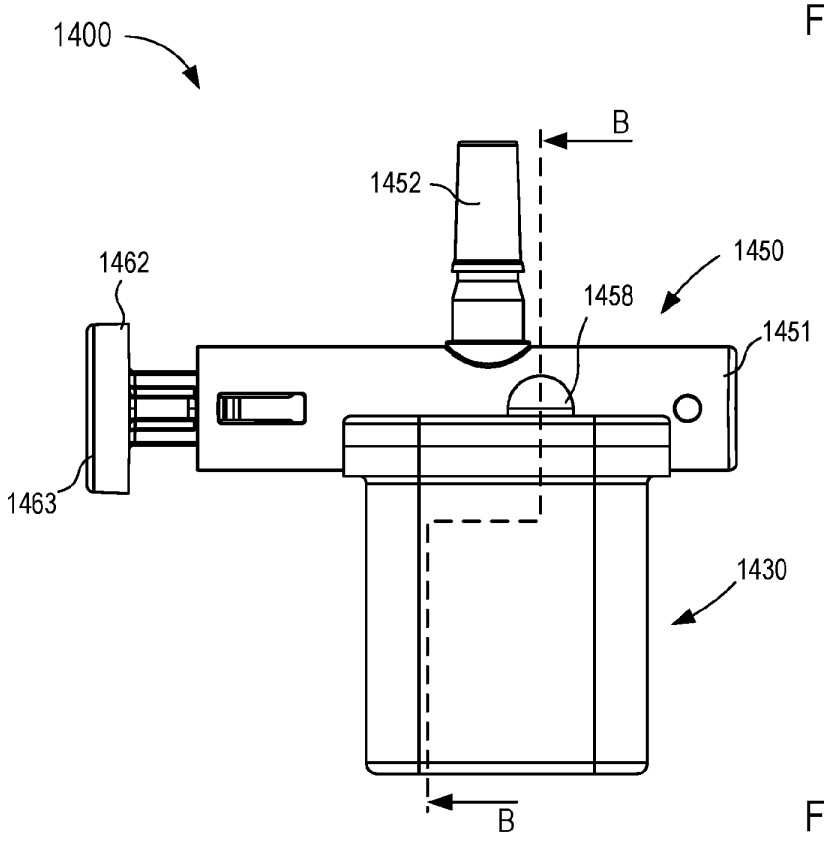

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1430
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FIG. 42

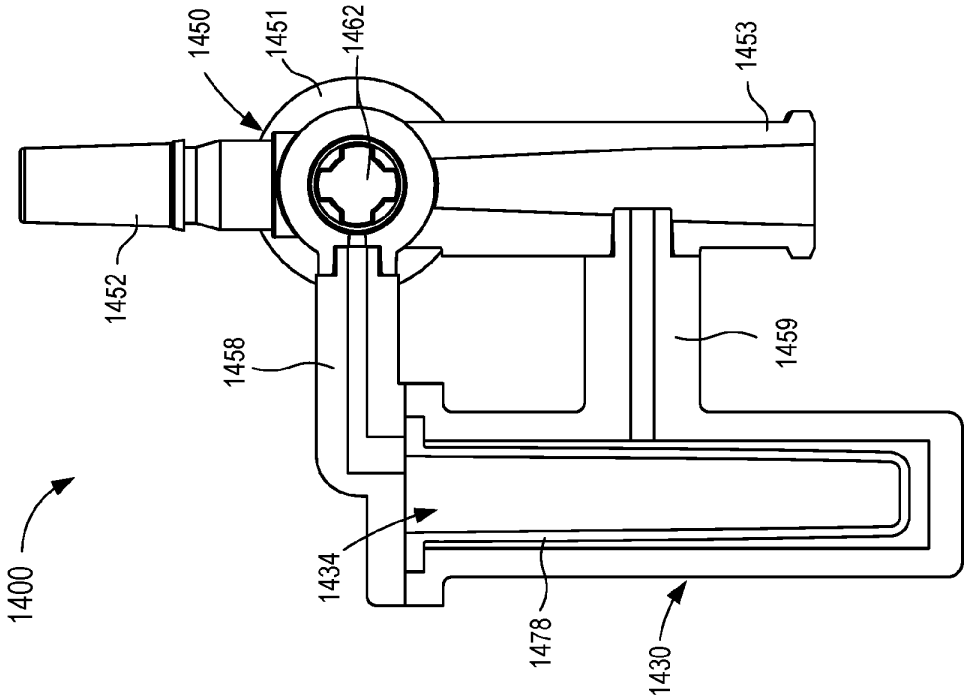

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SECTION B-B

FIG. 44

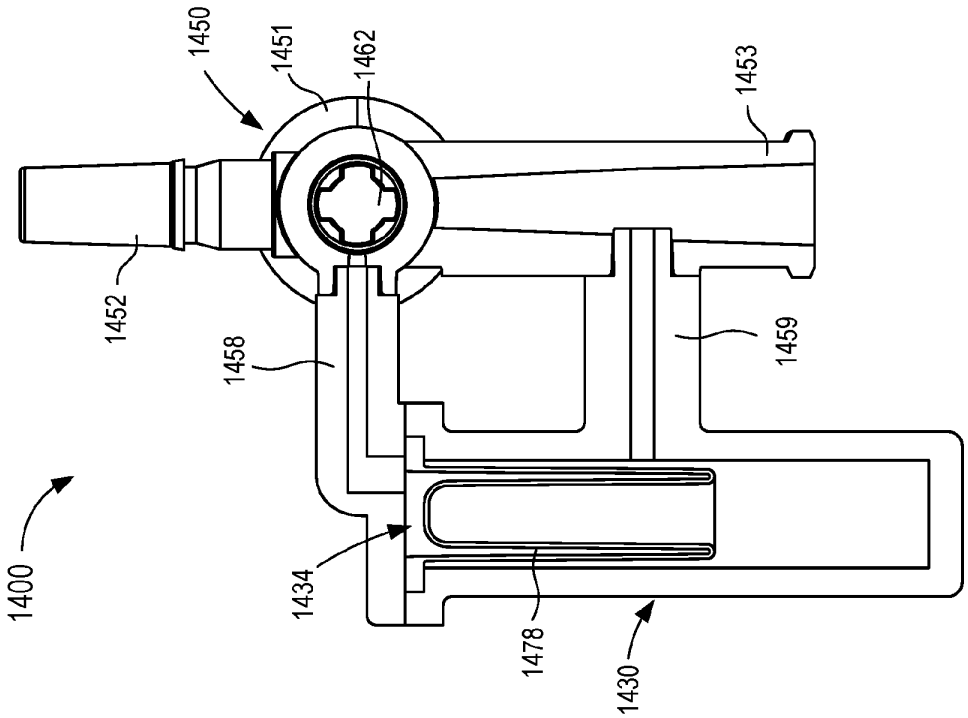

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SECTION B-B

FIG. 43

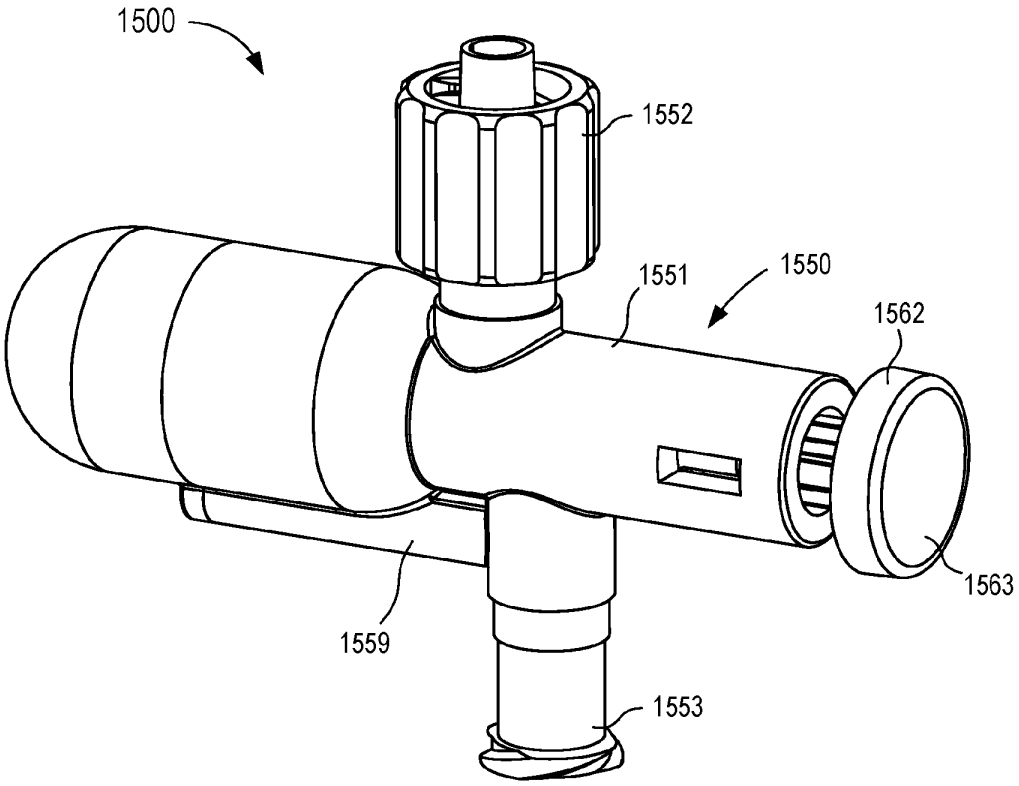

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FIG. 45

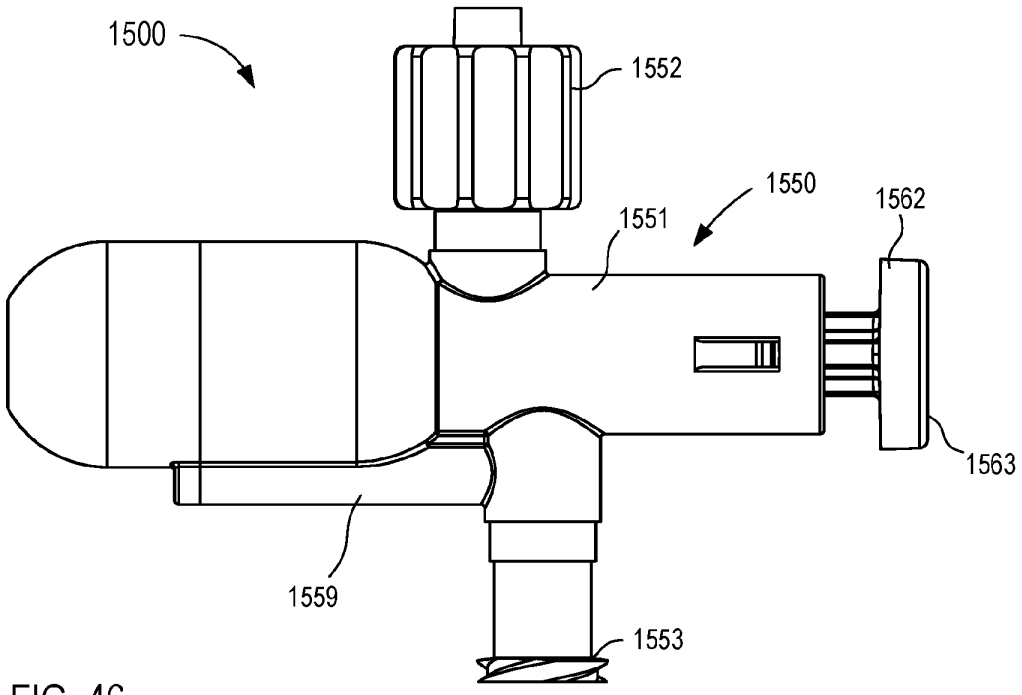

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FIG. 46

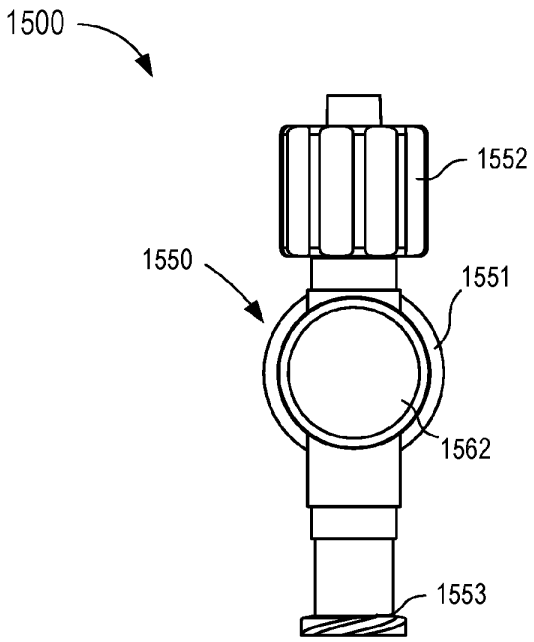

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FIG. 47

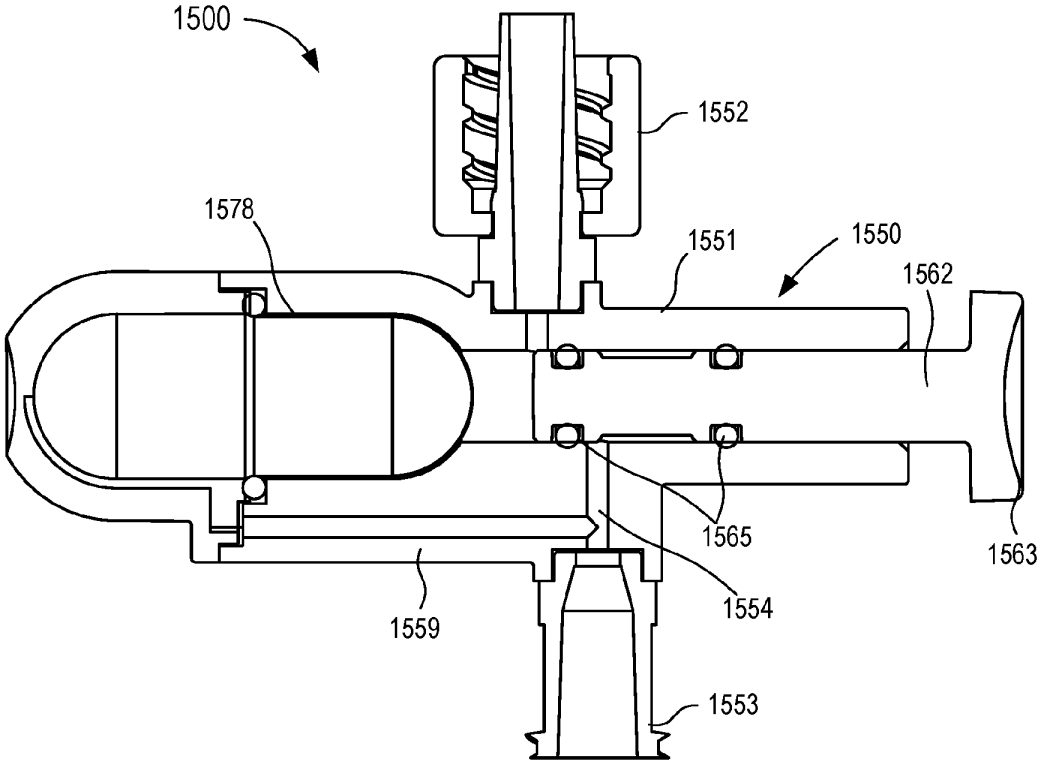

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FIG. 48

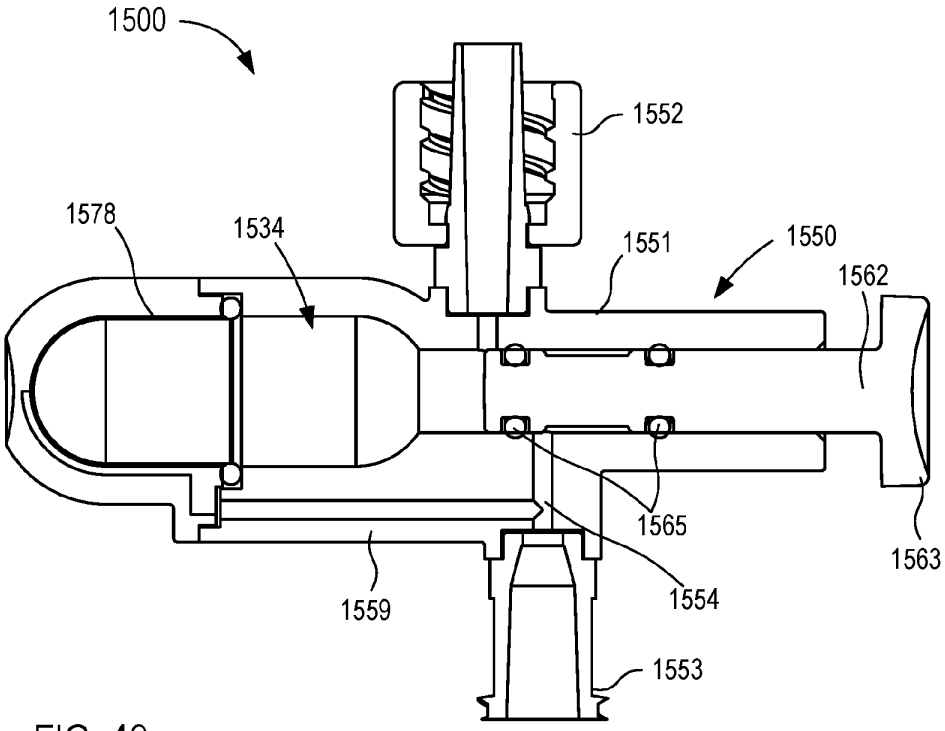

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FIG. 49

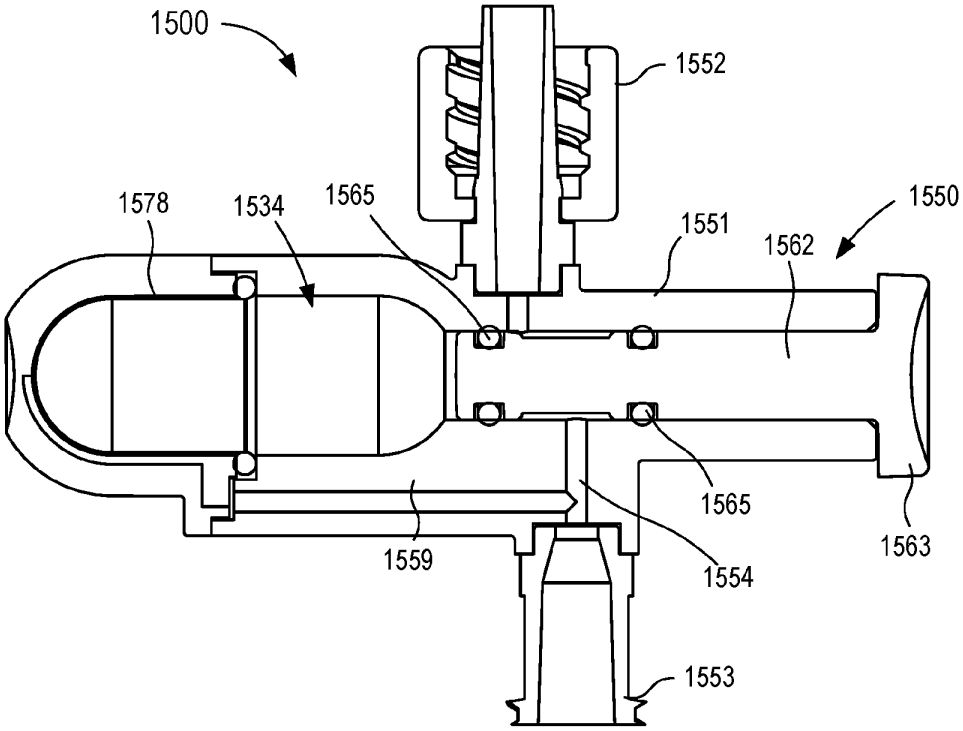

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FIG. 50

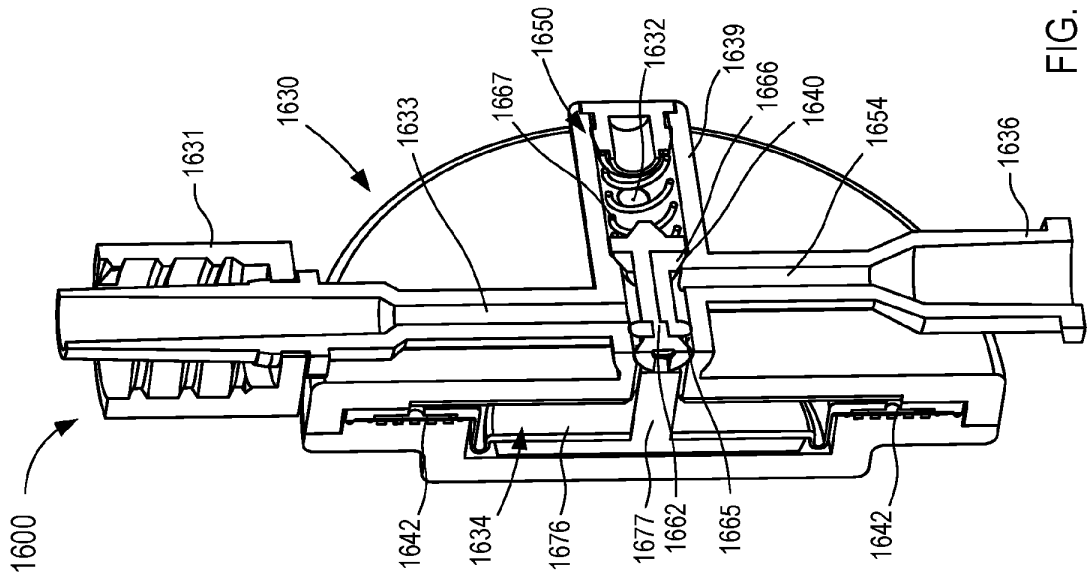

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FIG. 52

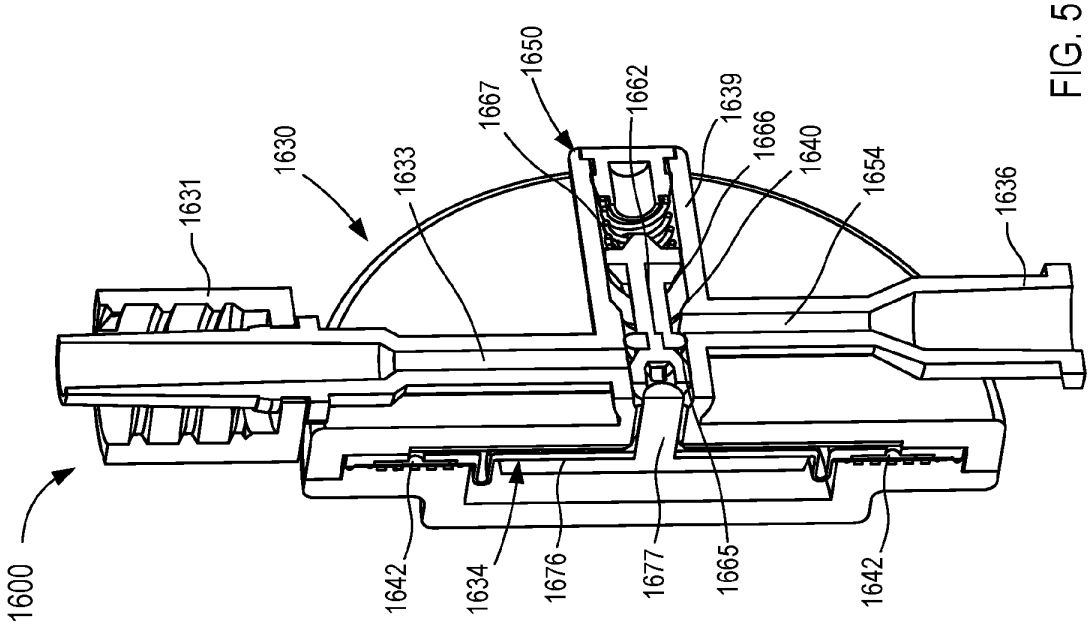

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FIG. 51

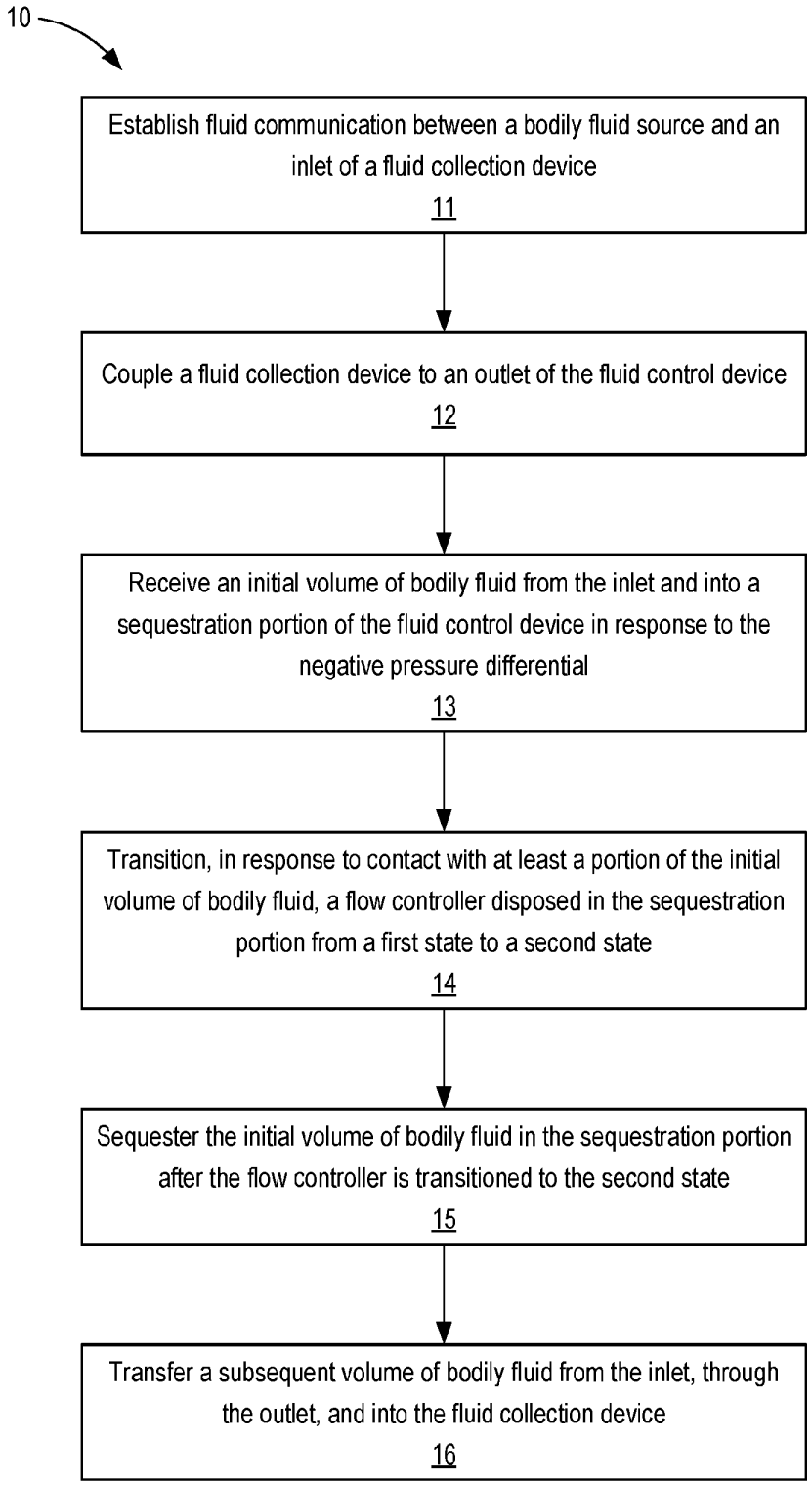

10
Establish fluid communication between a bodily fluid source and an inlet of a fluid collection device
11
Couple a fluid collection device to an outlet of the fluid control device
12
Receive an initial volume of bodily fluid from the inlet and into a sequestration portion of the fluid control device in response to the negative pressure differential
13
Transition, in response to contact with at least a portion of the initial volume of bodily fluid, a flow controller disposed in the sequestration portion from a first state to a second state
14
Sequester the initial volume of bodily fluid in the sequestration portion after the flow controller is transitioned to the second state
15
Transfer a subsequent volume of bodily fluid from the inlet, through the outlet, and into the fluid collection device
16

FIG. 53

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/50621

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61B 5/00, A61B 17/00, A61M 1/00, A61M 39/00 (2018.01)

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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)

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 --- A	US 2014/0163419 A1 (MAGNOLIA MEDICAL TECHNOLOGIES, INC.) 12 June 2014 (12.06.2014), entire document, especially Figs. 11-15; paras [0079]-[0099])	1-3, 8-21, 24, 29, 32-36 --- 4-5, 25, 30 --- 6-7, 22-23, 26-28, 31
Y --- A	US 6,511,439 B1 (TABATA et al.) 28 January 2003 (28.01.2003), entire document, especially Fig. 1; col 4, ln 48-51; col 9; ln 48-51	4-5, 25, 30 --- 6-7, 22-23, 26-28, 31
A	US 8,876,734 B2 (MAGNOLIA MEDICAL TECHNOLOGIES, INC.) 4 November 2014 (04.11.2014), entire document	1-36
A	US 2014/0107564 A1 (MAGNOLIA MEDICAL TECHNOLOGIES, INC.) 17 April 2014 (17.04.2014), entire document	1-36
A	US 2013/0116599 A1 (BULLIUNGTON et al.) 9 May 2013 (09.05.2013), entire document	1-36
A	US 2015/0018715 A1 (WALTERSPIEL) 15 January 2015 (15.01.2015), entire document	1-36
A	US 2017/0020428 A1 (CALLIOPE SOLUTIONS, INC.) 26 January 2017 (26.01.2017), entire document	1-36

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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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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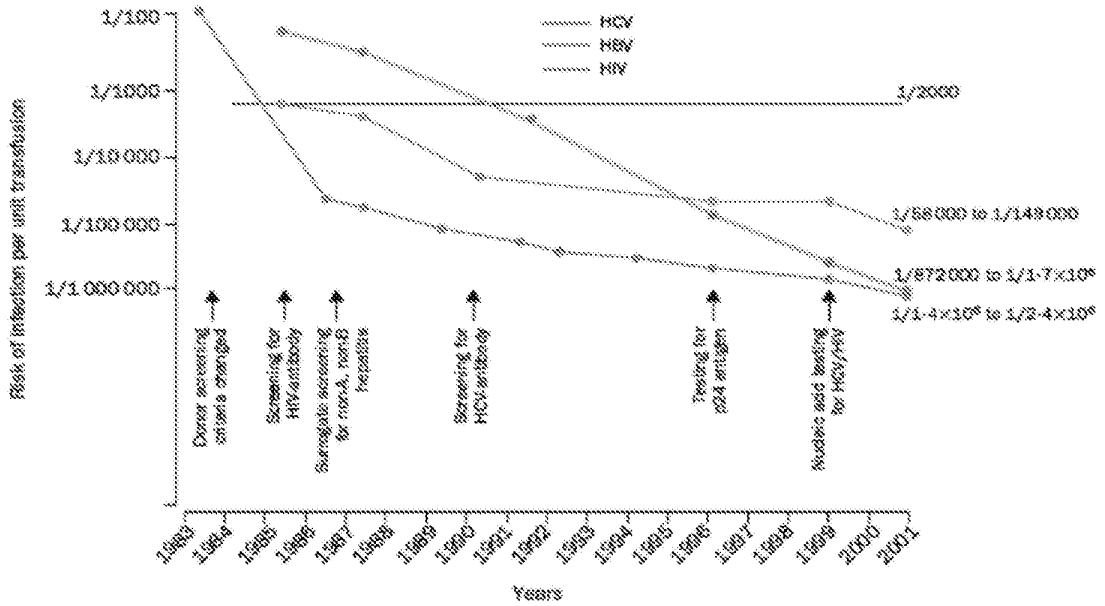


FIG. 1. Risk of infectious disease transmission per unit transfused by year, 1983 to 2001. Reprinted from reference 27 with permission of the publisher.

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).

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

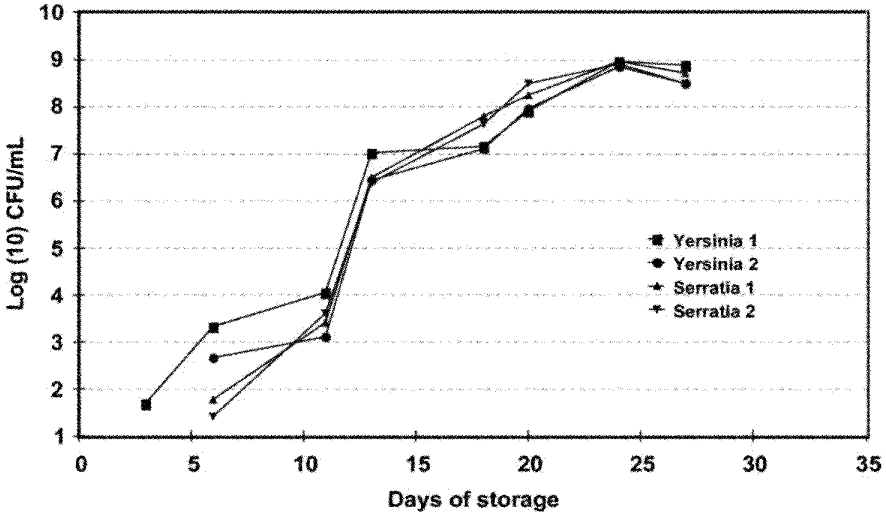


FIG. 2. Growth curves of four units of AS-3 red blood cells inoculated with *S. liqueifaciens* (two units inoculated to 4.2 CFU/ml) and *Y. enterocolitica* (two units inoculated to 11.6 CFU/ml) (5a). Bacteria were not detectable by culture until days 3 to 6. Isolates were from strains actually implicated 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

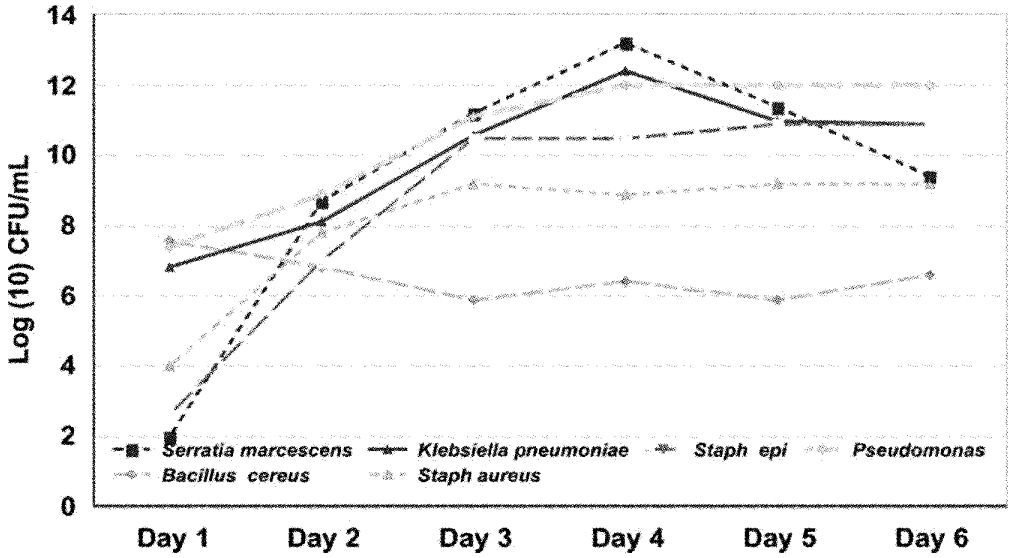


FIG. 3. Growth curves of six bacteria species (*S. marcescens*, $n = 7$; *K. pneumoniae*, $n = 21$; *S. epidermidis*, $n = 21$; *Pseudomonas* sp., $n = 15$; *B. cereus*, $n = 9$; *S. aureus*, $n = 22$) in 95 platelet units. All bacteria were inoculated on day zero at 10–50 CFU/ml (10).

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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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-

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.

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-

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-

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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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 is currently under processing

☐ 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 (Continuing)

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

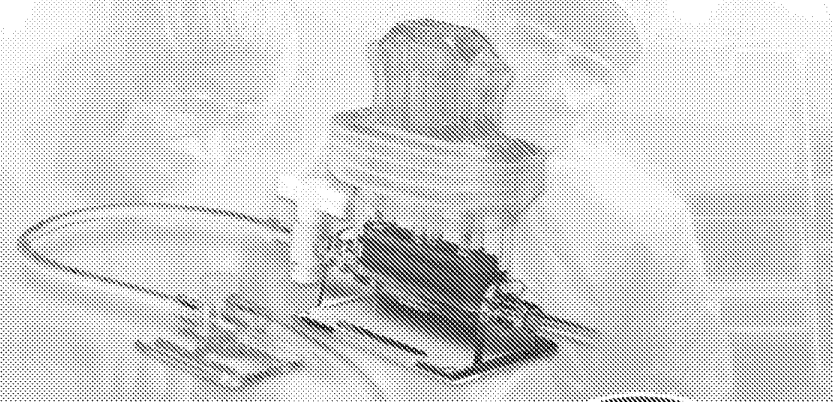
blood sampling collection device prevent backflow

blood sampling device valve restricts backflow controls flow

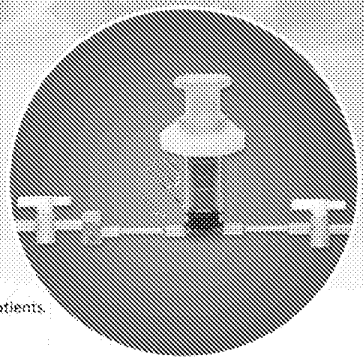
blood sequestration junction prevents backflow blood sequestration junction flow restriction

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	

Conservation. Safety. Simplicity. Edwards VAMP and VAMP Jr. Systems.



VAMP System
Venous Arterial blood Management Protection System



VAMP Jr. System
for pediatric and neonatal patients

Edwards

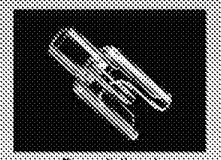


Figure 1

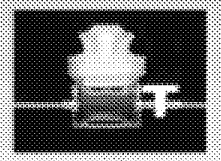


Figure 2 VAMP Reservoir

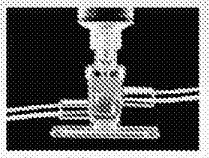


Figure 3 2-site sampling port

VAMP Kits

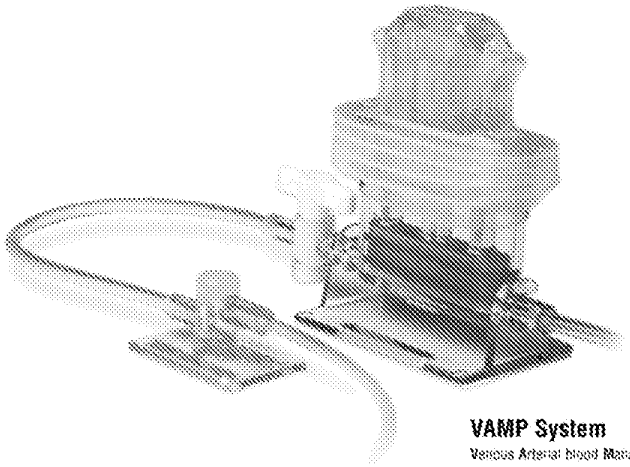
The closed blood sampling system that protects patient from the Edwards TruWave Disposable Pressure Transducer. The Edwards VAMP system provides the safest and easiest method of needleless blood sampling. The blunt cannula design (Figure 1) provides safety by eliminating the needlesticks associated with 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 2-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.

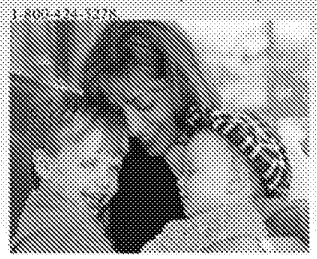
A unique in-line reservoir puts safety first.

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.

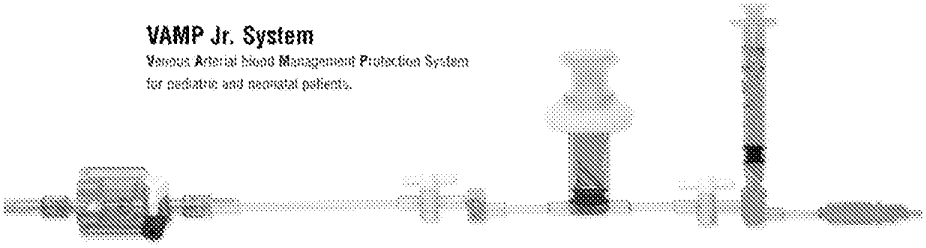
The VAMP Jr. system fits the special needs of your special patients.

The VAMP Jr. system is designed to require decreased volume over a smaller diameter for more accurate sampling and flushing in pediatric and neonatal patients. For the added convenience of accurate pressure monitoring, the VAMP Jr. system is available preassembled with TruWave disposable pressure transducers (DPTs) in kit configurations to meet the specific needs of your specific patients.

To learn more about the VAMP Jr. system, contact your Edwards Lifesciences Corporation Representative at 1-800-424-3278.



Jr.™. 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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Edwards Lifesciences

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Edwards Lifesciences S.A. - Ch. du Glapin 8 - 1162 Saint-Prex - Switzerland - Phone 41.21.823.4300
Edwards Lifesciences Japan - 2-8 Nakanoshima - Kita-ku, Osaka 530-0005 - Japan - Phone 81.6.6133.3700

EXHIBIT H

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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
	Gregory	J.	Bullington	

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

City	State/Province	Country of Residence
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Postal Code	98006
Country	US

Inventor 2 Remove

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Inventor 3 Remove

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	Shan	E.	Gaw	

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	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

City	Seattle	State/Province	WA	Country of Residence	US

Mailing Address of Inventor:

Address 1	4027 Sunnyside Ave. N		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98103	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jay	M.	Miazga	

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

City	Seattle	State/Province	WA	Country of Residence	US

Mailing Address of Inventor:

Address 1	4025 McKinley Pl. N		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98103	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jed		McCann	

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

City	Seattle	State/Province	WA	Country of Residence	US

Mailing Address of Inventor:

Address 1	7321 22nd Ave. NW		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98117	Country	US

Inventor 6 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Paul		Goldenbaum	

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

City	San Antonio	State/Province	TX	Country of Residence	US

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

Mailing Address of Inventor:

Address 1	4218 Black Rock		
Address 2			
City	San Antonio	**State/Province**	TX
Postal Code	78253	**Country** i	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	58249		
Email Address	zpatdcdocketing@cooley.com	Add Email	Remove Email

Application Information:

Title of the Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS		
Attorney Docket Number	MGMD-012/01US 316052-MGMD	**Small Entity Status Claimed**	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	36	**Suggested Figure for Publication (if any)**	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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	68249		

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			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

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

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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.

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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

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	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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First Name	Michael	Last Name	Wintemitz	Registration Number	73102

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	MGMD-012/01US 316052-MGMD
	Application Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS

Background

[1001] Embodiments described herein relate generally to the parenteral procurement of bodily-fluid samples, and more particularly to systems and methods for parenterally procuring bodily-fluid samples, such as blood, with reduced hemolysis.

[1002] Health care practitioners routinely draw bodily-fluids from a patient for various testing and/or donation purposes. In some instances, the process of obtaining the bodily-fluids, and in particular, blood, can result in a degradation and/or breakdown of portions and/or constituents contained in the bodily-fluid. Specifically, hemolysis of red blood cells (i.e., a rupturing of the red blood cells and the release of cytoplasm) during blood draw is a known problem in the field of phlebotomy and/or medical testing. Hemolysis of blood is the most common pre-analytical source of error in clinical testing, accounting for nearly 60% of all rejected samples (Bonini P, Plebani M, Ceriotti F, Rubboli F (2002). Errors in laboratory medicine. *Clinical Chemistry*, 48, 691-698; and Plebani M, Carraro P (1997). Mistakes in a stat laboratory: types and frequency. *Clinical Chemistry*, 43, 1348-1351). Moreover, hemolyzed sample rates from hospital emergency rooms can be as high as 30% (Grant M (2003). The effect of blood drawing techniques and equipment on the hemolysis of ED laboratory blood samples. *Journal of Emergency Nursing*, 29 (2), 116-121, and Soderberg J, Jonsson PA, Wallin O, Grankvist K, Hultdin J (2009). Hemolysis index—an estimate of pre-analytical quality in primary health care. *Clinical Chemistry and Laboratory Medicine*, 47, 940-944). In some know blood draw systems, the arrangement and/or coupling of multiple devices to form a fluid flow path from a patient to, for example, a sample reservoir or container, shear stress exerted on or within the red blood cells, exposure time, and/or the like can lead to an increased likelihood of hemolysis within a sample volume.

[1003] Thus, a need exists for systems and methods for sample collection with reduced hemolysis.

Summary

[1004] Systems and methods for parenterally procuring bodily-fluid samples, such as blood, with reduced hemolysis are described herein. In some embodiments, a collection system has a proximal end portion, a distal end portion, and an inner surface defining a fluid flow path therethrough. The distal end portion is configured to be placed in fluid communication with a patient. The proximal end portion is configured to be placed in fluid communication with a fluid reservoir. The fluid flow path defined by the inner surface is associated with at least one flow characteristic configured to limit a stress within the flow of the bodily-fluid between the distal end portion and the proximal end portion.

Brief Description of the Drawings

[1005] FIG. 1 is a schematic illustration of a bodily-fluid collection device according to an embodiment.

[1006] FIG. 2 is a perspective view of a needle included in a bodily-fluid collection device according to an embodiment.

[1007] FIG. 3 is an enlarged view of a portion of the needle of FIG. 2, identified by the region A_1.

[1008] FIGS. 4-6 are illustrations of a needle used to deliver a cannula to a portion of the body according to an embodiment.

[1009] FIG. 7 is a perspective view of a portion of a needle included in a bodily-fluid collection device according to another embodiment.

[1010] FIG. 8 is a perspective view of a portion of a bodily-fluid collection device according to an embodiment.

[1011] FIG. 9 is a cross-sectional view of the bodily-fluid collection device of FIG. 8, taken along the line 9-9.

[1012] FIG. 10 is an enlarged view of a portion of the bodily-fluid collection device of FIG. 9, identified by the region A_2.

[1013] FIG. 11 is a front view of a portion of a bodily-fluid collection device according to an embodiment.

[1014] FIG. 12 is a cross-sectional view of the portion of the bodily-fluid collection device of FIG. 11, taken along the line 12-12.

[1015] FIG. 13 is an enlarged view of a portion of the bodily-fluid collection device of FIG. 12, identified by the region A_3.

[1016] FIG. 14 is a cross-sectional view of a portion of a bodily-fluid collection device according to another embodiment.

[1017] FIG. 15 is an enlarged view of a portion of the bodily-fluid collection device of FIG. 14, identified by the region A_4.

[1018] FIG. 16 is a cross-sectional view of a portion of a bodily-fluid collection device according to another embodiment.

[1019] FIG. 17 is a cross-sectional view of a portion of a bodily-fluid collection device according to another embodiment.

[1020] FIG. 18 is a perspective view of a portion of a bodily-fluid collection device according to an embodiment.

[1021] FIG. 19 is an exploded view of the portion of the bodily-fluid collection device of FIG. 18.

[1022] FIG. 20 is a cross-sectional view of the portion of the bodily-fluid collection device of FIG. 18, taken along the line 20-20.

[1023] FIG. 21 is a perspective view of a restrictor included in a bodily-fluid collection device according to an embodiment.

[1024] FIG. 22 is a cross-sectional view of the restrictor of FIG. 21, taken along the line 22-22.

[1025] FIG. 23 is a top view of a baffle included in the restrictor of FIG. 21.

[1026] FIG. 24 is a cross-sectional view of the baffle of FIG. 23, taken along the line 24-24.

[1027] FIG. 25 is a perspective view of a restrictor included in a bodily-fluid collection device according to an embodiment.

[1028] FIG. 26 is a cross-sectional view of the restrictor of FIG. 25, taken along the line 26-26.

[1029] FIG. 27 is a perspective view of an adapter included in a bodily-fluid collection device according to an embodiment.

[1030] FIG. 28 is a cross-sectional view of the adapter of FIG. 27, taken along the line 28-28.

[1031] FIG. 29 is a front view of a portion of the adapter of FIG. 27.

[1032] FIG. 30 is a cross-sectional view of the portion of the adapter illustrated in FIG. 29, taken along the line 30-30.

[1033] FIG. 31 is a perspective view of the portion of the adapter illustrated in FIG. 29 coupled to a fluid reservoir according to an embodiment.

[1034] FIG. 32 is an exploded view of the fluid reservoir of FIG. 31.

[1035] FIG. 33 is a cross-sectional view of the portion of the adapter and the fluid reservoir illustrated in FIG. 31, taken along the line 33-33.

[1036] FIG. 34 is a cross-sectional view of an adapter coupled to a fluid reservoir according to another embodiment.

[1037] FIG. 35 is a cross-sectional view of an adapter coupled to a fluid reservoir according to another embodiment.

[1038] FIG. 36 is a cross-sectional view of an adapter coupled to a fluid reservoir according to another embodiment.

[1039] FIG. 37 is a perspective view of an adapter coupled to a fluid reservoir according to another embodiment.

[1040] FIG. 38 is a cross-sectional view of the adapter and the fluid reservoir of FIG. 37, taken along the line 38-38.

[1041] FIG. 39 is a perspective view of an adapter coupled to a fluid reservoir according to another embodiment.

[1042] FIG. 40 is a perspective view of an adapter coupled to a fluid reservoir according to another embodiment.

[1043] FIGS. 41 and 42 are cross-sectional views of the adapter and the fluid reservoir of FIG. 40, taken along the line 41-41, in a first configuration and a second configuration, respectively.

[1044] FIG. 43 is a perspective view of an adapter and a fluid reservoir according to another embodiment.

[1045] FIG. 44 is a cross-sectional view of the adapter and the fluid reservoir of FIG. 43, taken along the line 44-44.

[1046] FIGS. 45-47 are cross-sectional views of an adapter and a fluid reservoir each according to a different embodiment.

[1047] FIG. 48 is a perspective of an adapter included in a bodily-fluid collection device according to another embodiment.

[1048] FIG. 49 is a cross-sectional view of the adapter of FIG. 48, taken along the line 49-49.

[1049] FIG. 50 is a perspective view of a fluid reservoir included in a bodily-fluid collection device according to an embodiment.

[1050] FIG. 51 is a cross-sectional view of the adapter illustrated in FIG. 49 coupled to the fluid reservoir illustrated in FIG. 50, taken along the line 51-51 in FIG. 50.

[1051] FIG. 52 is a perspective view of a fluid reservoir included in a bodily-fluid collection device according to another embodiment.

[1052] FIG. 53 is a cross-sectional view of the fluid reservoir of FIG. 52, taken along the line 53-53.

[1053] FIG. 54 is a perspective view of a fluid reservoir included in a bodily-fluid collection device according to another embodiment.

[1054] FIG. 55 is an exploded view of a plunger included in the fluid reservoir of FIG. 54.

[1055] FIG. 56 is a cross-sectional view of the fluid reservoir of FIG. 54, taken along the line 56-56.

[1056] FIG. 57 is a perspective view of a fluid reservoir included in a bodily-fluid collection device according to another embodiment.

[1057] FIG. 58 is a cross-sectional view of the fluid reservoir of FIG. 57, taken along the line 58-58.

[1058] FIG. 59 is a front view of a fluid reservoir included in a bodily-fluid collection device according to another embodiment.

[1059] FIG. 60 is a cross-sectional view of a fluid reservoir included in a bodily-fluid collection device according to another embodiment.

[1060] FIG. 61 is a perspective view of an adapter included in a bodily-fluid collection device according to another embodiment.

[1061] FIG. 62 is an exploded view of the adapter of FIG. 61.

[1062] FIG. 63 is a cross-sectional view of the adapter of FIG. 61, taken along the line 63-63.

[1063] FIG. 64 is a perspective view of an adapter included in a bodily-fluid collection device according to another embodiment.

[1064] FIG. 65 is an exploded view of the adapter of FIG. 64.

[1065] FIG. 66 is a cross-sectional view of the adapter of FIG. 65, taken along the line 66-66.

[1066] FIG. 67 is a perspective view of an adapter included in a bodily-fluid collection device according to another embodiment.

[1067] FIG. 68 is a cross-sectional view of the adapter of FIG. 67, taken along the line 68-68.

[1068] FIG. 69 is a perspective view of an adapter included in a bodily-fluid collection device according to another embodiment.

[1069] FIG. 70 is an exploded view of the adapter of FIG. 69.

[1070] FIG. 71 is a cross-sectional view of the adapter of FIG. 69, taken along the line 71-71.

Detailed Description

[1071] Systems and methods for parenterally procuring bodily-fluid samples, such as blood, with reduced hemolysis are described herein. In some embodiments, a collection system has a proximal end portion, a distal end portion, and an inner surface defining a fluid flow path therethrough. The distal end portion is configured to be placed in fluid communication with a patient. The proximal end portion is configured to be placed in fluid communication with a fluid reservoir. The fluid flow path defined by the inner surface is associated with at least one flow characteristic configured to limit a stress within the flow of the bodily-fluid between the distal end portion and the proximal end portion.

[1072] As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, the term "a member" is intended to mean a single member or a combination of members, "a material" is intended to mean one or more materials, or a combination thereof.

[1073] As used herein, "bodily-fluid" can include any fluid obtained from a body of a patient, including, but not limited to, blood, cerebrospinal fluid, urine, bile, lymph, saliva, synovial fluid, serous fluid, pleural fluid, amniotic fluid, and the like, or any combination thereof. Moreover, while the embodiments and/or devices herein are specifically described as reducing, limiting, inhibiting, and/or substantially preventing hemolysis of blood withdrawn therethrough, any of the embodiments and/or devices can be used for controlling a flow of any suitable bodily-fluid (e.g., such as those listed above) when withdrawn from the body of a patient through that device.

[1074] As used herein, the term "set" can refer to multiple features or a singular feature with multiple parts. For example, when referring to set of walls, the set of walls can be considered as one wall with distinct portions, or the set of walls can be considered as multiple walls. Similarly stated, a monolithically constructed item can include a set of walls. Such a set of walls can include, for example, multiple portions that are discontinuous from each other. A set of walls can also be fabricated from multiple items that are produced separately and are later joined together (e.g., via a weld, an adhesive, or any suitable method).

[1075] As used herein, the terms "proximal" and "distal" refer to the direction closer to and away from, respectively, a user who would place the device into contact with a patient. Thus, for example, the end of a device first touching the body of the patient would be the distal end, while the opposite end of the device (e.g., the end of the device being manipulated by the user) would be the proximal end of the device.

[1076] As used herein, the terms "about," "approximately," and "substantially" when used in connection with a numerical value is intended to convey that the value so defined is nominally the value stated. Said another way, the terms about, approximately, and substantially when used in connection with a numerical value generally include the value stated plus or minus a given tolerance. For example, in some instances, a suitable tolerance can be plus or minus 10% of the value stated; thus, about 0.5 would include 0.45 and 0.55, about 10 would include 9 to 11, about 1000 would include 900 to 1100. In other instances, a suitable tolerance can be plus or minus an acceptable percentage of the last significant figure in the value stated. For example, a suitable tolerance can be plus or minus 10% of the last significant figure; thus, about 10.1 would include 10.09 and 10.11, approximately 25 would include 24.5 and 25.5. Such variance can result from manufacturing tolerances or other practical considerations (such as, for example, tolerances associated with a measuring instrument, acceptable human error, or the like).

[1077] As used herein, the term "laminar" refers to an organized and/or orderly fluid flow in parallel layers without lateral mixing, crosscurrents, eddy currents, and/or the like. More generally, the term "laminar" is intended to convey a flow of fluid that is smooth and/or free of turbulence. Moreover, the term "substantially" when used in connection with "laminar" is intended to convey that a fluid flow so defined is nominally a laminar fluid flow. As one example, a portion of a fluid transfer device defining a lumen that is described as facilitating and/or otherwise causing a "substantially laminar" fluid flow therethrough is intended to

convey that, although laminar fluid flow is desirable, some non-laminar flow can occur. Such variances (e.g., turbulence or the like) can result from manufacturing tolerances, or other practical considerations. Thus, a fluid having a "substantially laminar" flow includes such non-laminar flow characteristics within an industry-accepted tolerance. For example, while it may be desirable that a bodily-fluid transfer device transfer a laminar flow of blood therethrough a "substantially laminar flow" of blood can be 99% laminar, 95% laminar, 90% laminar, or any other acceptable tolerance thereof.

[1078] The embodiments described herein can be formed or constructed of one or more biocompatible materials. Examples of suitable biocompatible materials include metals, glasses, ceramics, or polymers. Examples of suitable metals include pharmaceutical grade stainless steel, gold, titanium, nickel, iron, platinum, tin, chromium, copper, and/or alloys thereof. A polymer material may be biodegradable or non-biodegradable. Examples of suitable biodegradable polymers include polylactides, polyglycolides, polylactide-co-glycolides (PLGA), polyanhydrides, polyorthoesters, polyetheresters, polycaprolactones, polyesteramides, poly(butyric acid), poly(valeric acid), polyurethanes, and/or blends and copolymers thereof. Examples of non-biodegradable polymers include nylons, polyesters, polycarbonates, polyacrylates, polymers of ethylene-vinyl acetates and other acyl substituted cellulose acetates, non-degradable polyurethanes, polystyrenes, polyvinyl chloride, polyvinyl fluoride, poly(vinyl imidazole), chlorosulphonate polyolefins, polyethylene oxide, and/or blends and copolymers thereof.

[1079] In some current phlebotomy procedures, blood is drawn from a patient using multiple components that are physically and fluidically coupled to define a fluid flow path between the patient and a collection device and/or fluid reservoir used to capture the bodily-fluid sample. In some such systems, however, the physical and/or fluidic interfaces formed between the components can result in turbulent regions and/or eddy currents within the flow of the blood, which in turn, can result in a stress within the flow that is sufficient to sheer, rupture, and/or otherwise damage the red blood cells. In addition, the process of drawing blood from a patient often involves exposing the blood to a negative pressure differential produced, for example, by placing an evacuated container (e.g., a Vacutainer ™) in fluid communication with a portion of the body. In some instances, the pressure differential can increase an internal stress within a flow of blood to an extent that results in hemolysis of the red blood cells. In other instances, the pressure differential can be attributed to the physical

exertion associated with a clinician actuating, for example, a syringe with a force sufficient to rupture the red blood cells during the collection process. A number of factors (for example, small veins, dehydration, veins with scar tissue, presence of sclerosis, and/or the like) can make vascular access a challenge. In such cases, excess negative pressure exerted during the collection process can result in hemolysis.

[1080] While such a negative pressure differential often facilitates withdraw of the blood, it also can produce a relatively high shear stresses within the red blood cells and/or a relatively high flow velocity of the blood through a flow path defined between the patient and the fluid reservoir (e.g., evacuated container). As a result, the red blood cells contained within the flow of blood can be damaged as the cells pass through the physical and/or fluidic interfaces formed between different components of a transfer device. In some instances, the relatively high velocity of the blood flow as the blood enters the containers can result in the blood impacting an inner surface of the container with a force sufficient to damage the red blood cells and/or other components of the blood. In addition, exposure time of a needle and/or catheter within the vein can result in hemolysis of the red blood cells.

[1081] Thus, to mitigate the risk of hemolysis of a sample volume of blood, various portions of a fluid flow path between the patient and the sample reservoir can be optimized. Such optimization can be done holistically (i.e., a system wide optimization) or done piecemeal (i.e., optimization of at least one potential source of hemolysis). By way of example, in some instances, any of the embodiments described herein, can be used independently to mitigate the risk of hemolysis at a specific point along a fluid flow path between a patient and a sample reservoir. That is to say, the embodiments described herein can be characterized by the potential source of hemolysis that the embodiments, so characterized, mitigate. For example, the embodiments described herein generally address six potential categories, portions, and/or sources of hemolysis along a fluid flow path between a patient and a fluid reservoir. Namely, the embodiments described herein can be used to mitigate the risk of hemolysis otherwise associated with (1) blood flow from, for example, a vein into a puncture member, needle, cannula, and/or the like, (2) blood flow through changing geometries and/or physical and fluidic interfaces; (3) blood flow rates and/or velocity within the fluid flow path; (4) blood flow from an adapter, puncture member, needle, cannula, and/or the like into a fluid reservoir; (5) blood flow exposure to a negative

pressure differential within a fluid reservoir, and (6) blood flow through a multi-lumen adapter and/or the like.

[1082] FIG. 1 is a schematic illustration of a portion of a bodily-fluid collection device 100, according to an embodiment. Generally, the bodily-fluid collection device 100 (also referred to herein as "fluid collection device," "collection device," or "device") can be used to percutaneously withdraw bodily-fluid from a patient. In some instances, the device 100 can be used to withdraw a volume of blood from a patient that is to be used as a biological sample for testing and/or assays associated with medical diagnosis and/or treatment. In other instances, the device 100 can be used to withdraw a volume of blood for collection purposes such as, for example, blood donation or the like. More particularly, the device 100 is configured to limit, inhibit, and/or substantially prevent hemolysis of at least a portion of the blood drawn therethrough, as described in further detail herein.

[1083] The device 100 has a proximal end portion 101 and a distal end portion 102 and defines a lumen 104 therethrough. More specifically, the device 100 includes an inner surface 103 that defines the lumen 104. The device 100 can be any suitable device or group of devices (e.g., a system including multiple devices). In some embodiments, for example, the device 100 can be a needle, a cannula, a trocar, a catheter, and/or the like. In such embodiments, the distal end portion 102 of the device 100 can include a sharpened, angled, or beveled edge configured to puncture the cutaneous layer of the body to place the lumen 104 in fluid communication with, for example, a vascular structure and/or the like. The proximal end portion 101 of the device 100 can be physically and/or fluidically coupled to any other suitable device such as, for example, a collection reservoir (not shown in FIG. 1). As such, the lumen 104 defined by the device 100 defines fluid pathway through which blood can flow from the patient to an intermediary collection device and/or directly to the collection reservoir.

[1084] As described above, in some embodiments, the device 100 is configured to reduce, limit, inhibit, and/or substantially prevent hemolysis of blood withdrawn from the body and through the device. For example, in embodiments in which the device 100 is a needle, cannula, catheter, and/or the like, the distal end portion 102 of the device 100 can include rounded edges and/or a substantially smooth contour. As such, the constituents of the blood (e.g., the red blood cells or "erythrocytes") can flow relatively smoothly into the lumen

104 (e.g., in response to a negative pressure differential produced, for example, by a syringe and/or an evacuated container coupled thereto) substantially without being damaged.

[1085] Moreover, in some embodiments, the shape, size, and/or contour of the inner surface 103 can selectively control the flow of blood through the device 100. By way of example, in some embodiments, the inner surface 103 can form a substantially smooth contour, which can facilitate a laminar flow of the blood therethrough. In addition, the inner surface 103 can have a contour that can selectively control an amount of negative pressure within a region of the lumen 104. For example, in some embodiments, the inner surface 103 can have a diameter that is varied along the length of the device 100. That is to say, a first portion of the inner surface 103 can have a diameter that is different from a diameter of a second portion of the inner surface 103 and thus, can reduce, constrict, limit, and/or otherwise control a flow of blood therethrough. In some such embodiments, the first portion of the inner surface 103 can be disposed between the second portion of the inner surface 103 and a third portion of the inner surface 103 having a diameter greater than or equal to the diameter of the second portion of the inner surface 103. In such embodiments, a region of the lumen 104 having a relatively larger diameter can be associated with a larger pressure than a region of the lumen 104 having a relatively smaller diameter, while conversely, a velocity associated with the region of the lumen 104 having the relatively larger diameter is less than a velocity associated with the region of the lumen having the relatively smaller diameter based on the simplified Bernoulli's Equation mathematically represented by equation 1 below:

$$P_1 + {}^1/_2\,\rho V_1^2 = P_2 + {}^1/_2\,\rho V_2^2 \qquad \text{Equation 1}$$

wherein P is pressure within the lumen, ρ is density of the fluid, and V is velocity of the fluid.

[1086] While described above as being a needle, catheter, cannula, trocar, and/or the like, in other embodiments, the device 100 can be any suitable component included in a fluid transfer system. For example, the device 100 can be an adapter, a locking mechanism, a cannula, a coupling mechanism, a port, an inlet, and outlet, and/or the like. By way of example, in some embodiments, the device 100 can be an adapter configured to be physically and fluidically coupled to at least one other device such as, for example, a needle. Thus, the adapter (i.e., the device 100) can have an inner surface with a contour that can control a flow of bodily-fluid therethrough. Moreover, an interface between the device 100 and the needle

(and/or any other suitable device) can be arranged to reduce turbulence of a flow of bodily-fluid therebetween, as described in further detail herein.

[1087] In some embodiments, the device 100 can be coupled to a fluid reservoir or container (e.g., at the proximal end portion 101). As such, the contour of the inner surface 103 of the device 100 can control a flow of bodily-fluid therethrough (as described above), while the orientation of the device 100 relative to the fluid reservoir or container can control and/or direct the flow of bodily-fluid through the proximal end portion 101 toward an inner surface of the fluid reservoir to, for example, reduce a force associated with a portion of the flow of bodily-fluid impacting the inner surface. In some embodiments, the device 100 can be an insert or the like at least partially disposed within the fluid reservoir or container.

[1088] Although not shown in FIG. 1, in some embodiments, the device 100 can be used with (e.g., physically and fluidically coupled to) a device or mechanism configured to modulate a negative pressure within a fluid reservoir or container. For example, in some embodiments, the device 100 can be coupled to a syringe or the like configured to transition between a first configuration and a second configuration to produce a negative pressure within an inner volume. As such, a rate at which the syringe can be transitioned from the first configuration (e.g., associated with a plunger in a distal position) to the second configuration (e.g., associated with the plunger in a proximal position) can be constrained (e.g., limited, inhibited, slowed, governed, controlled, etc.), thereby reducing a negative pressure exerted through the lumen 104 of the device, as described in further detail herein.

[1089] While the device 100 is described above as including a surface, mechanism, portion, etc. configured to reduce hemolysis of a volume of blood in a mechanical manner (e.g., reducing pressure and/or turbulence within a flow path via a contour, restrictor, or the like; reducing forces associated with a portion of the volume of blood impacting a surface of a fluid reservoir via a coupling mechanism, interface, etc.; reducing damage to constituents in the volume of blood by limiting or eliminating sharp edges, corners, etc.; and/or the like), in other embodiments, the device can be configured to chemically modify one or more characteristics associated with the volume of blood. For example, in some embodiments, the inner surface 103 of the device 100 can be coated with a chemical configured to limit lysis of erythrocytes (red blood cells) by strengthening or weakening a cell wall of the erythrocytes. More specifically, in some embodiments, the device 100 can be configured to introduce a chemical into a flow of blood that can, for example, increase a rigidity of the cell wall of

erythrocytes (e.g., decrease flexibility), which in turn, can reduce a likelihood of lysis of the erythrocytes (e.g., hemolysis of the blood) as the blood flows through the device 100. In other embodiments, the device 100 can be configured to introduce a chemical into a flow of blood that can, for example, decrease a rigidity of the cell wall of erythrocytes (e.g., increase flexibility), which in turn, can reduce a likelihood of lysis of the erythrocytes as the blood flows through the device 100.

[1090] While described above as coating the inner surface 103 with the chemical configured to modify a characteristic of the cell wall of the erythrocytes, in other embodiments, the device 100 can include any suitable device, mechanism, and/or method for introducing such a chemical to the volume of blood flowing therethrough. For example, the device 100 can include a chamber containing such a chemical, a baffle impregnated with such a chemical, a dispensing or dispersing device (e.g., sprayer or the like) configured to dispense a volume of such a chemical, impregnation of the chemical directly into the material used to produce the device 100 and/or any other suitable means for introducing such a chemical.

[1091] FIGS. 2-7 illustrate embodiments configured to mitigate the risk of hemolysis as a volume of blood flows from the patient (e.g., a vein of a patient) and into a lumen-defining device such as a needle or the like. Specifically, FIGS. 2 and 3 illustrate a puncture member 210 coupled to an adapter 220 according to an embodiment. The puncture member 210 has a proximal end portion 211 and a distal end portion 212 and defines a lumen 213 therebetween. The proximal end portion 211 of the puncture member 210 is physically and fluidically coupled to a distal end portion 222 of the adapter 220, as described above with reference to FIG. 1. More specifically, the proximal end portion 211 of the puncture member 210 is coupled to the adapter 220 such that an interface therebetween forms a substantially smooth and/or continuous surface. Said another way, the interface between the puncture member 210 and the adapter 220 can be such that a transition between the lumen 213 of the puncture member 210 and a lumen (not shown in FIGS. 2-6) defined by the adapter is substantially smooth and/or continuous (i.e., does not introduce a discontinuity such as a change in alignment and/or diameter), as described in further detail herein.

[1092] The distal end portion 212 of the puncture member 210 is configured to be inserted through the cutaneous layer of the patient to transfer fluid to and/or from the patient. For example, the distal end portion 212 can be inserted into a vein of a patient and the adapter 220 can be coupled to a fluid reservoir and/or intermediary collection device configured to

receive a volume of blood from the patient via the lumen 213. More specifically, as shown in FIGS. 2 and 3, the distal end portion 212 of the puncture member 210 is sharpened, angled, and/or beveled, which facilitates the insertion of the puncture member 210 into the body. The lumen 213 of the puncture member 210 extends through the distal end portion 212, thereby defining an opening 214 that places the lumen 213 in fluid communication with, for example, a vascular structure (e.g., a vein) within which the distal end portion 212 is disposed. Furthermore, as shown in FIG. 3, a distal edge 215 of the puncture member 210 defining the opening 214 is substantially rounded, smoothed, contoured, blunted, and/or the like. In other words, the distal edge 215 defining the opening 214 forms a substantially round corner. Thus, blood drawn through the opening 214 and into the lumen 213 can flow past the distal edge 214 with reduced damage to, for example, the constituents of the blood (e.g., the erythrocytes) that would otherwise result from contact with a sharper, more abrupt, substantially orthogonal, and/or otherwise non-rounded distal edge 215.

[1093] In some instances, a puncture member can be used to deliver and/or place a portion of a catheter in a desired lumen within the body of a patient. For example, as shown in FIGS. 4-6, a puncture member 310 can be used to place a stented catheter and/or the like within a vein V. The puncture member 310 can be substantially similar to the puncture members 210 and/or 310 described above and thus, the puncture member is not described in further detail herein. As shown in FIG. 4, a user (e.g., a phlebotomist, nurse, technician, physician, doctor, etc.) can manipulate a portion of the puncture member 310 (e.g., either directly or indirectly) to place at least a distal end portion 312 of the puncture member 310 within a lumen defined by the vein V. Once disposed in the vein V, a guidewire 316 can be advanced through the lumen defined by the puncture member 310, as shown in FIG. 4. With the guidewire 316 positioned within the vein V, the user can advance an introducer catheter 317 and, for example, a stented catheter 318 along the guide wire 316 to dispose a distal end portion of at least the introducer catheter 317 within the lumen of the vein V, as indicated by the arrow AA in FIG. 5. In some instances, the stented catheter 318 can be inserted into the vein V concurrently with the introducer catheter 317. In other instances, the stented catheter 318 can be advanced within the introducer catheter 317 after the distal end portion of the introducer catheter 317 is disposed in the vein 317.

[1094] With the distal end portion of the stented catheter 318 disposed in the vein V, the guidewire 316 and the introducer catheter 317 can be moved in the proximal direction (i.e.,

withdrawn from the vein V), as indicated by the arrow BB in FIG. 6. In some embodiments, as the introducer catheter 317 is withdrawn from the vein V, the distal end portion of the stented catheter 318 can transition from a first configuration to a second configuration. For example, the stented catheter 318 can be in a collapsed configuration (e.g., the first configuration) when disposed in the introducer catheter 317 (FIG. 5) such that a diameter of the stented catheter 318 is substantially uniform. When the introducer catheter 318 is withdrawn from the vein (FIG. 6), the distal end portion of the stented catheter 318 can expand and/or otherwise reconfigure such that a diameter of the distal end portion of the stented catheter 318 is greater than a diameter of a portion of the stented catheter 318 still disposed in the introducer catheter 317.

[1095] In some embodiments, the distal end portion of the stented catheter 318 can expand to an extent that places an outer surface of the stented catheter 318 in close proximity to or directly in temporary contact with an inner surface of the vein V defining the lumen. As such, blood can be withdrawn from the vein V into a fluid reservoir (not shown in FIGS. 4-6) via a lumen defined by the stented catheter 318. Moreover, with the distal end portion of the stented catheter 318 in close proximity to or directly in contact with the inner surface of the vein, the stented catheter 318 can inhibit, limit, and/or substantially prevent a collapse of at least a portion of the vein V (e.g., in response to a negative pressure differential between the vein V and the fluid reservoir (not shown). In some embodiments, the arrangement of at least the distal end portion of the stented catheter 318, when in the second configuration, can allow a flow of blood to enter the stented catheter 318 substantially without damaging the constituents of the blood, as described above with reference to FIGS. 2 and 3. While the puncture member 310 is described above as being retracted once the stented catheter 318 is placed in a desired position with the vein, in other embodiments, the puncture member 310 need not be retracted. As such, the stented catheter 318 can be, for example, a sleeve or the like disposed about the distal end portion 312 of the puncture member 310 to control a flow of blood entering the lumen of the puncture member 310. Moreover, as described above with reference to the puncture member 210, a surface of the puncture member 310 and/or the stented catheter 318 defining a distal opening can be substantially rounded, smoothed, contoured, blunted, and/or the like. In other words, a distal edge of the puncture member 310 and/or stented catheter 318 defining the distal opening forms a substantially round corner. Thus, blood drawn through the opening can flow past the distal edge with reduced damage to

the erythrocytes that would otherwise result from contact with a sharper, more abrupt, substantially orthogonal, and/or otherwise non-rounded distal edge 215.

[1096] While described above as placing a stented catheter, in other embodiments, a puncture member can be used to place any suitable catheter and/or cannula. For example, FIG. 7 illustrates a puncture member 410 and a catheter 418 according to another embodiment. The puncture member 410 can be used, for example, to place at least a portion of the catheter 418 within a lumen defined by the body (e.g., a vein). As shown in FIG. 7, a distal end portion 412 of the puncture member 410 can include a substantially rounded distal edge 415, as described above with reference to the puncture member 210. In this manner, a flow of blood can flow past the distal edge 415 to enter a lumen 413 defined by the puncture member 410. Similarly, the catheter 418 can include a distal edge 418A that is substantially rounded. As shown in FIG. 7, the distal end portion 412 of the puncture member 410 extends beyond the distal edge 418A of the catheter 418. In some embodiments, the distal end portion 412 of the puncture member 410 can form and/or can define a recessed portion 419 or the like that corresponds with a position at or near the distal edge 418A of the catheter 418. In this manner, when the puncture member 410 is inserted into, for example, a vein of a patient, an opening in the vein defined by the puncturing can be a diameter that is substantially the same as an outer diameter of the catheter 418. As such, the catheter 418 can be positioned within the vein without rupturing and/or otherwise dilating the opening in the vein. In some instances, once the catheter 418 is disposed in the lumen defined by the vein, the puncture member 410 can be retracted through the catheter 418 while at least a distal end portion of the catheter 418 remains within the vein. In such instances, the substantially rounded distal edge 418A can reduce and/or can substantially prevent hemolysis of a volume of blood flowing to the catheter 418, as described above with reference to the puncture member 310 in FIGS. 2 and 3.

[1097] While the puncture members 210, 310, and 410 are particularly shown and described above, in other embodiments, any suitable puncture member can be coupled to any compatible adapter, which in turn, can place the puncture member in fluid communication with a fluid collection device. For example, FIGS. 8-17 illustrate embodiments configured to mitigate the risk of hemolysis as a volume of blood flows through changing geometries and/or physical and fluidic interfaces of one or more adapters. Specifically, FIGS. 8-10 illustrate a puncture member 510 coupled to an adapter 520, according to another

embodiment. In some embodiments, the puncture member 510 and the adapter 520 can be and/or can form, for example, a butterfly needle or the like. More specifically, the puncture member 510 has a proximal end portion 511 and a distal end portion 512 and defines a lumen 513 therethrough. The proximal end portion 511 is coupled to the adapter 520, as described in further detail herein. The distal end portion 512 of the puncture member 510 can be any suitable configuration. For example, the distal end portion 512 of the catheter 510 can be substantially similar to or the same as the distal end portion 212 of the catheter 210 described above with reference to FIGS. 2 and 3. That is to say, the arrangement of the distal end portion 512 of the catheter 510 can limit and/or substantially prevent damage (e.g., hemolysis) to blood as blood flow past the distal end portion 512 and into the lumen 513.

[1098] The adapter 520 has a proximal end portion 521, a distal end portion 522, and an inner surface 523. As described above, the adapter 520 can have an overall shape substantially similar to known butterfly needles. While shown in FIG. 8 as being substantially cylindrical with varying diameters, the adapter 520 can be any suitable shape, size, or configuration such as square, rectangular, polygonal, and/or any other non-cylindrical shape. In this manner, the overall shape of the adapter 520 can facilitate the handling of the transfer device 520 by including similar geometric features as known butterfly needles. The distal end portion 522 of the adapter 520 is physically and fluidically coupled to the proximal end portion 511 of the puncture member 510, as described in further detail herein. The proximal end portion 521 of the adapter 520 can be any suitable configuration. In some embodiments, the proximal end portion 521 can be a port and/or a portion of a locking mechanism. For example, in this embodiment, the proximal end portion 521 of the adapter 520 is a locking mechanism configured as a male portion of a Luer Lok ®. Moreover, in this embodiment, such a locking mechanism is disposed at a proximal end portion of a cannula configured to extend between the proximal end portion 521 and the distal end portion 522 of the adapter 520. In other embodiments, the adapter 520 is monolithically formed without a cannula between the proximal end portion 521 and the distal end portion 522. Although the proximal end portion 521 is described as including a locking mechanism, in other embodiments, the proximal end portion 521 can be any suitable configuration configured to interface with any suitable device such that blood flows in a substantially laminar, smooth, and/or non-turbulent flow between the adapter 520 and the device.

[1099] As shown in FIGS. 9 and 10, the inner surface 523 of the adapter 520 defines a lumen 524 extending through the proximal end portion 521 and the distal end portion 522. In some embodiments, the arrangement of the inner surface 523 can reduce, inhibit, and/or substantially prevent, for example, hemolysis of a volume of blood flowing within the lumen 524. More specifically, as shown in FIG. 10, the distal end portion 522 of the adapter 520 is coupled to the proximal end portion 511 of the puncture member 510 such that the lumen 513 of the puncture member 510 is substantially aligned with and substantially the same diameter as the lumen 524 of the adapter 520. That is to say, the proximal end portion 511 of the puncture member 510 is coupled to the distal end portion 522 of the adapter 520 such that a substantially smooth and/or continuous transition is defined between the lumen 513 of the puncture member 510 and the lumen 524 of the adapter 520. Similarly, in embodiments including the cannula extending between the end portions, a distal end portion of the cannula can be coupled to the distal end portion 522 of the adapter 520 in such a manner as to define a substantially smooth transition therebetween.

[1100] In addition, the inner surface 523 of the adapter 520 defines a tapered portion that extends between the puncture member 510 and the cannula. Expanding further, a first portion of the inner surface 523 (e.g., a more proximal portion) defines a first diameter that is substantially the same as an inner diameter defined by the cannula, while a second portion of the inner surface (e.g., a more distal portion) defines a second diameter, smaller than the first diameter, that is substantially the same as an inner diameter defined by the lumen 513 of the puncture member 510. As shown in FIG. 10, the tapered portion can form a substantially smooth transition between, for example, the first diameter and the second diameter. In some instances, such a smooth transition, for example, from the first diameter to the second diameter can facilitate, produce, encourage, and/or force a substantially laminar flow (e.g., consistent, uniform, non-turbulent, uninterrupted, smooth, etc.) of a volume of bodily-fluid (e.g., blood) through the lumen 524. Moreover, the smooth or substantially uniform transitions between the puncture member 510 and the adapter 520 and/or the smooth or substantially uniform transitions between the various components of the adapter 520 can reduce eddy currents (i.e., circulating currents often resulting from a discontinuity) or the like within the flow of blood. Thus, when the distal end portion 512 of the puncture member 510 is disposed in a vein or the like and the proximal end portion 521 (e.g., a locking mechanism) is physically and fluidically coupled to a fluid reservoir, a volume of blood can flow within the lumens 513 and 524 from the patient to the fluid reservoir with reduced damage to the

constituents of the blood (e.g., hemolysis of the erythrocytes) that might otherwise occur as a result of misaligned interfaces and/or discontinuities; abrupt changes in diameter; turbulence and/or eddy currents within a flow of blood therethrough; and/or the like.

[1101] While the adapter 520 is particularly shown and described above with reference to FIGS. 8-10, in other embodiments, an adapter can be any suitable configuration and can be arranged within a system of components to form a physical and/or fluidic interface therebetween. For example, FIGS. 11-13 illustrate a first adapter 620 coupled to a second adapter 630 according to an embodiment. The first adapter 620 has a proximal end portion 621, a distal end portion 622 and an inner surface 623. The inner surface 623 of the first adapter 620 defines a lumen 624 extending through its proximal end portion 621 and its distal end portion 622.

[1102] As shown in FIGS. 12 and 13, the inner surface 623 of the first adapter 620 includes and/or otherwise forms a shoulder 625. More specifically, the shoulder 625 formed by the inner surface 623 is associated with a change in diameter of the inner surface 623. As shown in FIG. 13, the shoulder 625 forms a substantially annular discontinuity that has substantially rounded corners or edges. In this manner, the transition from a diameter of the inner surface 623 proximal to the shoulder 625 to a diameter of the inner surface distal to the shoulder 625 can be relatively smooth rather than forming a relatively sharp, abrupt, and/or orthogonal corner (e.g., shoulder). As such, the arrangement of the shoulder 625 can limit, inhibit, and/or substantially prevent hemolysis of blood as the blood flows within the lumen 624 past the shoulder 625.

[1103] The second adapter 630 has a proximal end portion 631, a distal end portion 632, and an inner surface 633. The inner surface 633 of the second adapter 630 defines a lumen 624 extending through its proximal end portion 631 and its distal end portion 632. As shown in FIGS. 11-13, a portion of the second adapter 630 can be inserted into a portion of the lumen 624 defined by the first adapter 620 to couple the second adapter 630 to the first adapter 620. In some embodiments, the first adapter 620 and the second adapter 630 can form a friction fit and/or the like, which in turn, can define a substantially fluid tight seal therebetween. Thus, the second adapter 630 can be inserted into the first adapter 620 to couple the second adapter 630 thereto.

[1104] Similarly, the distal end portion 632 of the second adapter 630 is configured to reduce, limit, and/or substantially prevent hemolysis of blood as the blood flow therethrough. Specifically, as shown in FIG. 13, a distal most surface of the second adapter 630 and the inner surface 633 of the second adapter 630 form a rounded corner 635 and/or smooth transition therebetween. The rounded corner 635 formed by the second adapter 630 defines a relatively smooth transition from an outer diameter of the second adapter 630 (e.g., at the distal end) to an inner diameter of the second adapter 630 (e.g., at the distal end) rather than forming a relatively sharp, abrupt, and/or orthogonal corner. In some embodiments, a radius of curvature associated with the rounded corner 635 of the second adapter 630 can be substantially similar to a radius of curvature associated with the shoulder 625 of the first adapter 620. Thus, when the second adapter 630 is disposed within the first adapter 620, a volume of bodily-fluid (e.g., blood) can flow through the lumen 624 of the first adapter 620 and the lumen 634 of the second adapter 630 to be disposed within a fluid reservoir or the like. Moreover, the arrangement of the shoulder 625 of the first adapter 620 and the rounded corner 635 of the second adapter 630 can, for example, reduce, limit, and/or substantially prevent hemolysis of blood flowing therethrough that might otherwise result from contact substantially abrupt, sharp, and/or orthogonal corners or the like. In addition, the arrangement of the shoulder 625 of the first adapter 620 and the rounded corner 635 of the second adapter 630 can facilitate, produce, encourage, and/or otherwise result in a substantially laminar flow through the lumens 624 and 634, respectively (e.g., with little turbulence, eddy currents, etc.).

[1105] Although the first adapter 620 and the second adapter 630 are shown in FIGS. 11-13 as each forming substantially rounded corners and/or shoulders, in other embodiments, a first adapter and a second adapter can be coupled together to form an interface therebetween having any suitable arrangement and/or configuration. For example, FIGS. 14 and 15 illustrate a first adapter 720 coupled to a second adapter 730 according to another embodiment. The first adapter 720 has a proximal end portion 721, a distal end portion 722 and an inner surface 723. The inner surface 723 of the first adapter 720 defines a lumen 724 extending through its proximal end portion 721 and its distal end portion 722. Furthermore, the inner surface 723 includes and/or otherwise forms a shoulder 725. In this embodiment, the shoulder 725 is associated with a change in diameter of the inner surface 723. As shown in FIG. 15, the shoulder 725 forms a substantially annular discontinuity with a substantially orthogonal corner. Said another way, the shoulder 725 has a substantially non-rounded

corner (e.g., has no radius of curvature of a nominal radius of curvature) that defines an edge or the like.

[1106] The second adapter 730 has a proximal end portion 731, a distal end portion 732, and an inner surface 733. The inner surface 733 of the second adapter 730 defines a lumen 724 extending through its proximal end portion 731 and its distal end portion 732. As shown in FIGS. 14 and 15, a portion of the second adapter 730 can be inserted into a portion of the lumen 724 defined by the first adapter 720 to couple the second adapter 730 to the first adapter 720. As shown in FIG. 14, the distal most surface of the second adapter 730 and the inner surface 733 of the second adapter 730 form a substantially orthogonal corner 735 (e.g., a substantially non-rounded corner, as described above). In some embodiments, the first adapter 720 and the second adapter 730 can be substantially similar to known adapters (e.g., each adapter forms relatively abrupt and/or substantially orthogonal corners and/or edges).

[1107] While such corners, discontinuities, and/or edges are described above as a potential source of blood hemolyzation, in this embodiment, a gasket 726 is disposed between and in contact with the shoulder 725 of the first adapter 720 and the distal surface of the second adapter 730, as shown in FIG. 15. The gasket 726 can be, for example, an elastomeric gasket and/or the like that is in contact with the distal surface of the second adapter 730 and the shoulder 725 of the first adapter 720 to define a substantially fluid tight seal therebetween. Moreover, the gasket 726 defines an opening and/or lumen therethrough that can have a size and/or diameter substantially similar to the size and/or diameter of the lumens 724 and 734. Thus, the arrangement of the gasket 726 can reduce a magnitude of the discontinuities formed by the shoulder 725 of the first adapter 720 and the distal end of the second adapter 730. As a result, the gasket 726 disposed between the shoulder 725 of the first adapter 720 and the distal surface of the second adapter 730 can, for example, reduce, limit, and/or substantially prevent hemolysis of blood flowing therethrough that might otherwise result from relatively large changes and/or discontinuities in the diameters of the inner surfaces 723 and 733, respectively. In addition, the gasket 726 can facilitate, produce, encourage, and/or otherwise result in a substantially laminar flow of fluid through the lumens 724 and 734, respectively (i.e., with little to no turbulence, eddy currents, etc.).

[1108] In some embodiments, the gasket 726 can be configured to restrict, limit, reduce, and/or otherwise control a flow of blood and/or a pressure exerted therethrough. For example, while the gasket 726 is described above as having substantially the same size and/or

diameter as the lumens 724 and 734, in other embodiments, the gasket 726 can have a size and/or diameter that is greater than or less than the diameter of the lumens 724 and 734. Specifically, in some embodiments, the size and/or diameter of the gasket 726 can be less than the diameter of the lumens 724 and 734 and, as such, the gasket 726 can restrict, constrict, reduce, limit, and/or otherwise control a flow of blood therethrough. In some embodiments, such a reduction and/or restriction of the blood flowing through the gasket 726 can reduce a likelihood of hemolysis of the blood resulting from, for example, a flow rate and/or a large pressure differential between a volume having a relatively high pressure disposed on a first side of the gasket 726 and a volume having a relatively low pressure disposed on a second side of the gasket 726.

[1109] FIG. 16 illustrates a portion of a first adapter 820 coupled to a portion of a second adapter 830 according to another embodiment. The first adapter 820 has a proximal end portion 821 configured to be coupled to a distal end portion 832 of the second adapter 830, as described in further detail herein. Although only the proximal end portion 821 of the first adapter 820 is shown in FIG. 16, the first adapter 820 can be similar in size and/or shape as the first adapters 620 and/or 720, unless otherwise expressed. The first adapter 820 includes an inner surface 823 that defines a lumen 824 extending through at least its proximal end portion 821. As shown in FIG. 16, the inner surface 823 of the first adapter 820 includes and/or otherwise forms a shoulder 825. The shoulder 825 formed by the inner surface 823 is associated with a change in diameter of the inner surface 823. More specifically, the shoulder 825 is associated with and/or forms a tapered or chamfered portion of the inner surface 823, as described in further detail herein.

[1110] Although only the distal end portion 832 of the second adapter 830 is shown in FIG. 16, the second adapter 830 can be any suitable shape, size, or configuration. For example, the distal end portion 832 of the second adapter 830 can form and/or can include a locking mechanism or the like while a proximal end portion (not shown in FIG. 16) can be coupled to and/or can form any suitable portion of a fluid collection device such as, for example, a fluid reservoir, a conduit, a flow control mechanism, and/or the like. In this embodiment, the distal end portion 832 of the second adapter 830 includes and/or forms a locking mechanism configured to form a threaded coupling with, for example, the proximal end portion 821 of the first adapter 820. In other embodiments, the distal end portion 832 of the second adapter 830 can be any suitable configuration.

[1111] As shown in FIG. 16, the second adapter 830 includes an inner surface 833 that defines a lumen 834 extending through at least its distal end portion 832. Moreover, the distal end portion 832 of the second adapter 830 includes and/or forms a distal surface 835 that is substantially tapered or chamfered. In some embodiments, the distal surface 835 of the second adapter 830 can have a size, shape, angle, etc. that substantially corresponds with the shoulder 825 defined by the first adapter 820. Thus, when the first adapter 820 is coupled to the second adapter 830 (e.g., via a threaded coupling or the like), the distal surface 835 of the second adapter 830 can be brought into contact with the shoulder 825 of the first adapter 820. Moreover, the arrangement of the first adapter 820 and the second adapter 830 is such that when the distal surface 835 of the second adapter 830 is placed in contact with the shoulder 825 of the first adapter 820, the inner surfaces 833 and 823, respectively, are brought into alignment, as shown in FIG. 16. In this manner, the inner surfaces 823 and 833 can form a substantially continuous surface having, for example, a substantially constant diameter. Thus, by reducing and/or substantially eliminating a discontinuity otherwise associated with the physical and fluidic coupling of the first adapter 820 and the second adapter 830, blood can flow within the lumens 824 and 834 of the adapters 820 and 830, respectively, with little or substantially no hemolysis of the blood flowing therethrough.

[1112] Although the inner surfaces 823 and 833 of the first adapter 820 and the second adapter 830, respectively, are described above as having a substantially constant diameter, in other embodiments, a diameter of each inner surface 823 and 833 can be varied. Such arrangement, however, is such that the inner surfaces 823 and 833 form a substantially smooth transition between, for example, a smaller diameter and a larger diameter. Thus, the substantially smooth transition in the diameters of the inner surfaces 823 and 833 can still facilitate a substantially laminar flow therethrough, which in some instances, can limit and/or substantially prevent hemolysis of blood flowing from the first adapter 820 and through the second adapter 830.

[1113] While the flow of bodily-fluid (i.e., blood) is described above as first flowing through the first adapter 820 and then flowing through the second adapter 930, in other embodiments, the flow through a set of adapters can be reversed. For example, FIG. 17 illustrates a first adapter 920 and a second adapter 930 according to another embodiment. The first adapter 920 has a distal end portion 922 configured to be coupled to a proximal end portion 931 of the second adapter 930, as described in further detail herein. Although only

the distal end portion 922 of the first adapter 920 is shown in FIG. 17, the first adapter 920 can be similar in size and/or shape as the first adapters 620 and/or 720, unless otherwise expressed. The first adapter 920 includes an inner surface 923 that defines a lumen 924 extending through at least its distal end portion 922. As shown in FIG. 17, a portion of the second adapter 930 is inserted into the lumen 924, as described in further detail herein.

[1114] Although only the proximal end portion 931 of the second adapter 930 is shown in FIG. 17, the second adapter 930 can be any suitable shape, size, or configuration. For example, the proximal end portion 931 of the second adapter 930 can form and/or can include a locking mechanism or the like while a proximal end portion (not shown in FIG. 17) can be coupled to and/or can form any suitable portion of a fluid collection device such as, for example, a puncture member, a needle, a conduit, a flow control mechanism, and/or the like. In this embodiment, the proximal end portion 931 of the second adapter 930 includes and/or forms a locking mechanism configured to form a threaded coupling with, for example, the distal end portion 922 of the first adapter 920. In other embodiments, the proximal end portion 931 of the second adapter 930 can be any suitable configuration.

[1115] As shown in FIG. 17, the second adapter 930 includes an inner surface 933 that defines a lumen 934 extending through at least its proximal end portion 931. Moreover, a region of the proximal end portion 931 of the second adapter 930 is disposed within the lumen 924 of the first adapter 920. For example, the inner surface 923 of the first adapter 920 has a diameter that corresponds to an outer diameter associated with the region of the proximal end portion 931 of the second adapter 930. Thus, as shown in FIG. 17, the diameter defined by the inner surface 923 of the first adapter 920 is greater than a diameter defined by the inner surface 933 of the second adapter 930, as described in further detail herein.

[1116] The proximal end portion 931 of the second adapter 930 includes and/or forms a proximal surface 935 with a substantially rounded corner and/or smooth transition. For example, the proximal surface 935 formed by the second adapter 930 defines a relatively smooth transition from an inner diameter of the second adapter 930 (e.g., defined by the inner surface 933) to an outer diameter of the second adapter 930 (e.g., at the distal end) rather than forming a relatively sharp, abrupt, and/or orthogonal corner. When a portion of the second adapter 930 is disposed within the lumen 923 of the first adapter 920, a volume of bodily-fluid (e.g., blood) can flow through the lumen 934 of the second adapter 930 and into the lumen 924 of the first adapter 920. Thus, the arrangement of the proximal surface 935 of the

second adapter 930 can, for example, facilitate, produce, encourage, and/or otherwise result in a substantially laminar flow of a volume of bodily-fluid (i.e., blood) as the volume flows from the lumen 934 of the second adapter 930 into the lumen 924 of the first adapter 920. Specifically, the proximal surface 935 of the second adapter 930 allows for a gradual transition from the diameter associated with the lumen 934 of the second adapter 930 (i.e., the smaller diameter) to the diameter associated with the lumen 924 of the first adapter 920 (i.e., the larger diameter). Such a smooth transition can, for example, reduce eddy currents and/or other forms of turbulence that can otherwise result from a substantially abrupt change in diameter or the like. Thus, the arrangement of the first adapter 920 and the second adapter 930 can allow a volume of blood to expand as the flow of blood exits the lumen 934 of the second adapter 930, which in some instances, can reduce, limit, and/or substantially prevent hemolysis of blood flowing therethrough.

[1117] While the first adapters 620, 720, 820, and 920 are shown and described above as receiving and/or otherwise being directly coupled to the second adapters 630, 730, 830, and 930, respectively, in other embodiments, a first adapter can be indirectly coupled to a second adapter via an intervening structure. In such embodiments, the intervening structure can define a lumen that can place the first adapter in fluid communication with the second adapter. Moreover, the intervening structure can limit, modulate, and/or control a flow rate of a volume of fluid (i.e., blood) therethrough. For example, FIGS. 18-26 illustrate embodiments configured to mitigate the risk of hemolysis otherwise associated with a relatively high flow rate and/or velocity along a fluid flow path that exceeds known shear force and exposure time limits that can rupture red blood cells. Specifically, FIGS. 18-20 illustrate a first adapter 1020 indirectly coupled to a second adapter 1030 via a restrictor 1050, according to an embodiment. The first adapter 1020 includes a proximal end portion 1021, a distal end portion 1022, and an inner surface 1023. The inner surface 1023 defines a lumen 1024 extending through the proximal end portion 1021 and the distal end portion 1022 (see e.g., FIG. 20). In some embodiments, the first adapter 1020 can be substantially similar to and/or the same as the first adapter 720 described above with reference to FIGS. 14 and 15. Thus, aspects of the first adapter 1020 are not described in further detail herein.

[1118] The second adapter 1030 has a proximal end portion 1031, a distal end portion 1032, and an inner surface 1033. The inner surface 1033 of the second adapter 1030 defines a lumen 1024 extending through its proximal end portion 1031 and its distal end portion 1032

(see e.g., FIG. 20). In some embodiments, the second adapter 1030 can be substantially similar to and/or the same as the second adapter 730 described above with reference to FIGS. 14 and 15. Thus, aspects of the second adapter 1030 are not described in further detail herein.

[1119] The restrictor 1050 has a proximal end portion 1051, a distal end portion 1052, and an inner surface 1053. The inner surface 1053 of the restrictor 1050 defines a lumen 1054 extending through its proximal end portion 1051 and its distal end portion 1052 (see e.g., FIG. 20). In this embodiment, the restrictor 1050 is coupled between the first adapter 1020 and the second adapter 1030 to define a fluid pathway therebetween (e.g., via the lumen 1054). More specifically, the restrictor 1050 can include any suitable interface, locking mechanism, surface, etc. at or near the proximal end portion 1051 and the distal end portion 1052 configured to couple the restrictor 1050 to the first adapter 1020 or the second adapter 1030. As shown in FIGS. 18-20, the restrictor 1050 includes a locking mechanism or the like at its distal end portion 1052 that is configured to couple the distal end portion 1052 of the restrictor 1050 to the proximal end portion 1021 of the first adapter 1020. For example, in some embodiments, the distal end portion 1052 of the restrictor 1050 can include a threaded female Luer Lok ® configured to form a threaded coupling with a corresponding threaded male Luer Lok ® of the first adapter 1020, as shown in FIG. 20.

[1120] As shown in FIGS. 19 and 20, the proximal end portion 1051 of the restrictor 1050 receives the second adapter 1030. For example, as described above with reference to the first adapter 620 and the second adapter 630 in FIGS. 11-13, a portion of the second adapter 1030 is inserted through the proximal end portion 1051 of the restrictor 1050 to be disposed in the lumen 1054. In some embodiments, the restrictor 1050 and the second adapter 1030 can form a friction fit and/or the like, which in turn, can define a substantially fluid tight seal therebetween. In other embodiments, the proximal end portion 1051 of the restrictor 1050 and the distal end portion 1032 of the second adapter 1030 can include any suitable coupling and/or locking mechanism configured to couple the second adapter 1030 to the restrictor 1050 (e.g., as described above with reference to the coupling between the first adapter 1020 and the restrictor 1050).

[1121] As shown in FIGS. 19 and 20, the restrictor 1050 or the first adapter 1020 includes a gasket 1026 configured to minimize a discontinuity between the lumen 1024 of the first adapter 1020 and the lumen 1054 of the restrictor 1050 when coupled. Similarly, the

second adapter 1030 or the restrictor 1050 includes a gasket 1036. The gaskets 1026 and 1036 can be substantially similar in form and function to the gasket 726 shown and described above with reference to FIGS. 14 and 15. Thus, the gaskets 1026 and 1036 are disposed within the lumen 1024 of the first adapter 1020 and the lumen 1054 of the restrictor 1050, respectively. The arrangement of the gaskets 1026 and 1036 can reduce a magnitude of the discontinuities formed between the inner surfaces 1023, 1033, and 1053 of the first adapter 1020, the second adapter 1030, and the restrictor 1050, respectively, which in turn, can reduce, limit, and/or substantially prevent hemolysis of blood flowing therethrough, as described in detail above. In some embodiments, the gaskets 1026 and 1036 can be configured to restrict and/or reduce a pressure and/or a flow rate associated with the first adapter 1020, the second adapter 1030, and/or the restrictor 1050, as described above with reference to the gasket 726. In some instances, restricting and/or reducing the pressure and/or flow rate associated with the first adapter 1020, the second adapter 1030, and/or the restrictor 1050 (e.g., via the gaskets 1026 and 1036) can, for example, limit shear forces and/or exposure time experienced by red blood cells as the red blood cells flow through the first adapter 1020, the second adapter 1030, and the restrictor 1050, and/or the interfaces therebetween.

[1122] The inner surface 1053 of the restrictor 1050 is configured to control a flow of fluid through the lumen 1053. For example, as shown in FIG. 20, the inner surface 1053 of the restrictor 1050 includes a choke portion 1055 or the like. In some embodiments, the choke portion 1055 corresponds to a portion of the inner surface 1053 having a reduced diameter relative to the other portions of the inner surface 1053. More specifically, the choke portion 1055 forms a relatively smooth transition (e.g., a gradual change) from a region of the inner diameter 1053 associated with a first diameter to a region (i.e., the choke portion 1055) associated with a second diameter, smaller than the first diameter. Thus, the choke portion 1055 restricts, controls, and/or reduces a flow of fluid therethrough.

[1123] Expanding further, the reduction in the diameter of the inner surface 1053 at or along the choke portion 1055 selectively controls a pressure within the lumen 1054. For example, in some embodiments, the second adapter 1030 can be fluidically coupled (e.g., either directly or indirectly) to an evacuated container or the like, resulting in a negative pressure within the lumens 1034, 1054, and 1024. Thus, the reduced diameter associated with the choke portion 1055 results in a reduced pressure differential between the lumen 1024

of the first adapter 1020 (i.e., at a time directly before the exposure to the negative pressure) and a portion of the lumen 1054 of the restrictor 1050 that is distal to the choke portion 1055. As such, when the first adapter 1020 is in fluid communication with, for example, a vascular structure (e.g., via a needle, catheter, cannula, etc.), a magnitude of the negative pressure exerted on or in the vascular structure is reduced, thereby limiting, reducing, and/or substantially preventing hemolysis of blood as it flows into the lumen 1024 defined by the first adapter 1020. Moreover, the smooth transition in the diameter of the inner surface 1053 from the first diameter to the second diameter (associated with the choke portion 1055), facilitates, encourages, and/or otherwise results in a substantially laminar flow through the lumen 1054 of the restrictor 1050.

[1124] While the restrictor 1050 is particularly shown and described above with reference to FIGS. 18-20, in other embodiments, a restrictor, configured to control a flow of fluid therethrough, can be any suitable configuration. For example, FIGS. 21-24 illustrate a restrictor 1150 according to another embodiment. The restrictor 1150 has a proximal end portion 1151, a distal end portion 1152, and an inner surface 1153. The inner surface 1153 of the restrictor 1150 defines a inner volume 1154 extending through its proximal end portion 1151 and its distal end portion 1152 (see e.g., FIG. 22). Although not shown in FIGS. 21-24, the restrictor 1150 can be disposed between two components of a fluid transfer device to define a fluid flow path therethrough. For example, in some embodiments, the proximal end portion 1151 can be coupled to an adapter such as, for example, the second adapter 1030, described above with reference to FIGS. 18-20. Similarly, the distal end portion 1152 can be coupled to an adapter such as, for example, the first adapter 1020, described above. As such, the proximal end portion 1151 and the distal end portion 1152 can be substantially similar to or the same as the proximal end portion 1051 and the distal end portion 1052, respectively, of the restrictor 1050 and thus, are not described in further detail herein.

[1125] As shown in FIGS. 22-24, the restrictor 1150 includes a baffle 1156 disposed in the inner volume 1154. The baffle 1156 can be any suitable shape, size, or configuration. For example, in this embodiment, the baffle 1156 is substantially rectangular (see e.g., FIG. 20) with a size that substantially corresponds to the inner volume 1154 of the restrictor 1150, as described in further detail herein. The baffle 1156 includes an inner surface 1157 that defines an inner volume 1158. As shown in FIG. 24, the inner surface 1157 of the baffle 1156 defines a gradual bow toward the center of the baffle 1156. More specifically, the

arrangement of the inner surface 1157 is such that a distance between opposite sides of the baffle 1156 gradually varies as the inner surface 1157 extends outward from a longitudinal centerline CL (shown in FIG. 22) of the baffle 1156. For example, in this embodiment, a distance between opposite portions of the inner surface 1157 gradually increases from a first distance, at a first position associated with a perimeter of the inner surface 1157, to second distance, at a second position disposed between the perimeter of the inner surface 1157 and the longitudinal centerline CL, and then gradually decreases from the second distance to a third distance, at a position associated with and/or near the longitudinal center CL. In this manner, the baffle 1156 can selectively control a flow of fluid through the inner volume 1158, as described in further detail herein.

[1126] Referring back to FIG. 22, in this embodiment, an outer surface of the baffle 1156 is in contact with the inner surface 1153 of the restrictor 1150 when disposed in the inner volume 1154. In some embodiments, the outer surface of the baffle 1156 and the inner surface 1153 of the restrictor 1150 define a friction fit or the like that forms a substantially fluid tight seal. As such, the arrangement of the baffle 1156 and the inner surface 1153 of the restrictor 1150 can limit, inhibit, and/or substantially prevent a flow of fluid between the outer surface of the baffle 1156 and the inner surface 1153 of the restrictor 1150. More specifically, the inner volume 1158 of the baffle 1156 defines a fluid flow path that places a first portion of the inner volume 1154, which is distal to the baffle 1156, in fluid communication with a second portion of the inner volume 1154, which is proximal to the baffle 1156. In this manner, the arrangement of the inner surface 1157 of the baffle 1156 can restrict, inhibit, guide, limit, choke, and/or otherwise control a flow of fluid through the restrictor 1150. Moreover, the smooth or gradual change in distance between opposite portions of the inner surface 1157 of the baffle (as described above) facilitates, encourages, and/or otherwise results in a substantially laminar flow through the inner volume 1154 of the restrictor 1150.

[1127] Although not shown in FIGS. 21-24, in some embodiments, the inner volume 1158 of the baffle 1156 can include a medium disposed therein. For example, in some embodiment, the baffle 1156 can include a substantially porous material or the like that can slow and/or filter a flow of fluid (e.g., blood) therethrough. In other embodiments, the user can manipulate the restrictor 1150 to modify and/or control a flow of fluid through the restrictor 1150. For example, in some instances, the user can exert a force on a portion of the

restrictor 1150 sufficient to deform that portion. As such, a portion of the force can correspondingly deform the baffle 1156, which in turn, can change a contour of the inner surface 1157. Thus, the user can exert a force on the restrictor 1150 to, for example, increase, decrease, or otherwise control a flow of fluid through the baffle 1156. By way of example, a user can exert a force of the restrictor 1150 to reduce a distance between opposite portions of the inner surface 1157, which in turn, can reduce a negative pressure differential produced by an evacuated container being placed in fluid communication with the restrictor 1150.

[1128] FIGS. 25 and 26 illustrate a restrictor 1250 according to another embodiment. The restrictor 1250 has a proximal end portion 1251, a distal end portion 1252, and an inner surface 1253. The inner surface 1253 of the restrictor 1250 defines a inner volume 1254 extending through its proximal end portion 1251 and its distal end portion 1252 (see e.g., FIG. 26). As described above, the restrictor 1250 can be physically and fluidically coupled between, for example, a pair of components of a fluid transfer device to restrict and/or otherwise control a flow of fluid therebetween. For example, although not shown in FIGS. 25-26, the proximal end portion 1251 can be coupled to an adapter such as, for example, the second adapter 1030, described above with reference to FIGS. 18-20. Similarly, the distal end portion 1252 can be coupled to an adapter such as, for example, the first adapter 1020, as described above. In this manner, the proximal end portion 1251 and the distal end portion 1252 can be substantially similar to or the same as the proximal end portion 1051 and the distal end portion 1052, respectively, of the restrictor 1050 and thus, are not described in further detail herein.

[1129] The restrictor 1250 includes and/or defines a set of chambers 1259, as shown in FIG. 26. More specifically, the restrictor 1250 includes a set of walls that can form, for example, a set of semi-spherical portions, which in turn, result in the inner surface 1253 defining the set of chambers 1259. Thus, the chambers 1259 are, for example, a set of semi-spherical portions of the inner volume 1254. As shown in FIG. 26, the chambers 1259 are serially arranged along a longitudinal centerline CL of the restrictor 1250. In some embodiments, the size and/or shape of each chamber 1259 can vary. For example, as shown in FIG. 26, the chamber 1259 disposed at or near the proximal end portion 1251 of the restrictor 1250 is smaller than the adjacent chamber 1259. In other embodiments, the size and/or shape of each chamber 1259 can be substantially uniform. With the inner surface 1253 defining the semi-spherical chambers 1259, a diameter of the inner volume 1254 (e.g.,

associated with a cross-sectional shape of the inner surface 1253) is varied along a length of the longitudinal centerline CL. For example, a diameter of the inner volume 1254 gradually increases or decreases in an alternating manner between a relatively smaller diameter, associated with a position along the longitudinal centerline substantially between adjacent chambers 1259 and a relatively larger diameter, associated with a position along the longitudinal centerline substantially in the center of a given chamber 1259.

[1130] In some embodiments, the arrangement of the chambers 1259 selectively controls a pressure within the inner volume 1254. For example, in some embodiments, the proximal end portion 1251 of the restrictor 1250 can be fluidically coupled (e.g., either directly or indirectly) to an evacuated container or the like, resulting in a negative pressure within the inner volume 1254. Thus, the alternating increase and decrease corresponding to each chamber 1259 results in a changing pressure differential along the longitudinal centerline CL. In some embodiments, such an alternating arrangement can, for example, act as a peristaltic pump or the like. Thus, the restrictor 1250 can draw a fluid through the inner volume 1254 via a pressure differential that is at least partially controlled by the arrangement of the inner surface 1253. That is to say, while an evacuated container is the source of a negative pressure, the arrangement of the chambers 1259 at least partially controls a pressure differential between the proximal end portion 1251 and the distal end portion 1252. In this manner, hemolysis of blood can be reduced and/or substantially prevented, which might otherwise occur in response to a shear force produced by a relatively rapid and/or relatively large pressure drop associated with placing an evacuated container in fluid communication with a vascular structure. Moreover, the smooth and/or gradual transitions in the diameter of the inner surface 1253 associated with the chambers 1259, facilitates, encourages, and/or otherwise results in a substantially laminar flow through the inner volume 1254 of the restrictor 1250.

[1131] Although not shown, any of the restrictors 1050, 1150, and/or 1250 can be fluidically coupled (either directly or indirectly) to and/or monolithically formed with an adapter configured to engage a fluid reservoir such as an evacuated container. In some embodiments, such adapters can include an inner surface configured to reduce discontinuities or the like within a portion of a fluid flow path and/or otherwise configured to facilitate a substantially laminar fluid flow therethrough, as described in detail above. Moreover, the adapters can engage any suitable fluid reservoir or container. For example, FIGS. 27-44

illustrate embodiments (i.e., adapters and fluid reservoirs) configured to mitigate the risk of hemolysis as blood flow from an adapter, a puncture member, a needle, a cannula, and/or the like into a fluid reservoir. Specifically, FIGS. 27-33 illustrate an adapter 1330 configured to engage a fluid reservoir 1360 (FIGS. 29-33) according to an embodiment. The adapter 1330 has a proximal end portion 1331, a distal end portion 1332, and an inner surface 1333. The inner surface 1333 defines a lumen 1334 extending through the proximal end portion 1331 and the distal end portion 1332 (see e.g., FIG. 27). As shown in FIGS. 27 and 28, in some embodiments, the adapter 1330 can include and/or can be coupled to a shroud 1343. In such embodiments, the shroud 1343 can define an inner volume 1344 within which a portion of a fluid reservoir can be disposed. In other embodiments, the adapter 1330 need not include and/or need not be coupled to the shroud 1343.

[1132] The adapter 1330 can be any suitable shape, size, or configuration. For example, as shown in FIGS. 29 and 30, the distal end portion 1332 of the adapter 1330 includes and/or is coupled to a lock mechanism or the like. In this embodiment, the distal end portion 1332 includes and/or forms a female portion of a Luer Lok ® or the like. Thus, the distal end portion 1332 of the adapter 1330 can be coupled to a corresponding male portion of a Luer Lok ® or the like, as described above with reference to the distal end portion 1052 of the restrictor 1050 shown in FIG. 20. The proximal end portion of the adapter 1330 includes and/or is coupled to a puncture member 1338 defining a lumen 1339 in fluid communication with the lumen 1334 of the adapter 1330. The puncture member 1338 can be any suitable configuration. For example, in some embodiments, the puncture member 1338 is a needle. As shown in FIG. 30, the puncture member 1325 is disposed within a sheath 1341. More specifically, the sheath 1341 is at least temporarily disposed about the puncture member 1338 and is configured to limit and/or substantially prevent an accidental contact with the puncture member 1338. Furthermore, the sheath 1341 can maintain the puncture member 1338 in a substantially sterile environment prior to use and can selectively control a flow of bodily-fluid through the puncture member 1338, as described in further detail herein.

[1133] As shown in FIG. 30, a diameter of the inner surface 1333 at or near the distal end portion 1332 is larger than a diameter of the puncture member 1338. In this manner, the inner surface 1333 forms and/or defines a smooth transition from a larger diameter at or near the distal end portion 1332 to a smaller diameter at or near the puncture member 1338. In some instances, such a smooth transition from the larger diameter to the smaller diameter can

facilitate, produce, encourage, and/or force a substantially laminar flow of a volume of bodily-fluid (e.g., blood) through the lumen 1334. Moreover, the smooth transition can reduce eddy currents or the like within the flow of blood that can otherwise result from a relatively abrupt change in diameter or the like. Thus, a volume of blood can flow within the lumens 1334 and 1339 with reduced damage to the constituents of the blood (e.g., hemolysis of the erythrocytes) that might otherwise occur as a result of misaligned interfaces and/or discontinuities; abrupt changes in diameter; turbulence and/or eddy currents within a flow of blood therethrough; and/or the like.

[1134] As described above, the adapter 1330 is configured to couple to and/or otherwise engage a fluid reservoir 1360. The fluid reservoir 1360 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 1360 is an evacuated container such as a Vacutainer™, a BacT/ALERT® SN, a BacT/ALERT® FA, and/or any other type of container, vial, bottle, reservoir, etc. As shown in FIGS. 31-33, the fluid reservoir 1360 includes a proximal end portion 1361 and a distal end portion 1362, and defines an inner volume 1364. The distal end portion 1362 includes a port 1363 through which the puncture member 1338 can be inserted to place the inner volume 1364 of the fluid reservoir 1360 in fluid communication with the lumen 1334 of the adapter 1330. For example, in some embodiments, the port 1363 can be a self-healing septum or the like. Thus, the port 1363 can be substantially in a sealed configuration prior to insertion of, for example, the puncture member 1338 and subsequently, can transition from an open configuration to the sealed configuration when, for example, the puncture member 1338 is removed from the port 1363.

[1135] In some embodiments, a fluid reservoir can include a flow control member or the like disposed in its inner volume. For example, as shown in FIGS. 32 and 33, the fluid reservoir 1360 includes a flow control member 1367 disposed within the inner volume 1364. In this embodiment, the flow control member 1367 can be, for example, an insert or funnel that defines a channel 1368 configured to receive a flow of fluid from the lumen 1339 of the puncture member 1338. More specifically, as shown in FIG. 33, a first end of the flow control member 1367 can be disposed adjacent to and/or can be coupled to the port 1363 and a second end, opposite the first end, can extend toward an inner surface of the fluid reservoir 1360. In this manner, the second end of the flow control member 1367 can be adjacent to the inner surface of the fluid reservoir 1360 such that an axis associated with a portion of the

channel 1368 at or near the second end is substantially parallel to and/or otherwise directed toward the inner surface of the fluid reservoir 1360.

[1136] In use, the adapter 1330 and/or the fluid reservoir 1360 can be manipulated to insert the puncture member 1338 through the port 1363 of the fluid reservoir 1360. As such, the sheath 1341 disposed about the puncture member 1338 can deform to allow the puncture member 1338 to be inserted through the port 1363. With the fluid reservoir 1360 being an evacuated container, the insertion of the puncture member 1338 is such that a negative pressure within the fluid reservoir 1360 is exerted through the lumen 1334 of the adapter 1330 (e.g., via the lumen 1339 of the puncture member 1338). Thus, when the distal end portion 1332 is fluidically coupled (either directly or indirectly) to a device or member in fluid communication with the body of a patient, the negative pressure draws a volume of bodily-fluid (e.g., blood) from the patient and into the fluid reservoir 1360. More specifically, the distal end portion 1332 of the adapter 1330 can be coupled (either directly or indirectly) to any suitable adapter, restrictor, and/or needle described herein to receive a flow of, for example, blood from the patient with reduced or substantially no hemolyzation of the blood. Furthermore, by disposing the flow control member 1367 in the inner volume 1364, a flow of blood can be directed within the channel 1338 toward the inner surface, which in turn, can decrease a force otherwise associated with an impact of the volume of blood contacting the inner surface. Thus, hemolysis of the blood associated with such a contact is reduced or substantially prevented.

[1137] While the adapter 1330 is shown in FIGS. 31-33 as not including and/or not be coupled to the shroud 1343, in other embodiments, the adapter 1330 can be coupled to the shroud 1343 when engaging the fluid reservoir 1360. Furthermore, while the flow control member 1367 is particularly shown in FIG. 33, in some embodiments, a second end of a flow control member can extend within the inner volume 1364 to a position adjacent to and/or substantially abutting a bottom or proximal surface (i.e., a surface opposite the port 1363). In other embodiments, a flow control member can extend in a spiral or helical manner from the port 1363. As such, a second end of the flow control member can be substantially tangential to the inner surface of the fluid reservoir and thus, fluid exiting a channel defined by the flow control member can flow along a circumference of the inner surface (e.g., tangent to the inner surface).

[1138] In other embodiments, a fluid reservoir can include any suitable flow control member. For example, FIG. 34 illustrates a fluid reservoir 1460 according to another embodiment. The fluid reservoir 1460 includes a proximal end portion 1461 and a distal end portion 1462, and defines an inner volume 1464. The distal end portion 1462 includes a port 1463 configured to receive, for example, a puncture member 1438 of an adapter 1430, as described in detail above with reference to FIGS. 31-33. The inner volume 1464 of the fluid reservoir 1460 includes and/or houses a flow control member 1467 operable to control a flow of fluid from, for example, the adapter 1430 into the inner volume 1464, as described in further detail herein. The fluid reservoir 1460 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 1460 is an evacuated container such as a Vacutainer™, a BacT/ALERT® SN, a BacT/ALERT® FA, and/or any other type of container, vial, bottle, reservoir, etc. In some embodiments, the fluid reservoir 1460 can be substantially similar to or the same as the fluid reservoir 1360 described above with reference to FIGS. 31-33. Thus, such similar aspects of the fluid reservoir 1460 are not described in further detail herein.

[1139] The fluid reservoir 1460 can differ from the fluid reservoir 1360, however, in the arrangement of the flow control member 1467. More specifically, while the flow control member 1367 is shown in FIG. 33 as tapering to a substantially uniform diameter as the flow control member 1367 extends away from the port 1363, in this embodiment, the flow control member 1467 has a varying diameter as the flow control member 1467 extends away from the port 1463. In this manner, a channel 1468 defined by the flow control member 1467 has a cross-sectional area and/or diameter that is dependent on, for example, a position along a longitudinal centerline CL defined by the flow control member 1467. For example, the channel 1468 can have a first diameter at a first end portion nearest to the port 1463, a second diameter at an end portion opposite the first end portion, and a third diameter at a portion disposed therebetween. As shown in FIG. 34, the end portions of the flow control member 1467 can be flared or the like such that the first diameter and the second diameter are each greater than the third diameter. Said another way, the diameter of the channel 1468 can taper along the longitudinal centerline CL from a larger diameter associated with the end portions of the flow control member 1467 to a smaller diameter at or near a center portion of the flow control member 1467.

[1140] With the fluid reservoir 1460 being an evacuated container or the like, a pressure (i.e., a negative pressure) within the channel 1468 is dependent on a position along the longitudinal centerline CL. That is to say, the pressure within the channel 1468 is dependent on the diameter of the channel 1468, in which a larger diameter is associated with a larger pressure. In a similar manner, the velocity of a flow of bodily-fluid (e.g., blood) within the channel 1468 is also dependent on the diameter of the channel 1468, however, such dependency is inverse to that associated with the pressure (i.e., a larger diameter is associated with less velocity). Thus, as blood (or other bodily-fluid) flows through the channel 1468, the increase in diameter at the end portion of the flow control member 1467 opposite the port 1463 results in a decrease in velocity associated with the flow of bodily-fluid therethrough. As such, a force otherwise associated with a volume of blood contacting an inner surface of the fluid reservoir 1460 is reduced, which in turn, can reduce and/or substantially prevent hemolysis of the volume of blood. Moreover, the diameter of the channel 1468 can be such that a pressure within the channel 1468 is maintained below a threshold that can otherwise result in hemolysis of blood flowing therethrough.

[1141] While the flow control members 1367 and 1467 are shown and described above as controlling a flow of, for example, blood through the channels 1368 and 1468, respectively, in other embodiments, a fluid reservoir can include a flow control member having any suitable configuration. For example, FIG. 35 illustrates a fluid reservoir 1560 according to another embodiment. The fluid reservoir 1560 includes a proximal end portion 1561 and a distal end portion 1562, and defines an inner volume 1564. The distal end portion 1562 includes a port 1563 configured to receive, for example, a puncture member 1538 of an adapter 1530, as described in detail above with reference to FIGS. 31-33. The inner volume 1564 of the fluid reservoir 1560 includes and/or houses a flow control member 1565 operable to control a flow of fluid from, for example, the adapter 1530 into the inner volume 1564, as described in further detail herein. The fluid reservoir 1560 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 1560 is an evacuated container such as a Vacutainer™, a BacT/ALERT® SN, a BacT/ALERT® FA, and/or any other type of container, vial, bottle, reservoir, etc. In some embodiments, the fluid reservoir 1560 can be substantially similar to or the same as the fluid reservoir 1360 described above with reference to FIGS. 31-33. Thus, such similar aspects of the fluid reservoir 1560 are not described in further detail herein.

[1142] As shown in FIG. 35, the flow control member 1565 is disposed within the inner volume 1564 at or near the port 1563. In this embodiment, the flow control member 1565 is a baffle insert or the like. Specifically, the flow control member 1565 forms and/or includes an angled baffle having a set of substantially parallel angled surfaces configured to direct a flow of blood or other bodily-fluid. For example, the puncture member 1538 of the adapter 1530 can be inserted through the port 1563 to place a distal end portion of the puncture member 1538 within the flow control member 1565. As such, when a flow of blood is expelled and/or drawn through a lumen defined by the puncture member 1538 (e.g., via a negative pressure differential produced by the evacuated container), the flow of blood contacts at least one angled surface of the flow control member 1565. Thus, the blood can flow along the angled surface toward an inner surface of the fluid reservoir 1560. By diverting, guiding, and/or otherwise directing the flow of blood to the inner surface, a force is reduced, which can otherwise result from an impact of the volume of blood contacting the inner surface. Thus, hemolysis of the blood associated with such a contact is reduced or substantially prevented.

[1143] While the flow control member 1565 is shown and described as forming and/or including a set of parallel angled surfaces configured to direct a flow of bodily-fluid toward the inner surface of the fluid reservoir 1560, in other embodiments, a flow control member can be any suitable baffle or the like. For example, in some embodiments, a flow control member can be an angled baffle or the like having a set of angled surfaces with an alternating orientation or the like. By way of example, a flow control member can include a first set of angled surfaces with a cross-sectional orientation (as shown in FIG. 35) that forms a 30° with a given plane and a second set of angled surfaces with a cross-sectional orientation that forms a 150° orientation with the given plane (i.e., a mirrored orientation), with each angled surface of the first set being disposed between two angled surfaces of the second set (or vice versa). In some embodiments, a baffle can include a set of surfaces that are each substantially V-shaped or U-shaped.

[1144] In other embodiments, a flow control member can be an absorbent or porous baffle or the like that can fill at least a portion of an inner volume of a fluid reservoir. In this manner, a flow of blood can be expelled or drawn from a lumen of an adapter (e.g., a lumen of a puncture member or the like) and absorbed by the absorbent baffle. In such embodiments, a volume of blood can be subsequently released or expelled from the absorbent

baffle via a centripetal or centrifugal action and/or the like. In some embodiments, a flow control member can be a baffle including a set of angled surfaces with an absorbent material disposed therebetween.

[1145] While the flow control members 1367, 1467, and 1565 are shown as independent components disposed within the fluid reservoirs 1360, 1460, and 1560, respectively, in other embodiment, a fluid reservoir can include a flow control member that is integral with another portion of the fluid reservoir such as, for example, a port. For example, FIG. 36 illustrates a fluid reservoir 1660 according to another embodiment. The fluid reservoir 1660 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 1660 is an evacuated container such as a Vacutainer™, a BacT/ALERT® SN, a BacT/ALERT® FA, and/or any of type of container, vial, bottle, reservoir, etc. In some embodiments, the fluid reservoir 1660 can be substantially similar to or the same as the fluid reservoir 1360 described above with reference to FIGS. 31-33. Thus, such similar aspects of the fluid reservoir 1660 are not described in further detail herein.

[1146] The fluid reservoir 1660 includes a proximal end portion 1661 and a distal end portion 1662, and defines an inner volume 1664. The distal end portion 1662 includes a port 1663 configured to receive, for example, a puncture member 1638 of an adapter 1630, as described in detail above with reference to FIGS. 31-33. The port 1663 in this embodiment, however, includes an inner surface 1665 configured to control a flow of fluid into the inner volume 1664 of the fluid reservoir 1660. As shown in FIG. 36, the inner surface 1665 of the port 1663 has a varied diameter that forms a constriction disposed between a proximal end portion and a distal end portion of the port 1663. For example, in some embodiments, the inner surface 1665 can form a constriction or otherwise can have a reduced diameter at or near a center of the port 1663 (i.e., at or near a midpoint between the proximal end portion and the distal end portion of the port).

[1147] In some embodiments, the inner surface 1665 can have a reduced diameter at a position that is proximal to the puncture member 1638 when the adapter 1630 is engaged with the fluid reservoir 1660. Similarly stated, the arrangement of the fluid reservoir 1660 and the adapter 1630 is such that when the adapter 1630 engages the fluid reservoir 1660, the puncture member 1638 is disposed in a distal position relative to a portion of the inner surface 1665 associated with the smallest diameter. Thus, the arrangement of the inner surface 1665 of the port 1663 can, for example, result in a venturi effect within a volume of

bodily-fluid as the volume of bodily-fluid flows from the puncture member 1638 into the port 1663. In other words, with the inner surface 1665 forming a constriction and/or reduction in diameter, a pressure associated with a volume on opposite sides of the constriction and/or reduction in diameter can be controlled. For example, the fluid reservoir 1660, being an evacuated container, defines a negative pressure within a portion of the inner volume 1664 proximal to the portion of the inner surface 1665 having the reduced diameter. In some embodiments, the constriction and/or reduced diameter formed by the inner surface 1665 results in a corresponding decrease in pressure associated with the reduced diameter. Thus, by selectively controlling a portion of the inner surface 1665 that is distal to the reduced diameter (i.e., selectively increasing the diameter of the inner surface 1665) a pressure within a volume distal to the reduced diameter can be less than, for example, the pressure within the volume proximal to the reduced diameter. Thus, hemolysis within a flow of blood is reduced or substantially prevented that might otherwise result from a rapid exposure to the negative pressure differential produced by the fluid reservoir 1660.

[1148] While the flow control members 1367, 1467, 1565, and the port 1663 are shown and described above as receiving and/or otherwise guiding a flow of bodily-fluid (e.g., blood) into the inner volumes 1364, 1464, 1564, 1664, respectively, in some embodiments, an adapter can be arranged to selectively direct a flow of bodily-fluid into a fluid reservoir. For example, FIGS. 37 and 38 illustrate an adapter 1760, according to another embodiment. The adapter 1760 is configured for selective engagement with a fluid reservoir 1760 to deliver a flow of bodily-fluid into an inner volume 1764. The adapter 1760 includes at least a shroud 1743 and a puncture member 1768. Although not shown in FIGS. 37 and 38, an inner surface of the adapter 1760 can be substantially similar to or the same as the inner surface 1363 of the adapter 1360 described above with reference to FIG. 30. That is to say, the adapter 1760 can include an inner surface that defines a substantially smooth transition between, for example, a lumen associated with an inlet of the adapter 1760 (e.g., a catheter, cannula, and/or locking mechanism) and a lumen of the puncture member 1768, thereby reducing and/or substantially preventing hemolysis of blood flowing therethrough.

[1149] As shown in FIG. 38, the arrangement of the adapter 1760 is such that the puncture member 1768 is disposed at non-orthogonal orientation relative to the shroud 1743. More specifically, at least a portion of the puncture member 1768 extends within an inner volume 1744 of the shroud 1743 and toward an inner surface. Thus, when the fluid reservoir

1760 is inserted into the inner volume 1744 of the shroud 1743, the puncture member 1768 punctures a port 1763 of the fluid reservoir 1760 (e.g., substantially similar to the port 1363 of the fluid reservoir 1360 described above with reference to FIGS. 31-33) at a substantially non-orthogonal angle. For example, the fluid reservoir 1760 can be inserted into the inner volume 1743 of the shroud 1744 with a substantially parallel or orthogonal orientation relative thereto. As the fluid reservoir 1760 is moved in the distal direction, the port 1763 is brought into contact with the puncture member 1768 and with the fluid reservoir 1760 parallel or orthogonal to the shroud 1743, the puncture member 1768 punctures the port 1763 at an angle associated with the orientation of the puncture member 1768 relative to the shroud (e.g., non-orthogonal). Therefore, as shown in FIG. 38, an end portion of the puncture member 1768 can be adjacent to, in contact with, and/or otherwise near an inner surface of the reservoir 1760 defining the inner volume 1764. In this manner, directing the flow of blood to the inner surface reduces a force, which can otherwise result from an impact of the volume of blood contacting the inner surface. Thus, hemolysis of the blood associated with such a contact is reduced or substantially prevented.

[1150] In some embodiments, the adapter 1730 can be configured to engage, for example, a standard fluid reservoir such as, for example, a Vacutainer ™ or the like. That is to say, in some embodiments, the adapter 1730 is configured to be compatible with existing fluid reservoirs without modifications being made thereto. In other embodiments, a fluid reservoir can have any suitable configuration. For example, FIG. 39 illustrates an adapter 1830 physically and fluidically coupled to a fluid reservoir 1860 according to another embodiment. The adapter 1830 can be any suitable adapter such as, for example, the adapter 1330 described above with reference to FIGS. 29 and 30. In this manner, the adapter 1830 includes a puncture member 1838 configured to puncture a port or the like of the fluid reservoir 1860, as described in further detail herein.

[1151] The fluid reservoir 1860 includes a proximal end portion 1861 and a distal end portion 1862, and defines an inner volume (not shown in FIG. 39). The distal end portion 1862 includes a port 1863 configured to receive, for example, the puncture member 1838 of the adapter 1830, as described in detail above with reference to FIGS. 31-33. The port 1863 in this embodiment, however, is disposed in a substantially horizontal position. More specifically, in some embodiments, the port 1863 can be disposed in a substantially tangential arrangement relative to, for example, an inner surface of the fluid reservoir 1860. Thus,

when the puncture member 1838 is inserted through the port 1863, an end portion of the puncture member 1838 can be placed adjacent to, at, or substantially near a portion of the inner surface of the fluid reservoir 1860, as described above with reference to the adapter 1730 and fluid reservoir 1760. Similarly stated, the arrangement of the port 1863 can be such that when the puncture member 1838 is inserted therethrough, at least the end portion of the puncture member 1838 (not shown in FIG. 39) is in a tangential orientation relative to the inner surface of the fluid reservoir 1860. In this manner, directing a flow of blood to the inner surface reduces a force, which can otherwise result from an impact of the volume of blood contacting the inner surface. Thus, hemolysis of the blood associated with such a contact is reduced or substantially prevented.

[1152] While a flow of bodily-fluid (e.g., blood) into the fluid reservoirs 1360, 1460, 1560, 1660, 1760, and 1860 is described above as being passively controlled by, for example, the flow control members 1367, 1467, 1565, the port 1663, the adapter 1730, and/or the port 1863, respectively, in other embodiments, a flow of bodily-fluid into a fluid reservoir can be actively controlled. That is to say, while the flow of bodily-fluid into the fluid reservoirs 1360, 1460, 1560, 1660, 1760, 1860 is controlled without user intervention (i.e., beyond the intervention of coupling the adapters 1330, 1430, 1530, 1660, 1760, and 1860 to the fluid reservoirs 1360, 1460, 1560, 1660, 1760, and 1860 respectively), in other embodiments, a user can manipulate an adapter and/or fluid reservoir to actively control a flow of fluid into the fluid reservoir. For example, FIGS. 40-42 illustrate an adapter 1930 and a fluid reservoir 1960, according to another embodiment. The fluid reservoir 1960 can be any suitable reservoir that defines an inner volume 1964 configured to receive a flow of bodily-fluid such as, for example, an evacuated container or the like. More specifically, as described above with reference to the fluid reservoir 1360 in FIGS. 31-33, the fluid reservoir 1960 includes a port 1963 through which a portion of the adapter 1930 can be inserted to gain access to the inner volume 1964, as described in further detail herein.

[1153] As shown in FIGS. 40-42, the adapter 1930 includes a proximal end portion 1931 and a distal end portion 1932, and defines an inner volume 1934. Although not shown, the distal end portion 1932 of the adapter 1930 can be coupled to any suitable lumen-defining device such as a needle, cannula, catheter, and/or sterile flexible tubing. In some embodiments, the distal end portion 1932 can include a locking mechanism or the like that can physically and fluidically couple the adapter 1930 to any suitable corresponding device

and/or component. The proximal end portion 1931 of the adapter 1930 receives a portion of the fluid reservoir 1960. For example, as shown in FIGS. 41 and 42, at least a portion of the port 1963 is inserted through the proximal end portion 1931 of the adapter 1930 to be disposed within a portion of the inner volume 1934.

[1154] As shown in FIGS. 41 and 42, the adapter 1930 further includes a cannula 1935 and an actuator 1945. Specifically, the cannula 1935 extends through the proximal end portion 1931 and the distal end portion 1932 of the adapter 1930, thereby defining a fluid pathway through the adapter 1930. The cannula 1935 can be any suitable shape, size, or configuration. For example, in some embodiments, the cannula 1935 is a substantially flexible tube formed of a biocompatible plastic or the like. In this manner, at least a portion of the cannula 1935 can be manipulated (e.g., by the actuator 1945) to bend, flex, kink, and/or otherwise reconfigure the cannula 1935, as described in further detail herein. The arrangement of the cannula 1935 can be such that when the fluid reservoir 1960 is inserted into the inner volume 1934 of the adapter 1930, an end portion of the cannula 1935 punctures the port 1963 of the fluid reservoir 1960 and thus, places the inner volume 1964 of the fluid reservoir 1960 in fluid communication with a lumen defined by the cannula 1935. Thus, a negative pressure within the fluid reservoir 1960 (e.g., the fluid reservoir 1960 is an evacuated container) exerts or draws suction through the lumen defined by the cannula 1935, as described in further detail herein.

[1155] The actuator 1945 of the adapter 1930 can be any suitable configuration. For example, as shown in FIGS. 41 and 42, the actuator 1945 can be a trigger or the like coupled to the adapter 1930 via a pivot point, pin, axle, etc. More specifically, a first portion of the actuator 1945 extends from and/or beyond an outer surface of the adapter 1930 and a second portion is disposed within the inner volume 1934 defined by the actuator 1930. Thus, a user (e.g., a phlebotomist, doctor, technician, nurse, etc.) can actuate the actuator 1945 by pivoting the actuator 1945 relative to the adapter 1930. In this manner, a portion of the actuator 1945 disposed in the inner volume 1934 of the adapter 1930 can be increased or decreased, for example, by exerting a force or removing a force, respectively, on the actuator 1945 (i.e., pivoting the actuator 1945 relative to the adapter 1930).

[1156] As shown, the portion of the actuator 1945 disposed within the inner volume 1934 of the adapter 1930 defines an opening 1946 through which the cannula 1935 can extend. Therefore, actuating the actuator 1945 (e.g., pivoting the actuator 1945 relative to the adapter

1930) results in a corresponding manipulation of a portion of the cannula 1935. For example, in some instances, while the actuator 1945 is in a first configuration, the position of the opening 1946 relative to the adapter 1930 can be such that the cannula 1935 (disposed therein) is pulled, bent, bowed, deformed, kinked, etc. Such deformation of the cannula 1935 can result in, for example, a constriction and/or pinching of the cannula 1935, which in turn, can constrict and/or at least partially obstruct the lumen defined by the cannula 1935, as shown in FIG. 41.

[1157] Conversely, a force can be exerted to actuate the actuator 1945, thereby pivoting the actuator 1945 relative to the adapter 1930. As described above, such pivoting motion can, for example, increase a portion of the actuator 1945 disposed in the inner volume 1934, which in turn, can change the position and/or orientation of the opening 1946 relative to the adapter 1930. Thus, the repositioning and/or reorienting of the opening 1946 actively (e.g., by exerting a force) or passively (e.g., by removing or reducing an existing force) reconfigures at least the portion of the cannula 1935 disposed therein. For example, as shown in FIG. 42, when the actuator 1945 is placed in the second configuration, the cannula 1935 can be substantially straight or substantially undeformed. Thus, the lumen defined by the cannula 1935 is substantially unobstructed and/or otherwise not constricted by the actuator 1945.

[1158] In use, when the fluid reservoir 1960 is placed in fluid communication with the lumen defined by the cannula 1935 (see e.g., FIGS. 41 and 42), the negative pressure and/or suction (described above) within the lumen of the catheter 1935 can be modulated by actuating the actuator 1945 between its first configuration, associated with a smaller amount of suction, and its second configuration, associated with a larger amount of suction. Moreover, when the distal end portion 1932 of the adapter 1930 is placed in fluid communication with the body of a patient (e.g., either directly or indirectly via a lumen-defining device, a needle, etc.), the negative pressure within the fluid reservoir 1960 draws blood, or other bodily-fluids, through the lumen defined by the cannula 1935 and into the inner volume 1964. In this manner, actuating the actuator 1945 to control or modulate the amount of suction or negative pressure within the lumen of the cannula 1935 can reduce a magnitude of negative pressure that would otherwise be exerted on the flow of blood. Thus, hemolysis of the blood is reduced or substantially prevented that might otherwise result from a rapid exposure to a negative pressure differential produced by the fluid reservoir 1960.

[1159] Although the lumen of the cannula 1935 is shown in FIG. 41 as being partially constricted when the actuator 1945 is in its first configuration, in other embodiments, the actuator 1945 can deform the cannula 1935 a sufficient amount to result in a substantially complete constriction of the lumen. Moreover, while not shown in FIGS. 40-42, in some embodiments, the actuator 1945 can include and/or can be operably coupled to a bias member such as a spring or the like. As such, the bias member can exert a force that at least temporarily maintains the actuator 1945 in, for example, the first configuration until an actuating force is exerted on the actuator 1945, which is sufficient to overcome the force of the bias member.

[1160] While the adapter 1930 is shown and described above as controlling a flow of bodily-fluid into the fluid reservoir 1960 by manipulating the cannula 1935, in other embodiments, an adapter can control a flow of bodily-fluid into a fluid reservoir in any suitable manner. For example, FIGS. 43 and 44 illustrate an adapter 2030 and a fluid reservoir 2060, according to another embodiment. The fluid reservoir 2060 can be any suitable reservoir that defines an inner volume 2064 configured to receive a flow of bodily-fluid such as, for example, an evacuated container or the like. More specifically, as described above with reference to the fluid reservoir 1360 in FIGS. 31-33, the fluid reservoir 2060 includes a port 2063 through which a portion of the adapter 2030 can be inserted to gain access to the inner volume 2064, as described in further detail herein.

[1161] As shown in FIGS. 43 and 44, the adapter 2030 includes a proximal end portion 2031 and a distal end portion 2032. The proximal end portion 2031 of the adapter 2030 is open and/or defines an opening configured to receive at least a portion of the port 2063 of the fluid reservoir 2060. The distal end portion 2032 of the adapter 2030 includes a port 2033 or the like that can be coupled to any suitable lumen-defining device such as a cannula, catheter, and/or sterile flexible tubing (not shown in FIGS. 43 and 44). In some embodiments, the distal end portion 2032 can include a locking mechanism or the like fluidically coupled to the port 2033 and configured to physically and fluidically couple the adapter 2030 to any suitable corresponding device and/or component.

[1162] As shown in FIG. 44, the adapter 2030 includes a puncture member 2038 that extends from a surface of the adapter 2030 to, for example, puncture the port 2063 of the fluid reservoir 2060. Furthermore, the adapter 2030 defines a lumen 2036 that extends through a portion of the adapter 2030 to fluidically couple the port 2033 to the puncture

member 2038. Thus, the puncture member 2038 can puncture the port 2063 of the fluid reservoir 2060 to place the inner volume 2064 of the fluid reservoir 2060 in fluid communication with, for example, the port 2033 of the adapter 2030, which in turn, can be in fluid communication (e.g., either directly or indirectly via an intervening structure) a portion of the body of a patient. Moreover, a negative pressure within the fluid reservoir 2060 (e.g., the fluid reservoir 2060 is an evacuated container) exerts or draws suction through the lumen 2036 and the port 2033 of the adapter 2030 to, for example, draw a flow of bodily-fluid from the patient through the adapter 2030 and into the inner volume 2064 of the fluid reservoir 2060.

[1163] As shown in FIGS. 43 and 44, the arrangement of the adapter 2030 is such that the fluid reservoir 2060 is in a substantially vertical orientation when coupled to the adapter 2030. Thus, when a volume of bodily-fluid (e.g., blood) is expelled from the puncture member 2038, in response to the negative pressure within the fluid reservoir 2060, the bodily-fluid flows in a substantially vertical direction from a lower position to an upper position. While the fluid reservoir 2060 defines a negative pressure that produces a suction force operable in drawing a flow of bodily-fluid from the puncture member 2038, the bodily-fluid expelled therefrom is also exposed to a substantially opposing force associated with gravitational acceleration (i.e., approximately 9.81 meters-per-second-squared ($^{m}/_{s^2}$)). Thus, when a volume of blood is drawn through the adapter 2030 and into the inner volume 2064 of the fluid reservoir 2060, the force associated with gravity acts to slow a velocity of the flow of blood within the inner volume 2064. As such, hemolysis of blood is reduced and/or substantially prevented that can otherwise result from a force associated with a volume of blood impacting an inner surface of the fluid reservoir 2060 defining the inner volume 2064.

[1164] While the adapters and fluid reservoirs described above with reference to FIGS. 27-44 control and/or direct a flow of fluid (i.e., blood) into a fluid reservoir to, for example, reduce hemolysis, in some embodiments, the arrangement of a fluid reservoir and/or an adapter can be such that a negative pressure operable in drawing a volume of blood into the fluid reservoir can be configured modulated and/or controlled. For example, FIGS. 45-60 illustrate embodiments configured to mitigate the risk of hemolysis associated with blood flow to a negative pressure differential within a fluid reservoir. Specifically, FIG. 45 illustrates an adapter 2130 and a fluid reservoir 2160 according to another embodiment. The adapter 2130 can be any suitable adapter such as, for example, the adapter 1330 described

above with reference to FIGS. 29 and 30. In this manner, the adapter 2130 includes a puncture member 2138 configured to puncture a port or the like of the fluid reservoir 2160, as described in further detail herein. The fluid reservoir 2160 includes a proximal end portion 2161 and a distal end portion 2162, and defines an inner volume 2164. The proximal end portion 2161 includes a port 2163A configured to receive, for example, an output member (e.g., a needle, puncture member, cannula, etc.) from, for example, a vacuum source or the like, as described in further detail herein. Similarly, the distal end portion 2162 includes a port 2163 configured to receive, for example, the puncture member 2138 of the adapter 2130, as described in detail above with reference to FIGS. 31-33. In some embodiments, the ports 2163A and 2163 can be substantially similar in form and/or function. In some embodiments, the port 2163A disposed at or near the proximal end portion 2161, for example, can include a frangible seal, a self-healing port, a one-way valve, and/or the like.

[1165] As shown in FIG. 45, the fluid reservoir 2160 includes an elastomeric member 2178 (and/or any other suitable member or material) disposed within the inner volume 2164. The elastomeric member 2178 is in contact with an inner surface of the fluid reservoir 2160 (defining at least a portion of the inner volume 2164) to form a substantially fluid tight seal therebetween. Thus, a portion of the inner volume 2164 that is proximal to the elastomeric member 2178 is substantially fluidically isolated from a portion of the inner volume 2164 that is distal to the elastomeric member 2178. In some embodiments, the portion of the inner volume 2164 disposed between the elastomeric member 2178 and the port 2163 (i.e., disposed at the distal end portion 2162 of the fluid reservoir 2160) can define, for example, a negative pressure, prior to the insertion of the puncture member 2138 through the port 2163. In other embodiments, both portions of the inner volume 2164 (e.g., on either side of the elastomeric member 2178) define a negative pressure, prior to the insertion of the puncture member 2138 through the port 2163. In still other embodiments, the inner volume 2164, in its entirety, need not define a negative pressure, prior to the insertion of the puncture member 2138 through the port 2163.

[1166] As shown in FIG. 45, the plunger 2145 can "float" and/or otherwise be disposed in a substantially fixed position within the inner volume 2164 prior to the port 2163A being fluidically coupled to a vacuum source (not shown in FIG. 45). Moreover, the arrangement of the fluid reservoir 2160 is such that when the actuator 2130 engages the fluid reservoir 2160, the puncture member 2138 is in a distal position relative to the elastomeric member

2178 and thus, substantially fluidically isolated from the portion of the inner volume 2164 that is proximal to the elastomeric member 2178. In a similar manner, the fluid reservoir 2160 can be manipulated such that an outlet of a vacuum source (not shown in FIG. 45) punctures and/or is otherwise inserted through the port 2163A to be placed in fluid communication with the portion of the inner volume 2164 proximal to the elastomeric member 2178. Thus, a user can actuate the vacuum source (e.g., via an electric switch, a pre-charged negative pressure created in a manufacturing process, mechanical actuation, and/or the like), such that the vacuum source draws a vacuum (e.g., a suction force) through its output and into the portion of the inner volume 2164 proximal to the elastomeric member 2178.

[1167] In some instances, the suction force and/or negative pressure can be sufficient to overcome a friction force between the elastomeric member 2178 and the inner surface, thereby resulting in a movement of the elastomeric member 2178 within the inner volume 2164 towards the port 2163A. The movement of the elastomeric member 2178 results in a change in volume associated with the portions of the inner volume 2164 disposed on either side of the elastomeric member 2178. In some instances, the increase in volume of the portion of the inner volume 2164 distal to the elastomeric member 2178 results in a negative pressure that is sufficient to draw a flow of bodily-fluid through the puncture member 2138 and into the inner volume 2164. As such, in some instances, a rate and/or magnitude of the vacuum drawn by the vacuum source can be controlled to, for example, change a characteristic associated with a pressure difference within the inner volume 2164 of the fluid reservoir 2160 and, for example, the adapter 2130. Thus, hemolysis of the blood is reduced or substantially prevented that might otherwise result from a rapid exposure to a negative pressure differential produced by the fluid reservoir 2160.

[1168] While the elastomeric member 2178 is shown and described above as "floating" within the inner volume 2164, in other embodiments, a fluid reservoir can include an elastomeric member and/or the like that is coupled to a plunger. For example, FIG. 46 illustrates an adapter 2230 and a fluid reservoir 2260 according to another embodiment. The adapter 2230 can be any suitable adapter such as, for example, the adapter 1330 described above with reference to FIGS. 29 and 30. In this manner, the adapter 2230 includes a puncture member 2238 configured to puncture a port or the like of the fluid reservoir 2260, as described in further detail herein.

[1169] The fluid reservoir 2260 includes a proximal end portion 2261 and a distal end portion 2262, and defines an inner volume 2264. The proximal end portion 2261 includes a port 2263A configured to be coupled to, for example, a vacuum source or the like, as described in further detail herein. Similarly, the distal end portion 2262 includes a port 2263 configured to receive the puncture member 2238 of the adapter 2230, as described in detail above with reference to FIGS. 31-33. In some embodiments, the ports 2263A and 2263 can be substantially similar in form and/or function. In some embodiments, the port 2263A disposed at or near the proximal end portion 2261, for example, can include a frangible seal, a self-healing port, a one-way valve, a locking mechanism, and/or the like. Thus, the port 2263A can physically and fluidically couple to a corresponding outlet port of a vacuum source (not shown in FIG. 46). For example, in some embodiments, an outlet port of a vacuum source and the port 2263A can form a threaded coupling or the like. In such embodiments, when the vacuum source is actuated, the port 2263A can be transitioned from a first, substantially sealed configuration to a second, substantially open configuration.

[1170] As shown in FIG. 46, the fluid reservoir 2260 includes a plunger 2275 disposed within the inner volume 2264. The plunger 2275 includes and/or is coupled to an elastomeric member 2278 disposed within the inner volume 2264. The elastomeric member 2278 is in contact with an inner surface of the fluid reservoir 2260 (defining at least a portion of the inner volume 2264) to form a substantially fluid tight seal therebetween. Thus, a portion of the inner volume 2264 that is proximal to the elastomeric member 2278 is substantially fluidically isolated from a portion of the inner volume 2264 that is distal to the elastomeric member 2278, as described above with reference to the elastomeric member 2178 in FIG. 46. In this embodiment, at least a portion of the plunger 2275 is movably disposed within a support member 2264A extending from a surface of the fluid reservoir 2260. As shown, the support member 2264A can, for example, divide the inner volume into a first portion and a second portion. Moreover, the support member 2264A can include a seal or the like that is in contact with an outer surface of the plunger to form a substantially fluid tight seal therebetween. Thus, the first portion of the inner volume 2264 can be substantially isolated from the second portion of the inner volume 2264.

[1171] The arrangement of the fluid reservoir 2260 is such that when the actuator 2230 engages the fluid reservoir 2260, the puncture member 2238 is in a distal position relative to the elastomeric member 2278 and thus, substantially fluidically isolated from the portion of

the inner volume 2264 that is proximal to the elastomeric member 2278. A user can similarly manipulate the fluid reservoir to couple the port 2263A to an outlet of a vacuum source (not shown in FIG. 46). In this manner, the portion of the inner volume 2264 that is proximal to the support member 2264A is placed in fluid communication with the vacuum source. Thus, a user can actuate the vacuum source (e.g., via an electric switch, a pre-charged negative pressure created in a manufacturing process, mechanical actuation, and/or the like) such that the vacuum source draws a vacuum (e.g., a suction force) through its output and into the portion of the inner volume 2264 proximal to the support member 2264A.

[1172] In some instances, the suction force and/or negative pressure can be sufficient to move the plunger 2275 within the inner volume 2264 towards the port 2263A. The movement of the plunger 2275 results in a corresponding movement of the elastomeric member 2278 and thus, changes a volume associated with the portions of the inner volume 2264 disposed on either side of the elastomeric member 2278. In some instances, the increase in volume of the portion of the inner volume 2264 distal to the elastomeric member 2278 results in a negative pressure that is sufficient to draw a flow of bodily-fluid through the puncture member 2238 an into the inner volume 2264. As such, in some instances, a rate and/or magnitude of the vacuum drawn by the vacuum source can be controlled to, for example, change a characteristic associated with a pressure difference within the inner volume 2264 of the fluid reservoir 2260 and, for example, the adapter 2230. Thus, hemolysis of the blood is reduced or substantially prevented that might otherwise result from a rapid exposure to a negative pressure differential produced by the movement of the plunger 2375 within the fluid reservoir 2260.

[1173] In some embodiments, the arrangement of the plunger 2275 and the support member 2264A can, for example, maintain a sterility of a portion of the inner volume 2264 distal to the support member 2264A. Specifically, as described above, the support member 2264A can include the seal that engages the outer surface of the plunger 2275 to fluidically isolate a portion of the inner volume 2264 proximal to the support member 2264A from a different portion of the inner volume 2264 distal to the support member 2264A. As such, when the port 2263A is placed in fluid communication with the vacuum source (not shown in FIG. 46), the portion of the inner volume 2264 proximal to the support member 2264A can be exposed, for example, to a non-sterile environment (e.g., associated with the vacuum source), while the sterility of the portion of the inner volume 2264 is maintained.

[1174] FIG. 47 illustrates an adapter 2330 and a fluid reservoir 2360 according to another embodiment. The adapter 2330 can be any suitable adapter such as, for example, the adapter 1330 described above with reference to FIGS. 29 and 30. In this manner, the adapter 2330 includes a puncture member 2338 configured to puncture a port or the like of the fluid reservoir 2360, as described in further detail herein.

[1175] The fluid reservoir 2360 includes a proximal end portion 2361 and a distal end portion 2362, and defines an inner volume 2364. The proximal end portion 2361 includes a port 2363A configured to be coupled to, for example, a vacuum source or the like, as described in further detail herein. Similarly, the distal end portion 2362 includes a port 2363 configured to receive the puncture member 2338 of the adapter 2330, as described in detail above with reference to FIGS. 31-33. As shown in FIG. 47, the fluid reservoir 2360 includes a plunger 2375 disposed within the inner volume 2364. The plunger 2375 includes and/or is coupled to an elastomeric member 2378 disposed within the inner volume 2364. The elastomeric member 2378 is in contact with an inner surface of the fluid reservoir 2360 (defining at least a portion of the inner volume 2364) to form a substantially fluid tight seal therebetween. As such, the fluid reservoir 2360 can be substantially similar to the fluid reservoir 2260 described above with reference to FIG. 46.

[1176] The fluid reservoir 2360 can differ from the fluid reservoir 2260, however, by including a bias member 2377 (e.g., a linear spring, a torsion spring, a leaf spring, a compression member, and/or the like) disposed about and in contact with a portion of the plunger 2375. In this manner, when the port 2363A is physically and fluidically coupled to an outlet of a vacuum source (not shown in FIG. 47) and the vacuum source is actuated, the vacuum source draws a vacuum (e.g., a suction force) through its output and into the portion of the inner volume 2364. Thus, the vacuum source can exert a suction force within a portion of the inner volume 2364 that results in a proximal movement of the plunger 2375. The arrangement of the bias member 2377, however, is such that the bias member 2377 exerts a reaction force in response to the movement of the plunger 2375. As such, the bias member 2377 can at least partially control a movement of the plunger 2375 within the inner volume 2364, for example, to reduce speed at which the plunger 2375 is moved. Thus, hemolysis of the blood is reduced or substantially prevented that might otherwise result from a rapid exposure to a negative pressure differential produced by the movement of the plunger 2375 within the fluid reservoir 2360.

[1177] While the adapters in the embodiments above have been shown and described as being physically and/or fluidically coupled to a corresponding fluid reservoir configured as an evacuated container, in other embodiments, an adapter can be configured to physically and/or fluidically couple to any suitable fluid reservoir and/or any suitable intervening structure. For example, FIGS. 49 and 50 illustrate an adapter 2430 according to another embodiment. The adapter 2430 can be any suitable shape or size and can be configured to be placed in fluid communication with any suitable fluid reservoir. For example, as described in further detail herein with reference to FIGS. 51 and 52, in some instances, the adapter 2430 can be physically and fluidically coupled to a fluid reservoir 2460 configured as, for example, a syringe or the like.

[1178] As shown in FIGS. 49 and 50, the adapter 2430 has a proximal end portion 2431 and a distal end portion 2432. In this embodiment, the distal end portion 2432 of the adapter 2430 includes, for example, a locking mechanism (e.g., a Luer Lok® or the like) that can physically and fluidically couple the adapter 2430 to a corresponding locking mechanism of any other suitable device such as, for example, an extension set or the like. In other embodiments, the distal end portion 2432 can be any suitable configuration such as, for example, a port, a septum, and/or the like. In a similar manner, the proximal end portion 2431 of the adapter 2430 includes, for example, a locking mechanism (e.g., a Luer Lok® or the like) that can physically and/to fluidically couple the adapter 2430 to, for example, the fluid reservoir 2460, as described in further detail herein.

[1179] The adapter 2430 includes a delivery member 2438 that extends from a portion of adapter 2430 toward the proximal end portion 2431. The delivery member 2438 defines a lumen 2439 extending at least partially through the delivery member 2438. More specifically, in this embodiment, the lumen 2439 extends through the distal end portion 2432 of the adapter 2430 but does not extend through the proximal end portion 2431. Similarly stated, the lumen 2439 does not extend through a proximal surface of the delivery member 2438. For example, as shown in FIGS. 49 and 50, the delivery member 2438 can have a substantially rounded or hemispherical proximal surface that is substantially closed and/or continuous. Alternatively, the delivery member 2438 defines at least one opening 2440 disposed along a circumference of the delivery member 2438 at a position distal to, for example, the proximal surface. Thus, while the delivery member 2438 does not define an

opening though a proximal most surface, opening(s) 2440 place a proximal end portion of the lumen 2439 in fluid communication with a volume outside of the delivery member 2438.

[1180] As described above, the adapter 2430 can be physically and fluidically coupled to the fluid reservoir 2460 (see e.g., FIG. 52). The fluid reservoir 2460 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 2460 is a syringe or the like, as shown in FIG. 51. The fluid reservoir 2460 has a proximal end portion 2461 and a distal end portion 2462 and defines an inner volume 2464. The distal end portion 2462 is configured to be physically and fluidically coupled to an adapter such as, for example, the adapter 2430. For example, the distal end portion 2462 can include a locking mechanism (e.g., a Luer Lok® or the like) configured to be physically and fluidically coupled to the proximal end portion 2431 (e.g., the corresponding locking member included therein) of the adapter 2430. Moreover, when the adapter 2430 is coupled to the fluid reservoir 2460, the delivery member 2438 is at least partially disposed in the inner volume 2464 of the fluid reservoir 2460 and as such, the opening(s) 2440 defined by the delivery member 2438 place the lumen 2439 of the adapter 2430 in fluid communication with the inner volume 2464 of the fluid reservoir 2460, as described in further detail herein.

[1181] As shown in FIGS. 51 and 52, the proximal end portion 2461 movably receives a plunger 2475 that is at least partially disposed in the inner volume 2464, as described in further detail herein. As shown in FIG. 52, the fluid reservoir 2460 includes a seal member 2479 disposed within the inner volume 2464. More specifically, the seal member 2479 is disposed within a proximal portion of the inner volume 2464 and about a portion of the plunger 2475. As such, the seal member 2479 forms a substantially fluid tight seal between an inner surface of the fluid reservoir 2460 and an outer surface of the seal member 2479 and an outer surface of the plunger 2475 and an inner surface of the seal member 2479. Furthermore, the seal member 2479 defines an opening 2479A extending therethrough that can place a portion of the inner volume 2464 proximal to the seal member 2479 in fluid communication with a portion of the inner volume 2464 distal to the seal member 2479. The arrangement of the fluid reservoir 2460 is such that the seal member 2479 is maintained in a substantially fixed position when the plunger 2475 is moved within the inner volume 2464, as described in further detail herein.

[1182] As shown in FIG. 52, the plunger 2475 has a proximal end portion 2476 and a distal end portion 2477. The distal end portion 2477 of the plunger 2475 includes and/or is

coupled to an elastomeric member 2478 or the like. For example, in some embodiments, the elastomeric member 2478 can form a substantially fluid tight seal with an inner surface of the fluid reservoir 2460. As described above, the plunger 2475 is movably disposed within the inner volume 2464 of the fluid reservoir 2460. More specifically, the plunger 2475 can be moved within the inner volume 2464 in an axial direction between a first position (e.g., a distal position) and a second position (e.g., a proximal position) relative to the fluid reservoir 2460. For example, in some embodiments, the plunger 2475 can be disposed in a distal position relative to the fluid reservoir 2460 prior to use. A user can then manipulate the fluid reservoir 2460 and/or the plunger 2475 to move the plunger 2474 in a proximal direction within the inner volume 2464. With the elastomeric member 2478 in contact with the inner surface of the fluid reservoir 2460, the proximal movement of the plunger 2475 relative to the fluid reservoir 2460 produces a negative pressure within a portion of the inner volume 2464 that is distal to the elastomeric member 2478.

[1183] When the adapter 2430 is coupled to the fluid reservoir 2460 (as shown in FIG. 52), the negative pressure within the portion of the inner volume 2464 results in a suction through the lumen 2439 of the delivery member 2438. Thus, when the distal end portion 2431 of the adapter 2430 is coupled to a device or other intervening structure, which in turn, is in fluid communication with a portion of the body and/or intervening device (e.g. catheter, fluid reservoir, etc.), the suction force within the lumen 2439 can draw a bodily-fluid (e.g., blood) through the lumen 2439 and into the inner volume 2464 of the fluid reservoir 2460. Moreover, the arrangement of the seal member 2479 within the inner volume 2464 can reduce, limit, modulate, and/or otherwise at least partially control a rate at which the plunger 2479 can be moved within the inner volume 2464. For example, with the elastomeric member 2478 forming a substantially fluid tight seal with the inner surface of the fluid reservoir 2460, the proximal movement of the plunger 2464 reduces and/or compresses a volume defined between the elastomeric member 2478 and the seal member 2479, which in turn, increases a pressure within that volume. Therefore, with the seal member 2479 similarly forming a substantially fluid tight seal with the inner surface of the fluid reservoir 2460 and with an outer surface of the plunger 2475, air within the volume between the seal member 2479 and the elastomeric member 2478 is forced through the opening 2479A defined by the seal member 2479, thereby limiting the rate at which the plunger 2479 is moved within the inner volume 2464. As such, a negative pressure and/or a suction force drawn through the lumen 2439 of the adapter 2430 is correspondingly controlled and/or modulated.

[1184] As described above, in some embodiments, the arrangement of the delivery member 2438 can also limit and/or otherwise modulate a pressure and/or a suction force within the lumen 2439. In this manner, when withdrawing a volume of blood, hemolysis of the blood flowing through the lumen 2439 and into the inner volume 2464 of the fluid reservoir 2460 is reduced or substantially prevented. Specifically, the arrangement opening(s) 2440 and the lumen 2439 of the delivery member 2438 can, for example, reduce a negative pressure within the lumen 2439 and/or can slow a flow of blood delivered to the inner volume 2464 of the fluid reservoir 2460 to an extent that can reduce and/or substantially prevent hemolysis of the blood that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like. In addition, the arrangement of an inner surface defining the lumen 2439 can, for example, reduce turbulence, eddy currents, and/or any other disturbance that can otherwise result from a discontinuity or the like.

[1185] While the fluid reservoir 2460 is particularly shown and described above with reference to FIGS. 51 and 52, in other embodiments, any suitable fluid reservoir can be coupled to, for example, the adapter 2430 to receive a volume of blood with reduced hemolysis of its constituents. For example, FIGS. 53 and 54 illustrate a fluid reservoir 2560 according to another embodiment. In this embodiment, the fluid reservoir 2560 is, for example, a syringe or the like having a proximal end portion 2561 and a distal end portion 2562 and defining an inner volume 2564. The distal end portion 2562 is configured to be physically and fluidically coupled to an adapter such as, for example, the adapter 1530, as described in detail above.

[1186] The proximal end portion 2561 of the fluid reservoir 2560 is substantially open and receives at least a portion of a plunger 2575. Moreover, the proximal end portion 2561 of the fluid reservoir 2560 includes an actuator 2570 that is operable in moving the plunger 2575 within the inner volume 2564. For example, as shown in FIGS. 53 and 54, the fluid reservoir 2560 includes a protrusion 2569 to which the actuator 2570 is pivotally coupled. More specifically, the actuator 2570 includes a first end portion 2571, a second end portion 2572, and a pivot portion 2573 disposed therebetween. The second end portion 2572 of the actuator 2570 is coupled to a portion of the plunger 2575, as described in further detail herein. The pivot portion 2573 is coupled to the protrusion 2569 via, for example, a pin, an axle, a rod, and/or the like configured to allow the actuator 2570 to pivot about the protrusion

2569 (e.g., about an axis defined by the protrusion 2569) in response to a force exerted on the first end portion 2571. In this manner, the actuator 2570 can be arranged, for example, as a trigger or the like which when actuated, is operable in moving the plunger 2575 relative to the fluid reservoir 2560, as described in further detail herein.

[1187] As shown in FIG. 54, the plunger 2575 has a proximal end portion 2576 and a distal end portion 2577. The distal end portion 2577 of the plunger 2575 includes and/or is coupled to an elastomeric member 2578 or the like. For example, in some embodiments, the elastomeric member 2578 can form a substantially fluid tight seal with an inner surface of the fluid reservoir 2560. As described above, the plunger 2575 is movably disposed within the inner volume 2564 of the fluid reservoir 2560. More specifically, the proximal end portion 2576 of the plunger 2575 is coupled to the second end portion 2572 of the actuator 2570 such that an actuation of the actuator 2570 results in a movement of the plunger 2570 within the inner volume 2564.

[1188] For example, a user can exert a force on the first end portion 2571 (e.g., with his or her thumb or finger) of the actuator 2570, which in turn, results in a pivoting motion about the protrusion 2569 that places the first end portion 2571 in a position closer to an outer surface of the fluid reservoir 2560 and places the second end portion 2572 in a corresponding position farther away from the fluid reservoir 2560. In other words, the pivoting of the actuator 2570 about the protrusion 2569 moves the second end portion 2572 in a proximal direction. Moreover, the trigger arrangement of the actuator 2570 (as described above) defines a range of motion through which the actuator 2570 can pivot and thus, defines a range of motion through which the plunger 2575 is moved in the proximal direction (i.e., a stroke length). As such, the user can serially actuate the actuator 2570 to move the plunger 2575 a desired distance in the proximal direction.

[1189] With the elastomeric member 2578 of the plunger 2575 forming a substantially fluid tight seal with the inner surface of the fluid reservoir 2560, the proximal movement of the plunger 2575 relative to the fluid reservoir 2560 produces a negative pressure within a portion of the inner volume 2564 that is distal to the elastomeric member 2578. Thus, when the fluid reservoir is coupled to an adapter and/or any other suitable lumen-defining device in fluid communication with the body of a patient, the negative pressure results in a suction force within that lumen that can draw a bodily-fluid (e.g., blood) through the lumen and into the inner volume 2564 of the fluid reservoir 2560. Moreover, by limiting the stroke length

(as described above) of the plunger 2575, a rate at which the plunger 2575 can be moved within the inner volume 2564 is reduced, limited, modulated, and/or otherwise at least partially controlled. As a result, a negative pressure and/or a suction force drawn through, for example, the lumen of the lumen-defining device is correspondingly controlled and/or modulated. Therefore, by limiting the stroke of the plunger 2575, a negative pressure within the inner volume 2564 of the fluid reservoir 2560 and/or a rate at which blood (or other bodily-fluid) flows into the inner volume 2564 can be controlled to an extent that can reduce and/or substantially prevent hemolysis of the blood that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like.

[1190] While the actuator 2570 is particularly shown in FIGS. 52 and 53, in other embodiments, the actuator 2570 can be any suitable device, mechanism, and/or member that is operative in moving the plunger 2575 within the fluid reservoir 2560. For example, while actuator 2570 is described above as being actuated by a user's thumb or finger, in other embodiments, and actuator can include a first end portion that extends a given length of the fluid reservoir as to be engaged by a user's palm or more than one finger (e.g., each finger excluding the thumb of the user). In other embodiments, a fluid reservoir can include an actuator that is a switch, a push button, a toggle, and/or the like configured to close an electric circuit or the like when actuated. Thus, when the electric circuit is closed, a current can flow through the electric circuit, for example, to a mechanism (e.g., including an electric motor) configured to move a plunger within the fluid reservoir.

[1191] FIGS. 54-56 illustrate a fluid reservoir 2660 according to another embodiment. The fluid reservoir 2660 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 2660 is a syringe or the like, as shown in FIG. 54. The fluid reservoir 2660 has a proximal end portion 2661 and a distal end portion 2662 and defines an inner volume 2664 (see e.g., 56). The distal end portion 2662 is configured to be physically and fluidically coupled to an adapter (not shown in FIGS. 54-56) such as, for example, the adapter 2430 described above with reference to FIGS. 48-51.

[1192] The proximal end portion 2661 of the fluid reservoir 2660 movably receives a plunger 2675 that is at least partially disposed in the inner volume 2664. As shown in FIGS. 55 and 56, the plunger 2675 has a proximal end portion 2676 and a distal end portion 2677. The distal end portion 2677 of the plunger 2675 includes and/or is coupled to an elastomeric member 2678 or the like. For example, in some embodiments, the elastomeric member 2678

can form a substantially fluid tight seal with an inner surface of the fluid reservoir 2660, as described in detail above. The proximal end portion 2676 of the plunger 2675 is coupled to an actuator 2670. For example, in some embodiments, at least a portion of the actuator 2670 can be hollow and configured to be movably disposed (e.g., in an axial direction) about the proximal end portion 2676 of the plunger 2675. Expanding further, the proximal end portion 2676 of the plunger 2675 includes a set of protrusions 2676A or the like (e.g., tabs, pins, bumps, etc.) configured to engage and/or otherwise disposed in a corresponding set of openings 2670A when the actuator 2670 is disposed about the proximal end portion 2676. In some embodiments, each protrusion 2676A can include an indicator or the like that can be viewable when disposed in a corresponding opening 2670A of the actuator 2670, as described in further detail herein.

[1193] As shown in FIGS. 55 and 56, the plunger 2675 includes a bias member 2674 (e.g., a linear spring, a torsion spring, and/or the like) disposed between the proximal end portion 2676 and the actuator 2670. In this manner, the bias member 2674 can, for example, maintain the actuator 2670 is a substantially fixed position relative to the proximal end portion 2676 until a force is exerted on the actuator 2670 or the plunger 2675 that is sufficient to overcome a force exerted by the bias member 2674. For example, in some embodiments, a user can manipulate the fluid reservoir 2660 to fluidically couple the distal end portion 2662, for example, to an adapter (e.g., the adapter 2430), which in turn can be directly or indirectly coupled to a device in fluid communication with a portion of the body. Thus, the inner volume 2664 of the fluid reservoir 2660 is placed in fluid communication with the portion of the body. With the fluid reservoir 2660 in fluid communication with the portion of the body, the user can manipulate the actuator 2670, for example, to move the plunger 2675 within the inner volume 2664. For example, a user can exert a force on the actuator 2670 to move the actuator 2670 and the plunger 2675 in the proximal direction relative to the fluid reservoir 2660. The arrangement of the bias member 2674 can be such that at least a portion of the force exerted by the user on the actuator 2670 transitions the bias member 2674 from a first configuration (e.g., a compressed configuration) to a second configuration (e.g., an extended configuration). Thus, the bias member 2674 can absorb at least a portion of the force (e.g., an excess portion of force above a predetermined threshold), exerted by the user, that would otherwise be exerted on the plunger 2675. In this manner, a rate at which the plunger 2675 is moved within the inner volume 2664 can be at least partially controlled and/or otherwise limited, which in turn, can reduce and/or substantially prevent hemolysis of the blood drawn

into the inner volume 2664 that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like.

[1194] In some embodiments, the arrangement of the protrusions 2676A of the proximal end portion 2676 within the openings 2670A of the actuator 2670, for example, can define a range of motion of the actuator 2670 relative to the plunger 2675 (e.g., can prevent a movement of the actuator 2675 beyond a predetermined threshold relative to the plunger 2675. In some embodiments, the protrusions 2676A can each include an indicator or the like that are viewable through the openings 2670A and therefore, can provide an indication to the user associated with the movement of the actuator 2670 relative to the plunger 2675. For example, in some embodiments, when a force is exerted on the actuator 2670 that is greater than a predetermined threshold, the actuator 2670 can be moved relative to the plunger 2675 and at least a portion of the force can transition the bias member 2674 from its first configuration to its second configuration. Thus, when the bias member 2674 is in its second configuration (e.g., an extended configuration), the actuator 2670 can be in a position relative to the plunger 2675 that is associated with at least a portion of the indicator of the protrusions 2676A being viewable through the openings 2670A. As such, the indicators can provide a visual indication of when a force exerted by the user exceeds a predetermined threshold. In some embodiments, the arrangement of the protrusions 2676A and the openings 2670A can be such that when a force exerted on the actuator 2670 exceeds the predetermined threshold, the plunger 2675 and/or the actuator 2670 also provide an auditory (e.g., a clicking sound) or a haptic indication.

[1195] While the actuators 2570 and 2670 are particularly shown and described above, in other embodiments, a fluid reservoir can include any suitable actuator operable in moving a plunger within an inner volume of the fluid reservoir. For example, FIGS. 57 and 58 illustrate a fluid reservoir 2760 according to another embodiment. The fluid reservoir 2760 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 2760 is a syringe or the like, as shown in FIG. 57. The fluid reservoir 2760 has a proximal end portion 2761 and a distal end portion 2762 and defines an inner volume 2764 (see e.g., 56). The distal end portion 2762 is configured to be physically and fluidically coupled to an adapter (not shown in FIGS. 57 and 58) such as, for example, the adapter 2430 described above with reference to FIGS. 48-51. The proximal end portion 2761 of the fluid reservoir 2760 movably receives a plunger 2775 that is at least partially disposed in the inner

volume 2764. As shown in FIG. 58, the plunger 2775 has a proximal end portion 2776 and a distal end portion 2777. The distal end portion 2777 of the plunger 2775 includes and/or is coupled to an elastomeric member 2778 or the like, as described in detail herein. The proximal end portion 2776 of the plunger 2775 is coupled to an actuator 2770 operable in moving the plunger 2775 relative to the fluid reservoir 2760.

[1196] The actuator 2770 can be any suitable shape, size, or configuration. For example, as shown in FIGS. 57 and 58, the actuator 2770, in this embodiment, is a dial rotatably coupled to the fluid reservoir 2760 and the plunger 2775. More specifically, the actuator 2770 can be disposed about the proximal end portion 2761 of the fluid reservoir 2760 such that the actuator 2770 can rotate relative thereto without, for example, unthreading or removing the actuator 2770 from the fluid reservoir 2760. In other words, the actuator 2770 can be coupled to the proximal end portion 2761 of the fluid reservoir 2760 for rotational motion while substantially preventing a linear motion of the actuator 2770 relative to the fluid reservoir 2760. As shown in FIG. 58, an outer surface of the plunger 2775 includes and/or otherwise forms a set of continuous threads 2775A arranged in a helical manner along a length of the plunger 2775 (e.g., substantially the entire length). Moreover, a portion of the plunger 2775 is configured to extend through, for example, a threaded opening defined by the actuator 2770. Thus, the set of threads 2775A engage a surface of the actuator 2770 to define a threaded coupling therebetween, which can allow the plunger 2775 to be moved in an axial direction within the inner volume 2764 of the fluid reservoir 2760.

[1197] Specifically, in use, the fluid reservoir 2760 can be manipulated to couple the distal end portion 2762 to an adapter or other device in fluid communication with a portion of the body, thereby placing the inner volume 2764 of the fluid reservoir 2760 in fluid communication with the portion of the body and/or intervening device (e.g. catheter, etc.). With the inner volume 2764 in fluid communication with the portion of the body, the actuator 2770 can be rotated relative to the fluid reservoir 2760, which in turn, results in the threads 2775A being advanced along a surface of the actuator 2770. Thus, the plunger 2775 is moved in an axial direction (e.g., a proximal direction) within the inner volume 2764, which in turn, increases a portion of the inner volume 2764 that is distal to the elastomeric member 2778. Such an increase results in, for example, a negative pressure within the portion of the inner volume 2764 distal to the elastomeric member 2778 and therefore, a suction force is exerted that is operable in drawing a bodily-fluid (i.e., blood) into the inner volume 2764 of

the fluid reservoir 2760. In some embodiments, the arrangement of the actuator 2770 and the plunger 2775 (i.e., the threaded coupling) limits a rate at which the plunger 2775 is moved within the inner volume 2764. In this manner, limiting the rate at which the plunger 2775 is moved within the inner volume 2764 can reduce and/or substantially prevent hemolysis of the blood drawn into the inner volume 2764 that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like.

[1198] While the actuator 2770 is shown and described above as forming a threading coupling with the plunger 2775, in other embodiments, a fluid reservoir can include an actuator that is monolithically formed with a plunger. For example, FIG. 59 illustrates a fluid reservoir according to another embodiment. The fluid reservoir 2860 has a proximal end portion 2861 and a distal end portion 2862 and defines an inner volume 2864. The distal end portion 2862 is configured to be physically and fluidically coupled to an adapter (not shown in FIG. 59) such as, for example, the adapter 2430 described above with reference to FIGS. 48-51. In this embodiment, the fluid reservoir 2860 includes an outer surface that defines a set of continuous threads arranged in a helical manner along a length of the fluid reservoir 2860, as described above with reference to the plunger 2775 in FIG. 58.

[1199] The fluid reservoir 2860 is rotatably coupled to an actuator 2870. The actuator 2870 includes a proximal end portion 2871, a distal end portion 2872, and a plunger 2875. The actuator 2870 further includes an inner surface that defines a set of continuous threads 2899 (e.g., female threads or grooves) arranged in a helical manner along a length of the inner surface. In this manner, the actuator 2870 can be disposed about the fluid reservoir 2860 such that the set of threads 2860A of the fluid reservoir 2860 are disposed within the corresponding set of threads 2899 of the actuator 2870, while the plunger 2875 extends from the proximal end portion 2871 of the actuator 2870 within the inner volume 2864 of the fluid reservoir 2860. Moreover, as shown in FIG. 59, a distal end portion 2877 of the plunger 2875 includes and/or is coupled to an elastomeric member 2878 configured to form a substantially fluid tight seal with an inner surface of the fluid reservoir 2860, as described in detail herein.

[1200] Thus, in use, the fluid reservoir 2860 can be manipulated to couple the distal end portion 2862 to an adapter or other device in fluid communication with a portion of the body, thereby placing the inner volume 2864 of the fluid reservoir 2860 in fluid communication with the portion of the body. With the inner volume 2864 in fluid communication with the

portion of the body, the actuator 2870 can be rotated relative to the fluid reservoir 2860, which in turn, results in the threads 2899 of the actuator 2870 being advanced along the corresponding threads 2860A of the fluid reservoir 2860. Thus, the actuator 2870 can be moved in the proximal direction relative to the fluid reservoir 2860, which results in the plunger 2875 being moved in an axial direction (e.g., a proximal direction) within the inner volume 2864. As such, a portion of the inner volume 2864 that is distal to the elastomeric member 2878 is increased. Such an increase results in, for example, a negative pressure within the portion of the inner volume 2864 distal to the elastomeric member 2878 and therefore, a suction force is exerted that is operable in drawing a bodily-fluid (i.e., blood) into the inner volume 2864 of the fluid reservoir 2860. In some embodiments, the arrangement of the actuator 2870 and the fluid reservoir 2860 (i.e., the threaded coupling) limits a rate at which the plunger 2875 is moved within the inner volume 2864. In this manner, limiting the rate at which the plunger 2875 is moved within the inner volume 2864 can reduce and/or substantially prevent hemolysis of the blood drawn into the inner volume 2864 that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like.

[1201] FIG. 60 illustrates a fluid reservoir 2960 according to another embodiment. The fluid reservoir 2960 can be any suitable shape, size, or configuration. For example, in this embodiment, the fluid reservoir 2960 can be configured to receive a portion of an actuator 2970 (e.g., arranged as a syringe or the like), as described in further detail herein. The fluid reservoir 2960 has a first chamber 2990 and a second chamber 2991, which are formed unitarily (e.g., joined at a proximal end portion of the fluid reservoir 2960. The first chamber 2990 includes a proximal end portion 2961 and a distal end portion 2962 and defines an inner volume 2964. The distal end portion 2962 is configured to be physically and fluidically coupled to an adapter such as, for example, the adapter 2430 described above with reference to FIGS. 48-51. The proximal end portion 2961 movably receives a first plunger 2975 of the actuator 2970, which is at least partially disposed in the inner volume 2964, as described in further detail herein. In this manner, the first chamber 2990 is configured to receive and at least temporarily store a volume of bodily-fluid, as described in further detail herein.

[1202] Similarly, the second chamber 2991 includes a proximal end portion 2992 and a distal end portion 2993 and defines an inner volume 2994. The distal end portion 2993 of the second chamber 2991 is closed (i.e., does not define a port or other opening). The proximal

end portion 2992 movably receives a second plunger 2995 of the actuator 2970, which is at least partially disposed in the inner volume 2994, as described in further detail herein. As shown in FIG. 60, the second chamber 2991 has a size and/or shape that are/is smaller than the first chamber 2990. Thus, in some embodiments, the second chamber 2991 can be an auxiliary chamber or the like. For example, with the distal end portion 2993 of the second chamber 2991 being closed and/or sealed, in this embodiment, the second chamber 2991 can act as a dampener or the like configured to dampen a movement of the actuator 2970 relative to the fluid reservoir 2960.

[1203] As described above, the actuator 2970 includes the first plunger 2975 movably disposed in the inner volume 2964 of the first chamber 2990 and the second plunger 2995 movably disposed in the inner volume 294 of the second chamber 2991. As shown in FIG. 60, the first plunger 2975 has a proximal end portion 2976 and a distal end portion 2977. The proximal end portion 2976 of the first plunger 2975 is coupled to and/or otherwise unitarily formed a proximal end portion 2996 of the second plunger 2995. The distal end portion 2977 of the first plunger 2975 includes and/or is coupled to an elastomeric member 2978 or the like. In some embodiments, the elastomeric member 2978 can form a substantially fluid tight seal with an inner surface of the first chamber 2990, as described in detail above. Similarly, the second plunger 2995 has the proximal end portion 2996 and a distal end portion 2997. The proximal end portion 2996 of the second plunger 2995 is coupled to and/or otherwise unitarily formed with the proximal end portion 2976 of the first plunger 2975. The distal end portion 2997 of the second plunger 2995 includes and/or is coupled to an elastomeric member 2998. As described above with reference to the elastomeric member 2978, the elastomeric member 2998 of the second plunger 2995 can form a substantially fluid tight seal with an inner surface of the second chamber 2991. In this manner, the actuator 2970 can be moved relative to the fluid reservoir 2960 to move the first plunger 2975 within the inner volume 2964 of the first chamber 2990 and the second plunger 2995 within the inner volume 2994 of the second chamber 2991 in a substantially concurrent movement, as described in further detail herein.

[1204] In use, for example, the fluid reservoir 2960 can be manipulated to couple the distal end portion 2962 to an adapter or other device in fluid communication with a portion of the body, thereby placing the inner volume 2964 of the fluid reservoir 2960 in fluid communication with the portion of the body and/or intervening device (e.g. catheter, etc.).

Once the inner volume 2964 is placed in fluid communication with the portion of the body, the actuator 2970 can be moved in the proximal direction relative to the fluid reservoir 2960, which in turn, moves the first plunger 2975 within the inner volume 2964. More specifically, with the elastomeric member 2978 of the plunger 2975 forming a substantially fluid tight seal with the inner surface of the fluid reservoir 2960, the proximal movement of the first plunger 2975 relative to the fluid reservoir 2960 produces a negative pressure within a portion of the inner volume 2964 that is distal to the elastomeric member 2978. Thus, when the fluid reservoir is coupled to an adapter and/or any other suitable lumen-defining device in fluid communication with the body of a patient, the negative pressure results in a suction force within that lumen that can draw a bodily-fluid (e.g., blood) through the lumen and into the inner volume 2964 of the fluid reservoir 2960.

[1205] In a similar manner, the proximal movement of the actuator 2970 moves the second plunger 2995 within the inner volume 2994 of the second chamber 2991 substantially concurrently with the first plunger 2975, thereby increasing a portion of the inner volume 2994 that is distal to the elastomeric member 2998. With the elastomeric member 2998 of the second plunger 2995 forming a substantially fluid tight seal with the inner surface of the second chamber 2991, such an increase in the portion of the inner volume 2994 that is distal to the elastomeric results in a negative pressure within that portion of the inner volume 2994. Moreover, with the distal end portion 2993 of the second chamber 2991 being closed and/or sealed, the movement of the second plunger 2995 within the second chamber 2991, for example, can act to dampen the movement of the actuator 2970 relative to the fluid reservoir 2960. Specifically, the increase of the portion of the inner volume 2994 distal to the elastomeric member 2998 produces, for example, a suction force therein that resists the proximal movement of the second plunger 2995. Thus, an effective force exerted on the actuator 2970 to move the first plunger 2975 within the first chamber 2990 and the second plunger 2995 within the second chamber 2991 can be modulated, reduced, limited, and/or otherwise controlled, which in turn, can limit a rate at which the actuator 2970 is moved relative to the fluid reservoir 2960. In other words, the arrangement of the second chamber 2991 and the second plunger 2995 dampen the force exerted on the actuator 2970 and thus, the movement of the actuator 2970 relative to the fluid reservoir 2960. Therefore, by limiting the rate at which the actuator 2970 is moved relative to the fluid reservoir 2960, a negative pressure within the inner volume 2964 of the first chamber 2991 and/or a rate at which blood (or other bodily-fluid) flows into the inner volume 2964 can be controlled to an extent that

can reduce and/or substantially prevent hemolysis of the blood that can otherwise result from, inter alia, a volume of blood being exposed to a rapid pressure drop or the like.

[1206] While the embodiments are shown and described above as defining a single flow path from the patient to a fluid reservoir, in some embodiments, a fluid transfer device and/or system can include, for example, any suitable extension set, Y-adapter, T-adapter, junction, split, and/or the like configured to define more than one fluid flow path. Moreover, in such embodiments, a fluid transfer device and/or system can include any suitable coupling mechanism, lock mechanism, hub, and/or the like configured to couple, for example, a first lumen-defining device to a second lumen-defining device such that hemolysis of a flow of blood therethrough is limited and/or substantially prevented. For example, FIGS. 61-71 illustrate embodiments configured to mitigate the risk of hemolysis as blood flows through a multi-lumen adapter and/or the like. Specifically, FIGS. 61-63 illustrate a hub 3020 configured to receive a lumen-defining device 3080 according to an embodiment.

[1207] The hub 3020 has a proximal end portion 3021, a distal end portion 3022 and an inner surface 3023 defining a lumen 3024 therethrough (see e.g., FIG. 63). The distal end portion 3022 of the hub 3020 includes and/or is coupled to a cannula 3022A and/or other suitable lumen-defining device. Although not shown in FIGS. 61-63, in some embodiments, the cannula 3022A can be coupled to an adapter, a restrictor, locking mechanism, and/or the like. In some embodiments, the cannula 3022A can be, for example, an indwelling cannula with a distal end portion disposed within the body of a patient. In other embodiments, the distal end portion 3022 of the hub 3020 can include and/or can form a locking mechanism configured to physically and fluidically couple the hub 3020 to any suitable device. The proximal end portion 3021 of the hub 3020 includes and/or is coupled to a proximal cap 3027 and an actuator 3045. For example, in some embodiments, the proximal cap 3027 can be coupled to the proximal end portion 3021 via a press fit, a snap fit, a friction fit, a threaded coupling, an adhesive, ultrasonic welding and/or the like. Moreover, the proximal cap 3027 defines an opening 3028 that is, for example, substantially aligned with the lumen 3024 defined by the inner surface 3023. In this manner, a portion of the lumen-defining device 3080 can be inserted through the opening 3028 of the proximal cap 3027 to be disposed within the hub 3020, as described in further detail herein.

[1208] As shown in FIGS. 62 and 63, the actuator 3045 is disposed between the proximal end portion 3021 and the proximal cap 3027. More specifically, the actuator 3045 forms a

substantially annular ring or the like that is movably disposed within a space defined between a proximal surface of the hub 3020 and a distal surface of the proximal cap 3027. In this manner, the actuator 3045 defines an opening 3046 that can be selectively aligned with the opening 3028 of the proximal cap 3027 and the inner surface 3023 of the hub 3020. Moreover, the actuator 3045 includes and/or is coupled to a bias member 3047 (see e.g., FIG. 62), which can exert a force to temporarily maintain the actuator 3045 in a predetermined position relative to the hub 3020, for example, until a force is exerted on the actuator 3045 sufficient to overcome the force exerted by the bias member 3047, as described in further detail herein.

[1209] As shown in FIG. 63, the inner surface 3023 of the hub 3020 defines the lumen 3024 extending through its proximal end portion 3021 and its distal end portion 3022, which is configured to receive a portion of the lumen-defining device 3080. Furthermore, the inner surface 3023 includes and/or otherwise forms a shoulder 3025. In this embodiment, the shoulder 3025 is associated with a change in diameter of the inner surface 3023. For example, a first portion of the inner surface 3023 (e.g., a proximal portion) can have a first diameter that is larger than a diameter of a second portion of the inner surface (e.g., a distal portion). In this manner, the shoulder 3025 can be placed in contact with a surface of the lumen-defining device 3080 when inserted therein, as described in further detail herein.

[1210] The hub 3020 further includes a valve 3026 disposed within the lumen 3024. The valve 3026 can be, for example, a one-valve, a port, and/or the like, which can be transitioned between a first, substantially closed configuration and a second, substantially opened configuration. Thus, when in the first configuration, the valve 3026 can fluidically isolate a portion of the lumen 3024 that is proximal to the valve 3026 from a portion of the lumen 3024 that is distal to the valve 3026. Conversely, when the valve 3026 is in the second configuration, the lumen 3024 can define a fluid flow path substantially through the hub 3020. In some embodiments, the insertion of the portion of the lumen-defining device 3080 can be operable in transitioning the valve 3026 from the first configuration to the second configuration, as described in further detail herein.

[1211] The lumen-defining device 3080 has a proximal end portion 3031, a distal end portion 3032, and a flange 3086. The lumen-defining device 3080 also defines a notch 3085 and a lumen 3083 extending through the proximal end portion 3081 and the distal end portion 3082, as described in further detail herein. As shown in FIGS. 62 and 63, the distal end

portion 3082 of the lumen-defining device 3080 is configured to be inserted through the proximal cap 3027 and the actuator 3045 to be disposed within the hub 3020, as described in further detail herein. Moreover, the lumen-defining device 3080 includes a seal member 3087 disposed about an outer surface of the distal end portion 3082, which is placed in contact with the inner surface 3023 of the hub 3020 which the lumen-defining device 3080 is disposed therein.

[1212] As shown, for example, in FIGS. 61 and 63, the proximal end portion 3081 of the lumen-defining device 3080 is physically and fluidically coupled to a cannula 3088. The cannula 3088 can be any suitable configuration. For example, in this embodiment, the cannula 3088 is a bifurcated cannula having a first portion 3088A and a second portion 3088B (also referred to herein as a "first cannula" and a "second cannula," respectively). The first portion 3088A and second portion 3088B can be physically and fluidically coupled to any suitable device (e.g., at a proximal end). For example, as shown in FIG. 61, the second portion 3088B includes a port or locking mechanism that can physically and fluidically couple the second portion 3088B to, for example, a fluid source and/or the like. Although not shown, the first portion 3088A can include a port or the like substantially similar to that of the second portion 3088B that can physically and fluidically couple the first portion 3088A to, for example, a fluid reservoir and/or the like. In other embodiments, the first portion 3088A and the second portion 3088B can be arranged in any suitable manner and can each be physically and fluidically coupled to any suitable device, mechanism, and/or member included in a fluid transfer system.

[1213] In use, a portion of the lumen-defining device 3080 can be inserted into the hub 3020 to define a fluid flow path between the cannula 3022A, coupled to the distal end portion 3022 of the hub 3020, and the cannula 3088 coupled to the proximal end portion 3081 of the lumen-defining device 3080. More specifically, in some instances, a user can manipulate the hub 3020 by exerting a force on the actuator 3045, thereby moving the actuator 3045 from a first position, in which the opening 3046 of the actuator 3045 is substantially unaligned with the opening 3028 of the proximal cap 3027, to a second position, in which the opening 3046 is aligned with the opening 3028. Thus, with the actuator 3045 in the second position, the opening 3028 of the proximal cap 3027, the opening 3046 of the actuator 3046, and the lumen 3024 of the hub 3020 are sufficiently aligned to allow the distal end portion 3082 of the lumen-defining device 3080 to be inserted through the proximal cap 3027, the actuator

3045, and into the lumen 3024. As shown in FIG. 63, the lumen-defining device 3080 can be inserted into the hub 3020 by a predetermined amount that places the distal end portion 3082 extends through the valve 3026, thereby transitioning the valve 3026 from its first, substantially closed configuration to its second, substantially open configuration. Moreover, a distal surface of the lumen-defining device 3080 in contact with the shoulder 3025, as shown in FIG. 63.

[1214] With the distal surface of the lumen-defining device 3080 in contact with the shoulder 3025, the flange 3086 of the lumen-defining device 3080 is disposed within a recessed surface defined by the proximal cap 3027. In some embodiments, the shape and/or size of the recessed surface and the flange 3086 can be such that the lumen-defining device 3080 is placed into a predetermined radial position such that the lumen 3024 of the hub 3020 and the lumen 3083 of the lumen-defining device 3080 are substantially aligned, as shown in FIG. 63. Moreover, the seal member 3087 disposed about the outer surface at or near the distal end portion 3082 of the lumen-defining device 3080 is placed in contact with the inner surface 3023 of the hub 3020. In this manner, the arrangement of the flange 3086 disposed within the recessed surface of the proximal cap 3027 and the seal member 3087 in contact with the inner surface 3023 of the hub 3020, the lumen-defining device 3080 is placed in a predetermined radial position relative to the hub 3020. For example, in this embodiment, the lumen 3083 of the lumen-defining device 3080 and the lumen 3024 of the hub 3020 form a substantially continuous transition therebetween. That is to say, the lumens 3083 and 3024 are substantially aligned and/or a discontinuity defined therebetween is sufficiently minimized or obviated so as to not produce turbulence within a flow of bodily-fluid therethrough.

[1215] In addition, once the lumen-defining device 3080 is disposed in the desired and/or predetermined position within the hub 3020, the user can remove the force exerted on the actuator 3045. As such, the bias member 3047 can exert a force to move the actuator 3045 from its second position to its first position (e.g., a biased position). Thus, as shown in FIG. 63, the actuator 3045 is moved out of alignment with the hub 3020, resulting in a portion of the actuator 3045 being disposed in the notch 3085 defined by the lumen-defining device 3080, which in turn, can maintain the lumen-defining device 3080 in a substantially fixed position within the hub 3020. In this manner, a user can couple the first portion 3088A or the second portion 3088B of the cannula 3088 to, for example, a fluid reservoir such as those

described herein, which in turn, can exert a suction force (e.g., in response to a negative pressure differential) through the lumen-defining device 3080 and the hub 3020. Therefore, when the cannula 3022A is in fluid communication with the body of a patient (e.g., either directly or indirectly via an intervening structure), a volume of, for example, blood can be withdrawn with a reduced amount of hemolysis. Specifically, the alignment of the lumen 3024 defined by the hub 3020 and the lumen 3083 of the lumen-defining device 3080, for example, can reduce turbulence, eddy currents, and/or any other disturbance that can otherwise result from a discontinuity or the like. Thus, the flow of blood therethrough can be substantially laminar and substantially free of hemolysis.

[1216] Although the valve 3026 is particularly shown and described above with reference to FIGS. 62 and 63, in other embodiments, a hub can include any suitable valve. For example, FIGS. 64-66 illustrate a hub 3120 configured to receive a lumen-defining device 3180 according to another embodiment. The hub 3120 and the lumen-defining device 3080 can be substantially similar in form and/or function as the hub 3020 and the lumen-defining device 3080 described above with reference to FIGS. 61-63. Thus, such similar aspects are not described in further detail herein.

[1217] As shown in FIGS. 64-66, the hub 3120 has a proximal end portion 3121, a distal end portion 3122, and an inner surface 3123 defining a lumen 3124 therethrough (see e.g., FIG. 66). The distal end portion 3122 of the hub 3120 includes and/or is coupled to a cannula 3122A and/or other suitable lumen-defining device. While the hub 3020 is shown and described as being coupled to a single cannula and/or a cannula defining a single lumen, in this embodiment, the hub 3120 is coupled to a bifurcated cannula having a first portion (also referred to herein as "first cannula" or "cannula 3122A") and a second portion 3122B. In other embodiments, the hub 3120 can be coupled to a single cannula and/or a cannula defining a single lumen. The proximal end portion 3121 of the hub 3120 includes and/or is coupled to a proximal cap 3127 and an actuator 3145, as described in detail above. The proximal cap 3127 defines an opening 3128 that is, for example, substantially aligned with the lumen 3124 defined by the inner surface 3123. In this manner, a portion of the lumen-defining device 3180 can be inserted through the opening 3128 of the proximal cap 3127 to be disposed within the hub 3120, as described in further detail herein.

[1218] As shown in FIGS. 65 and 66, the actuator 3145 is disposed between the proximal end portion 3121 and the proximal cap 3128. The actuator 3145 forms a substantially annular

ring or the like that is movably disposed within a space defined between a proximal surface of the hub 3120 and a distal surface of the proximal cap 3127. In addition, the actuator 3145 includes and/or is coupled to a bias member 3147, which can exert a force to temporarily maintain the actuator 3145 in a predetermined position relative to the hub 3120, for example, until a force is exerted on the actuator 3145 sufficient to overcome the force exerted by the bias member 3147. In this manner, the arrangement of the proximal end portion 3121 of the hub 3120, the proximal cap 3127, and the actuator 3145 can be substantially similar to the proximal end portion 3021 of the hub 3020, the proximal cap 3027, and the actuator 3045 described above with reference to FIGS. 62 and 63.

[1219] As shown in FIG. 66, the inner surface 3123 of the hub 3120 defines the lumen 3124 extending through its proximal end portion 3121 and its distal end portion 3122, which is configured to receive a portion of the lumen-defining device 3180. Furthermore, the inner surface 3123 includes a valve and a sealing surface 3125. As shown in FIG. 66, in this embodiment, the valve is a ball valve 3126, which can be transitioned between a first, substantially closed configuration and a second, substantially opened configuration. More specifically, the hub 3120 includes a bias member 3148 in contact with the ball valve 3126. In this manner, the bias member 3148 can exert a force on the ball valve 3126 that places the ball valve 3126 in contact with the sealing surface 3125. Thus, a contact sufficient to maintain a substantially fluid tight seal can be maintained when the ball valve 3126 is in contact with the sealing surface 3125 (e.g., in the first configuration) via a force exerted by the bias member 3148. Conversely, when a force exerted on the ball valve 3126, opposite the force exerted by the bias member 3148, is sufficient to overcome the force exerted by the bias member 3148, the ball valve 3126 can be removed from contact with the sealing surface 3125 and thus, a fluid flow path can be defined therethrough. In some embodiments, the insertion of the portion of the lumen-defining device 3180 can be operable in transitioning the ball valve 3126 from the first configuration to the second configuration, as described in further detail herein.

[1220] The lumen-defining device 3180 has a proximal end portion 3181, a distal end portion 3182, and a flange 3186. The lumen-defining device 3180 also defines a notch 3185 and a lumen 3183 extending through the proximal end portion 3181 and the distal end portion 3182, as described in further detail herein. As shown, for example, in FIGS. 64-66, the proximal end portion 3181 of the lumen-defining device 3180 is physically and fluidically

coupled to a cannula 3188. The cannula 3188 can be any suitable configuration. For example, in this embodiment, the cannula 3188 is a single cannula and/or a cannula that defines a single lumen. In other embodiments, the cannula 3188 can be a bifurcated cannula, as described in detail above with reference to the cannula 3088 in FIG. 61. Moreover, although not shown in FIGS. 64-66, the cannula 3188 can include any suitable port, locking mechanism, and/or the like, as described above.

[1221] As shown in FIGS. 65 and 66, the distal end portion 3182 of the lumen-defining device 3180 is configured to be inserted through the proximal cap 3127 and the actuator 3145 to be disposed within the hub 3120, as described in further detail herein. Moreover, the lumen-defining device 3180 includes a seal member 3187 disposed about an outer surface of the distal end portion 3182, which is placed in contact with the inner surface 3123 of the hub 3120 which the lumen-defining device 3180 is disposed therein. As shown in FIG. 66, the lumen 3183 of defined by the lumen-defining device 3080 at or near the distal end portion 3182 is diverted, for example, into one or more channels and defining a substantially smooth transition therebetween. In some embodiments, the one or more channels, for example, can be offset from the lumen 3183 (e.g., non-coaxial). In other words, each channel is radially offset from a longitudinal centerline CL, as shown in FIG. 66. Thus, when a distal surface of the lumen-defining device 3180 is placed in contact with, for example, the ball valve 3126, the channels and/or the lumen 3183 are/is substantially unobstructed, as described in further detail herein.

[1222] In use, a portion of the lumen-defining device 3180 can be inserted into the hub 3120 to define a fluid flow path between the cannula 3122A, coupled to the distal end portion 3122 of the hub 3120, and the cannula 3188 coupled to the proximal end portion 3181 of the lumen-defining device 3180. More specifically, in some instances, a user can manipulate the hub 3120 by exerting a force on the actuator 3145, thereby moving the actuator 3145 from a first position, in which the opening 3146 of the actuator 3145 is substantially unaligned with the opening 3128 of the proximal cap 3127, to a second position, in which the opening 3146 is aligned with the opening 3128, as described in detail above. As shown in FIG. 66, the lumen-defining device 3180 can be inserted into the hub 3120 by a predetermined amount that places a distal surface of the lumen-defining device 3180 in contact with the ball valve 3126. In this manner, the lumen-defining device 3180 can be inserted into the hub 3180 until the flange 3186 of the lumen-defining device 3180 is disposed within a recessed surface

defined by the proximal cap 3127, thereby aligning the lumen-defining device 3180, as described in detail above. Moreover, the seal member 3187 disposed about the outer surface at or near the distal end portion 3182 of the lumen-defining device 3180 is placed in contact with the inner surface 3123 of the hub 3120. In this manner, the lumen-defining device 3180 can be inserted into a position that removes the ball valve 3126 from the sealing surface 3125, thereby defining a fluid flow path between the lumen 3124 of the hub 3120 and the lumen 3183 (and/or channels) of the lumen-defining device 3180.

[1223] Once the lumen-defining device 3180 is disposed in the desired and/or predetermined position within the hub 3120, the user can remove the force exerted on the actuator 3145. As such, the bias member 3147 can exert a force to move the actuator 3145 from its second position to its first position (e.g., a biased position), resulting in a portion of the actuator 3145 being disposed in the notch 3185 defined by the lumen-defining device 3180. Thus, the actuator 3145 can maintain the lumen-defining device 3180 in a substantially fixed position within the hub 3120, as described in detail above. In this manner, a user can couple the cannula 3188, for example, to a fluid reservoir such as those described herein. Therefore, when the cannula 3122A is in fluid communication with the body of a patient (e.g., either directly or indirectly via an intervening structure), a volume of, for example, blood can be withdrawn with a reduced amount of hemolysis, as described in detail above. Specifically, the alignment of the lumen 3124 defined by the hub 3120 and the channels and/or lumen 3183 of the lumen-defining device 3180, for example, can reduce turbulence, eddy currents, and/or any other disturbance that can otherwise result from a discontinuity or the like. Thus, the flow of blood therethrough can be substantially laminar and substantially free of hemolysis.

[1224] Although the hubs 3020 and 3120 have a proximal end portion including an actuator, in other embodiments, a hub can have any suitable configuration and need not include an actuator. For example, FIGS. 67 and 68 illustrate a hub 3320 configured to receive a lumen-defining device 3280 according to another embodiment. The hub 3220 and the lumen-defining device 3280 can be substantially similar in form and/or function as the hub 3020 and the lumen-defining device 3080 and/or the hub 3120 and the lumen-defining device 3180, described in detail above. Thus, such similar aspects are not described in further detail herein. As shown in FIGS. 67 and 68, the hub 3220 has a proximal end portion 3221, a distal end portion 3222, a secondary port 3289, and an inner surface 3223 defining a

lumen 3224 therethrough (see e.g., FIG. 68). The hub 3220 further includes a valve 3226 disposed within the lumen 3224, as described in further detail herein.

[1225] The distal end portion 3222 of the hub 3220 includes and/or is coupled to a cannula 3222A and/or other suitable lumen-defining device, as described above with reference to the hub 3020 in FIGS. 61-63. The proximal end portion 3221 of the hub 3220 includes and/or is coupled to a proximal cap 3227. As shown in FIGS. 67 and 68, in this embodiment, the proximal cap 3237 can be, for example, a locking mechanism or the like configured to form a treaded coupling with a portion of the lumen-defining device 3280, as described in further detail herein.

[1226] As shown in FIG. 68, the inner surface 3223 of the hub 3220 defines the lumen 3224 extending through its proximal end portion 3221 and its distal end portion 3222, which is configured to receive a portion of the lumen-defining device 3280. Furthermore, the inner surface 3223 includes and/or otherwise forms a shoulder 3225. In this embodiment, the shoulder 3225 is associated with a change in diameter of the inner surface 3223. For example, a first portion of the inner surface 3223 (e.g., a proximal portion) can have a first diameter that is larger than a diameter of a second portion of the inner surface (e.g., a distal portion). In this manner, the shoulder 3225 can be placed in contact with a surface of the lumen-defining device 3280 when inserted therein, as described in detail above with reference to the hub 3020. In some embodiments, the shoulder 3225 can form, for example, a seat or a recessed portion configured to receive a portion of the lumen-defining device 3280.

[1227] The valve 3226 of the hub 3220 can be, for example, a one-valve, a port, and/or the like, which can be transitioned between a first, substantially closed configuration and a second, substantially opened configuration. Thus, when in the first configuration, the valve 3226 can fluidically isolate a portion of the lumen 3224 that is proximal to the valve 3226 from a portion of the lumen 3224 that is distal to the valve 3226. Conversely, when the valve 3226 is in the second configuration, the lumen 3224 can define a fluid flow path substantially through the hub 3220. In some embodiments, the insertion of the distal end portion 3282 of the lumen-defining device 3280 can be operable in transitioning the valve 3226 from the first configuration to the second configuration, as described in further detail herein.

[1228] The secondary port 3289 of the hub 3280 can be any suitable port or the like. For example, in some embodiments, the hub 3220 can be arranged as a T-adapter or the like, in

which the proximal end portion 3221 defines a first port and the secondary port 3289 extends in a substantially perpendicular direction from the first port. In this manner, the secondary port 3289 is in fluid communication with the lumen 3224 defined by the hub 3220 and can be configured to receive and/or deliver a fluid from and/or to the lumen 3224 of the hub 3220. Moreover, the arrangement of the secondary port 3289 is such that when the valve 3226 is in its closed configuration, the secondary port 3289 is fluidically isolated from a portion of the lumen 3224 proximal to the valve 3226.

[1229] The lumen-defining device 3080 has a proximal end portion 3031, a distal end portion 3032, and a flange 3086. The lumen-defining device 3080 also defines a notch 3085 and a lumen 3083 extending through the proximal end portion 3081 and the distal end portion 3082, as described in further detail herein. As shown in FIGS. 62 and 63, the distal end portion 3082 of the lumen-defining device 3080 is configured to be inserted through the proximal cap 3027 and the actuator 3045 to be disposed within the hub 3020, as described in further detail herein. Moreover, the lumen-defining device 3080 includes a seal member 3087 disposed about an outer surface of the distal end portion 3082, which is placed in contact with the inner surface 3023 of the hub 3020 which the lumen-defining device 3080 is disposed therein.

[1230] The lumen-defining device 3280 has a proximal end portion 3281 and a distal end portion 3282, and defines a lumen 3283 therethrough. As shown, for example, in FIG. 68, the proximal end portion 3281 of the lumen-defining device 3280 is physically and fluidically coupled to a cannula 3288. The cannula 3288 can be any suitable configuration. For example, in this embodiment, the cannula 3288 is a single cannula and/or a cannula that defines a single lumen. In some embodiments, the cannula 3288 can be substantially similar to the cannula 3188 described above wither reference to FIGS. 64-66.

[1231] As shown in FIG. 68, the distal end portion 3282 of the lumen-defining device 3280 is configured to be inserted through the proximal cap 3227 to be disposed within the hub 3220. More specifically, a portion of the lumen-defining device 3280 can be inserted into the proximal cap 3227 and configured to form, for example, a threaded coupling or the like. For example, in some embodiments, a portion of an outer surface of the lumen-defining device 3280 can include a set of treads or the like configured to engage a corresponding set of threads included in and/or defined by the proximal cap 3227. Thus, in use, as the lumen-defining device 3280 is inserted through the proximal cap 3227, the proximal cap 3227

and/or the lumen-defining device 3280 can be rotated to form the threaded coupling therebetween. Moreover, the arrangement of the lumen-defining device 3280 can be such that when coupled to the proximal cap 3227, the distal end portion 3282 of the lumen-defining device 3280 extends through the valve 3226. Thus, the valve 3226 is transitioned from its first, substantially closed configuration to its second, substantially open configuration. In some embodiments, the valve 3226 can be configured to form a substantially fluid tight seal about a portion of the lumen-defining device 3280, which in turn, can maintain the secondary port 3289 in fluid isolation from, for example, the lumen 3283 of the lumen-defining device 3280. Moreover, the lumen-defining device 3280 is advanced such that a distal surface of the lumen-defining device 3280 is in contact with the shoulder 3225, as shown in FIG. 68.

[1232] In this embodiment, the arrangement of the lumen-defining device 3280 and the proximal cap 3227 (i.e., the coupling therebetween) is such that the lumen 3283 of the lumen-defining device 3280 and the lumen 3224 of the hub 3220 form a substantially continuous transition therebetween. That is to say, the lumens 3283 and 3224 are substantially aligned and/or a discontinuity defined therebetween is sufficiently minimized or obviated so as to not produce turbulence within a flow of bodily-fluid therethrough. Therefore, when the cannula 3222A is in fluid communication with the body of a patient (e.g., either directly or indirectly via an intervening structure), a volume of, for example, blood can be withdrawn with a reduced amount of hemolysis. Specifically, the alignment of the lumen 3224 defined by the hub 3220 and the lumen 3283 of the lumen-defining device 3280, for example, can reduce turbulence, eddy currents, and/or any other disturbance that can otherwise result from a discontinuity or the like. Thus, the flow of blood therethrough can be substantially laminar and substantially free of hemolysis.

[1233] While the hubs 3020, 3120, and 3220 are shown and described above as receiving the lumen-defining devices 3080, 3180, and 3280 (e.g., a connector), respectively, in other embodiments, a hub can be configured to receive a terminated end of a cannula or the like (e.g., without a connector or other lumen-defining device). For example, FIGS. 69-71 illustrate a hub 3320 configured to receive a cannula 3388 according to another embodiment. The hub 3320 and the lumen-defining device 3080 can be substantially similar in form and/or function as the hub 3020 and the lumen-defining device 3080 and/or the hub 3120 and the

lumen-defining device 3180, described in detail above. Thus, such similar aspects are not described in further detail herein.

[1234] As shown in FIGS. 69-71, the hub 3320 has a proximal end portion 3321, a distal end portion 3322, and an inner surface 3323 defining a lumen 3324 therethrough (see e.g., FIG. 71). The distal end portion 3322 of the hub 3320 includes and/or is coupled to a cannula 3322A and/or other suitable lumen-defining device. In some embodiments, the distal end portion 3322 of the hub 3320 can be substantially similar to the distal end portion 3322 of the hub 3020 described above with reference to FIGS. 61-63. The proximal end portion 3321 of the hub 3320 includes and/or is coupled to a proximal cap 3327, as described in detail above. The proximal cap 3327 defines an opening 3328 that is, for example, substantially aligned with the lumen 3324 defined by the inner surface 3323. In this manner, a portion of the cannula 3388 can be inserted through the opening 3328 of the proximal cap 3327 to be disposed within the hub 3320, as described in further detail herein.

[1235] As shown in FIGS. 70 and 71, the proximal end portion 3321 of the hub 3320 further includes and or is coupled to a first coupling member 3345 and a second coupling member 3349. As described above with reference to the actuator 3145, the first coupling member 3345 is disposed between the proximal end portion 3321 and the proximal cap 3327. The first coupling member 3345 is configured to selective receive a portion of the second coupling member 3349. The second coupling member 3349 is configured to be disposed about a portion of the cannula 3388. Thus, the second coupling member 3349 can be inserted substantially concurrently with the cannula 3388. Moreover, the second coupling member 3349 is configured to engage the first coupling member 3345 disposed within the hub 3320, for example, to at least temporarily maintain the cannula 3388 in a fixed position. For example, in some embodiments, the second coupling portion 3349 can form a snap fit, a press fit, a friction fit, and/or the like when placed in contact with the first coupling member 3345, as described in further detail herein.

[1236] As shown in FIG. 71, the inner surface 3323 of the hub 3320 defines the lumen 3324 extending through its proximal end portion 3321 and its distal end portion 3322, which is configured to receive a portion of the cannula 3388. Furthermore, the inner surface 3323 includes and/or otherwise forms a shoulder 3325. In this embodiment, the shoulder 3325 is associated with a change in diameter of the inner surface 3323. For example, a first portion of the inner surface 3323 (e.g., a proximal portion) can have a first diameter that is larger than

a diameter of a second portion of the inner surface (e.g., a distal portion). In this manner, the shoulder 3325 can be placed in contact with a surface of the cannula 3388 when inserted therein, as described in detail above with reference to the hub 3020.

[1237] The hub 3320 further includes a valve 3326 disposed within the lumen 3324. The valve 3326 can be, for example, a one-valve, a port, and/or the like, which can be transitioned between a first, substantially closed configuration and a second, substantially opened configuration. Thus, when in the first configuration, the valve 3326 can fluidically isolate a portion of the lumen 3324 that is proximal to the valve 3326 from a portion of the lumen 3324 that is distal to the valve 3326. Conversely, when the valve 3326 is in the second configuration, the lumen 3324 can define a fluid flow path substantially through the hub 3320. In some embodiments, the insertion of the portion of the cannula 3388 can be operable in transitioning the valve 3326 from the first configuration to the second configuration, as described in further detail herein.

[1238] In use, a portion of the cannula 3388 can be inserted into the hub 3320 to define a fluid flow path between the cannula 3322A, coupled to the distal end portion 3322 of the hub 3320, and the cannula 3388 coupled to the proximal end portion 3381 of the cannula 3388. More specifically, in some instances, a user can insert an end portion of the cannula 3388 through the second coupling member 3349. Once the second coupling member 3349 is disposed about the cannula 3380, the cannula 3388 can be inserted into the hub 3320 by a predetermined amount that extends, for example, a distal end portion of the cannula 3388 through the valve 3326, thereby transitioning the valve 3326 from its first, substantially closed configuration to its second, substantially open configuration. Moreover, a distal surface of the cannula 3388 in contact with the shoulder 3325, as shown in FIG. 71. As the cannula 3388 is moved into its desired position within the hub 3320, the second coupling member 3349 is inserted through the opening 3328 defined by the proximal cap 3327 and into contact with the first coupling member 3345. Thus, the second coupling member 3349 can engage the first coupling member 3345 to define, for example, a snap fit or the like. In some embodiments, the arrangement of the second coupling member 3349 can be such that when it engages the first coupling member 3349, a space through which the cannula 3388 extends is reduced. As such, the second coupling member 3349 can clamp the cannula 3388 and with the second coupling member 3349 being coupled to the first coupling member 3345, the first coupling member 3345 and the second coupling member 3349 can act to at least

temporarily maintain the cannula 3388 in a substantially fixed position relative to the hub 3320. Although described above as being moved substantially concurrently with the cannula 3388, in other embodiments, the second coupling member 3349 can be moved after the distal surface of the cannula 3388 is placed in contact with the shoulder 3325.

[1239] In some embodiments, the arrangement of the hub 3320 and the cannula 3388 is such that when the cannula 3388 is maintained in the substantially fixed position, the lumen 3324 of the hub 3320 is substantially aligned with a lumen defined by the cannula 3388. For example, in this embodiment, the lumen of the cannula 3388 and the lumen 3324 of the hub 3320 form a substantially continuous transition therebetween. That is to say, the lumens are substantially aligned and/or a discontinuity defined therebetween is sufficiently minimized or obviated so as to not produce turbulence within a flow of bodily-fluid therethrough. In this manner, a user can couple the cannula 3388 to, for example, a fluid reservoir such as those described herein, which in turn, can exert a suction force (e.g., in response to a negative pressure differential) through the cannula 3388 and the hub 3320. Therefore, when the cannula 3322A is in fluid communication with the body of a patient (e.g., either directly or indirectly via an intervening structure), a volume of, for example, blood can be withdrawn with a reduced amount of hemolysis. Specifically, the alignment of the lumen 3324 defined by the hub 3320 and the lumen of the cannula 3388, for example, can reduce turbulence, eddy currents, and/or any other disturbance that can otherwise result from a discontinuity or the like. Thus, the flow of blood therethrough can be substantially laminar and substantially free of hemolysis.

[1240] Although the embodiments are shown and described above as mitigating the risk of hemolysis of a volume of blood at a given point along a fluid flow path between a patient and a fluid reservoir, any embodiment configured to mitigate the risk of hemolysis at a given point along the fluid flow path can be used in conjunction with any suitable embodiment(s) configured to mitigate the risk of hemolysis at a different point along the fluid flow path. In some instances, a fluid transfer device can include any combination of the embodiments described herein, for example, to mitigate the risk of hemolysis otherwise associated with (1) blood flow from, for example, a vein into a puncture member, needle, cannula, and/or the like; (2) blood flow through changing geometries and/or physical and fluidic interfaces; (3) blood flow rates, pressures, and/or velocities within the fluid flow path; (4) blood flow from an adapter, puncture member, needle, cannula, and/or the like into a fluid reservoir; (5) blood

flow exposure to a negative pressure differential within a fluid reservoir; and/or (6) blood flow through a multi-lumen adapter and/or the like.

[1241] While the embodiments are shown and described above as mitigating the risk of hemolysis of a volume of blood during, for example, aspiration, blood draw, and/or any other procedure in which blood is withdrawn from the body, in other instances, any embodiment configured to mitigate the risk of hemolysis described herein, and/or any combination thereof, can be used in any suitable medical device and/or procedure in which it is desirable to reduce hemolysis. For example, any of the embodiments or combinations of the embodiments described herein such as the adapters, puncture members, restrictors, fluid reservoirs, gaskets, etc., and/or characteristics, geometries, and/or features thereof can be used to mitigate the risk of hemolysis in any suitable device and/or during any suitable medical procedure. Such devices and/or procedures can include but are not limited to, mechanical hearts and/or other organs, perfusion machines used, for example, during open-heart surgery, dialysis machines, and/or the like. In some instances, the embodiments and/or combination of embodiments described herein can be used to modulate pressure within such devices, produce a laminar flow through at least a portion of such devices, reduce and/or limit shear stress and/or exposure time experienced by red blood cells, and/or the like.

[1242] Although not shown or described herein, any of the embodiments can be used in a fluid transfer device configured to, for example, divert a predetermined pre-sample volume of bodily-fluid that can contain, for example, externally residing microbes prior to collection of a sample volume of bodily. For example, in some embodiments, the predetermined pre-sample volume can be about a drop or a few drops of blood, about 0.1 mL, about 0.3 mL, about 0.5 mL, about 1.0 mL, about 2.0 mL, about 3.0 mL, about 4.0 mL, about 5.0 mL, about 11.0 mL, about 20 mL, about 50 mL, and/or any volume or fraction of a volume therebetween. In other embodiments, the pre-sample volume can be greater than 50 mL or less than 0.1 mL. In other embodiments, the predetermined pre-sample volume can be between about 2 mL and about 5 mL. In one embodiment, the predetermined pre-sample volume can be about 3 mL. In some instances, a venipuncture event can result in trauma to the blood flowing within the punctured vein that can at least temporarily hemolyze a portion of the blood. Thus, in some embodiments, the diverted pre-sample volume of blood can include, for example, the hemolyzed portion of the blood. Furthermore, by collecting the

predetermined pre-sample volume, the predetermined sample volume disposed in one or more sample reservoirs can be substantially free-from externally residing microbes.

[1243] Fluid transfer devices configured to divert a predetermined pre-sample volume of bodily-fluid can be any suitable configuration. For example, in some embodiments, such a fluid transfer device can be substantially similar to or the same as the fluid transfer devices described in U.S. Patent No. 8,535,241 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed October 12, 2012; U.S. Patent No. 9,060,724 entitled, "Fluid Diversion Mechanism for Bodily-Fluid Sampling," filed May 29, 2013; U.S. Patent No. 9,155,495 entitled, "Syringe-Based Fluid Diversion Mechanism for Bodily-fluid Sampling," filed December 2, 2013; and/or U.S. Patent Publication No. 2014/0155782 entitled, "Sterile Bodily-Fluid Collection Device and Methods," filed December 4, 2012, the disclosures of which are incorporated herein by reference in their entireties and attached hereto as Exhibit A, Exhibit B, Exhibit C, and Exhibit D, respectively. Moreover, in some embodiments, such transfer devices can be configured to selectively obstruct a needle to prevent hemolyzed blood from entering a lumen defined by the needle during a venipuncture event. Such devices can be substantially similar to and/or the same as those described in U.S. Patent Publication No. 2014/0276578, entitled, "Methods and Apparatus for Selectively Occluding the Lumen of a Needle," filed September 18, 2014, the disclosure of which is incorporated herein by reference in its entirety and attached hereto as Exhibit E.

[1244] In some embodiments, the bodily-fluid transfer devices described herein can include and/or can be partially formed from antisepsis-saturated materials. For example, any of the valves, gaskets, seals, ports, and/or the like can be saturated with, for example, isopropyl alcohol. As such, when various components of a fluid transfer device are coupled and/or otherwise collectively form an interface, the components can be contemporaneously sterilized. In some embodiments, such a device can be substantially similar to or the same as those described in U.S. Patent Publication No. 2015/0246352 entitled, "Apparatus and Methods for Disinfection of a Specimen Container," filed March 3, 2015, the disclosure of which is incorporated herein by reference in its entirety and attached as Exhibit F.

[1245] While the device 100 is described above as including a surface, mechanism, portion, etc. configured to reduce hemolysis of a volume of blood in a mechanical manner (e.g., by mechanically changing one or more characteristics of a flow of blood within a fluid flow path), in other embodiments, any of the devices can be configured to chemically modify

one or more characteristics associated with the volume of blood. For example, in some embodiments, an inner surface of any of the embodiments described herein can be coated with a chemical configured to limit lysis of erythrocytes (red blood cells) by strengthening or weakening a cell wall of the erythrocytes. More specifically, in some embodiments, a can be configured to introduce a chemical into a flow of blood that can, for example, increase a rigidity of the cell wall of erythrocytes (e.g., decrease flexibility), which in turn, can reduce a likelihood of lysis of the erythrocytes (e.g., hemolysis of the blood) as the blood flows through the device. In other embodiments, a device can be configured to introduce a chemical into a flow of blood that can, for example, decrease a rigidity of the cell wall of erythrocytes (e.g., increase flexibility), which in turn, can reduce a likelihood of lysis of the erythrocytes as the blood flows through the device.

[1246] While described above as coating an inner surface of a device with the chemical configured to modify a characteristic of the cell wall of the erythrocytes, in other embodiments, any of the embodiments described herein can include any suitable device, mechanism, and/or method for introducing such a chemical to the volume of blood flowing therethrough. For example, a device can include a chamber containing such a chemical (e.g., a chamber within a Luer lock or the like), a baffle, wipe, valve, porous material (e.g., sintered glass or plastic), etc. impregnated with such a chemical, a dispensing or dispersing device (e.g., sprayer or the like) configured to dispense a volume of such a chemical, and/or any other suitable means for introducing such a chemical. Moreover, a device can include any suitable combination of devices, interfaces, members, mechanisms, etc. included in the embodiments described herein as well as any suitable means for introducing a chemical into a volume of blood flowing through such a device.

[1247] As described above, in some instances, introducing a chemical into a volume of blood (e.g., whole blood) can result in a strengthening of an erythrocyte membrane or outer structure, or in other words, can modify a magnitude of stability associated with the erythrocyte membrane. In some instances, such stabilization can result in an increased resistance to hemolysis caused by mechanical stress, osmotic stress, peroxyl radicals attack, heat, and/or the like. Examples of chemicals that can modify a characteristic associated with an erythrocyte membrane include phloridzin, cremophore (glycerol polyethylene glycol ricinoleate, lidocaine, antioxidants such as reduced glutathione (GSH), N-acetylcysteine, ebselen (2-phenyl-1, 2-benzoselenazol-3-one) and/or albumin, papaya leaf and/or other plant

extracts, tranquilizers and/or antihistamines such as phenothiazine, reserpine, and/or haloperidol, saponins and/or sapogenins, polyamines, anti-inflammatory drugs such as phenylbutazone, methylsergide, and/or indomethacin, and/or any other suitable chemical.

[1248] While various embodiments have been particularly shown and described, various changes in form and details may be made. While embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Although various embodiments have been described as having particular features and/or combinations of components, other embodiments are possible having any combination or sub-combination of any features and/or components from any of the embodiments described herein. For example, in some embodiments, a restrictor such as, for example, the restrictor 650 can be used when collecting a bodily-fluid using any of the fluid reservoirs described herein. Similarly, the hub 3020 and lumen-defining device 3080 described above with reference to FIGS. 61-63 can be used with any of the adapters described herein. Moreover, any suitable combination of components described herein can be physically and/or fluidically coupled together to form a bodily-fluid collection device configured, for example, to reduce hemolysis in a withdrawn volume of blood.

[1249] The specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. More specifically, the size and shape of the various components can be specifically selected for a desired rate of bodily-fluid flow into a fluid reservoir. While various components have been described above a being physically and fluidically coupled, in other embodiments, any of the devices and/or embodiments can be, for example, monolithically formed with and/or otherwise joined to any other suitable device and/or embodiment. For example, while the first adapter 1020, the second adapter 1030, and the restrictor 1050 are described above with reference to FIGS. 18-20 as being formed separately and subsequently coupled, in other embodiments, the first adapter 1020 and/or the second adapter 1030 can be monolithically formed with the restrictor 1050. In some instances, such a monolithically formed component can be included in, for example, a pre-assembled and sterile blood collection device and/or the like.

[1250] Where methods and/or events described above indicate certain events and/or procedures occurring in certain order, the ordering of certain events and/or procedures may

be modified. Additionally, certain events and/or procedures may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above.

Abstract

A collection system has a proximal end portion, a distal end portion, and an inner surface defining a fluid flow path therethrough. The distal end portion is configured to be placed in fluid communication with a patient. The proximal end portion is configured to be placed in fluid communication with a fluid reservoir. The fluid flow path defined by the inner surface is associated with at least one flow characteristic configured to limit a stress within the flow of the bodily-fluid between the distal end portion and the proximal end portion.

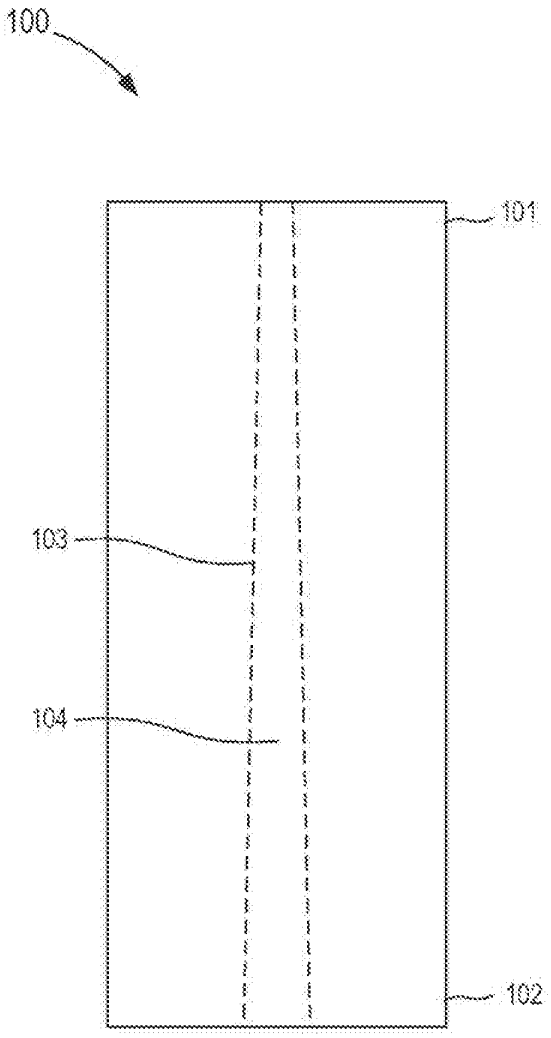


FIG. 1

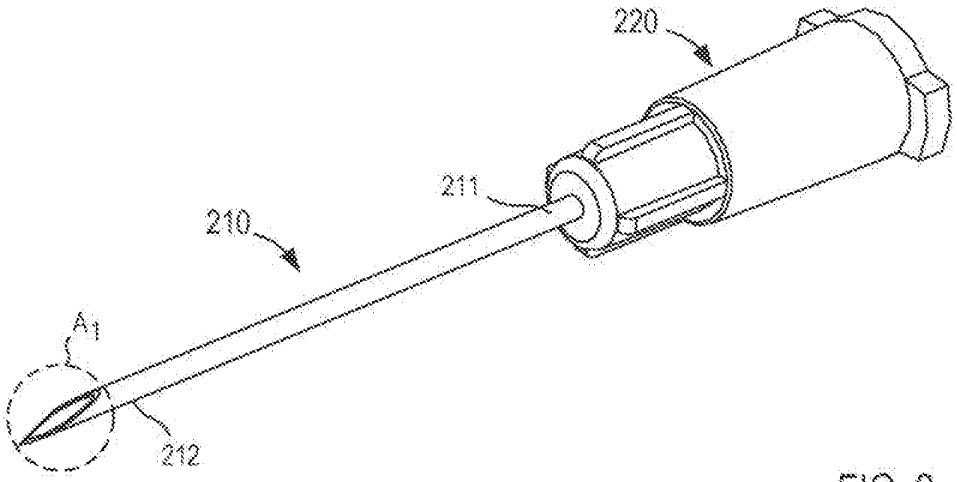


FIG. 2

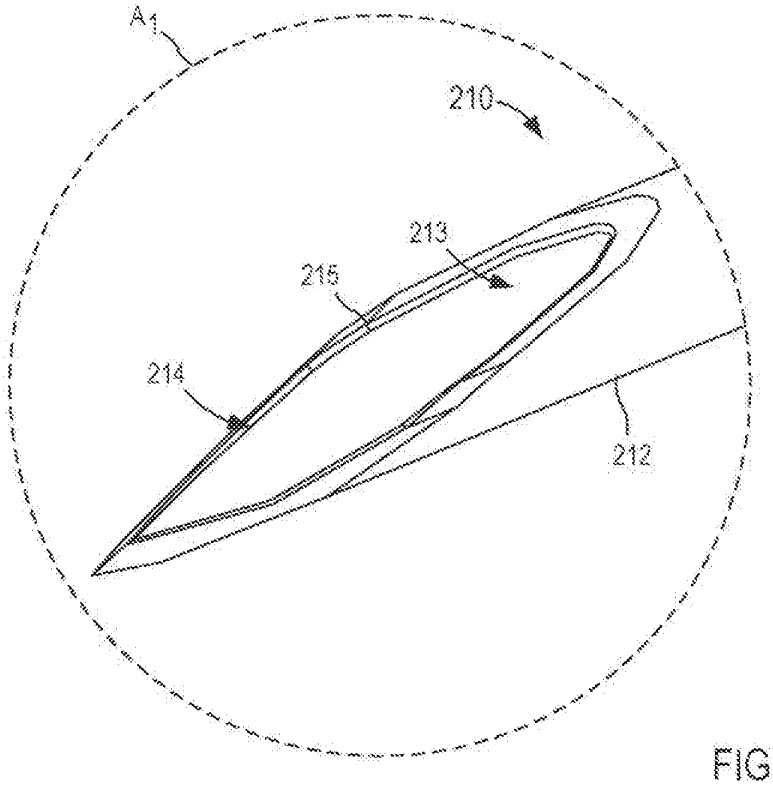


FIG. 3

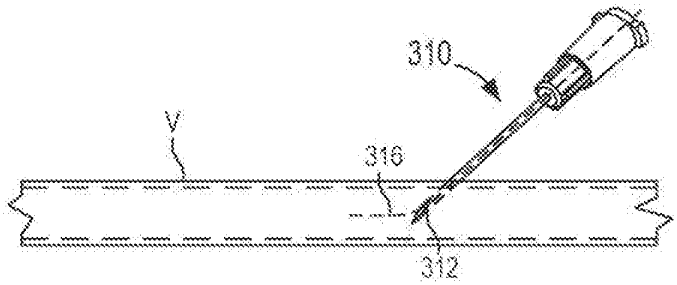


FIG. 4

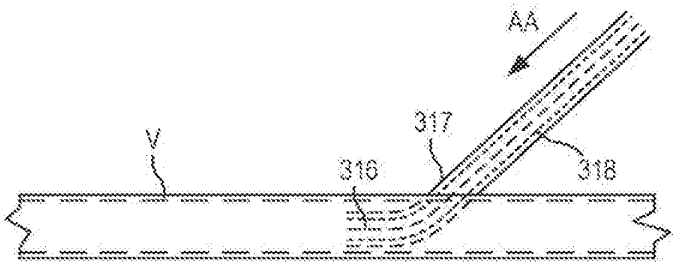


FIG. 5

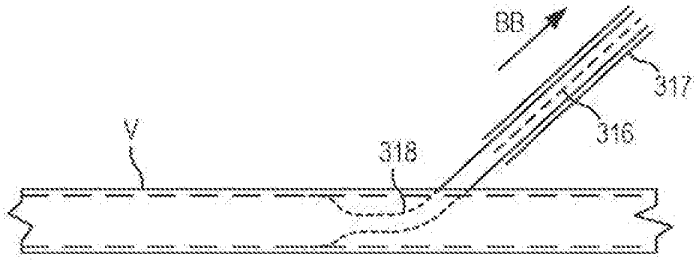


FIG. 6

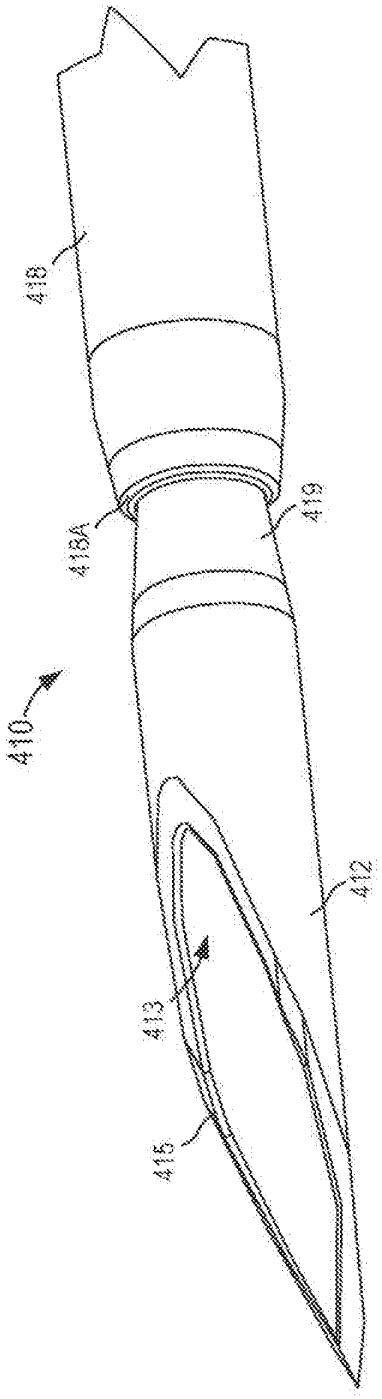


FIG. 7

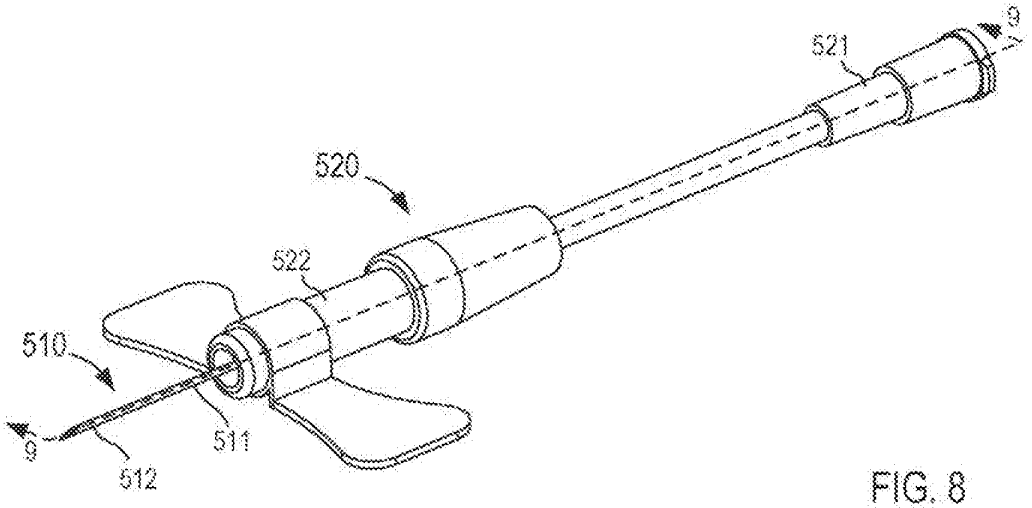


FIG. 8

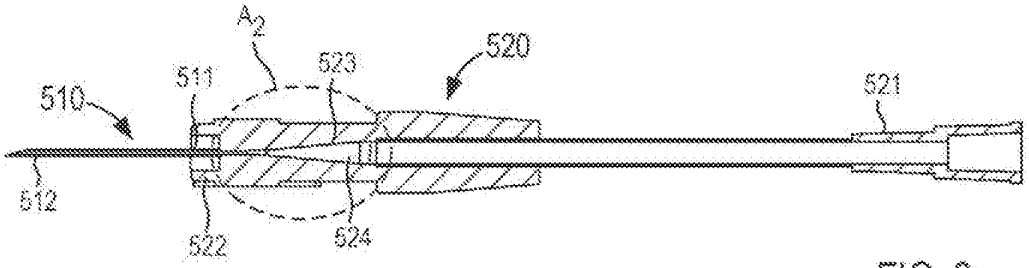


FIG. 9

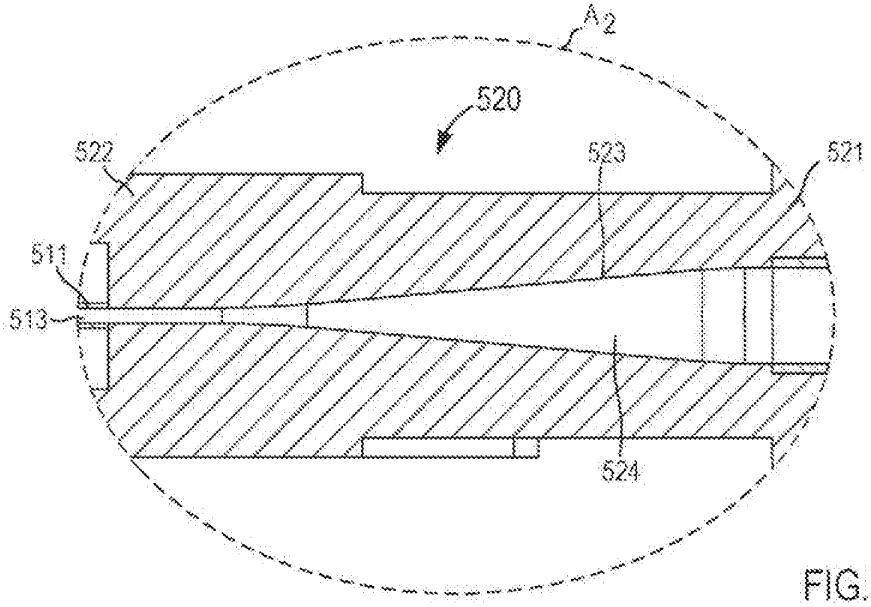


FIG. 10

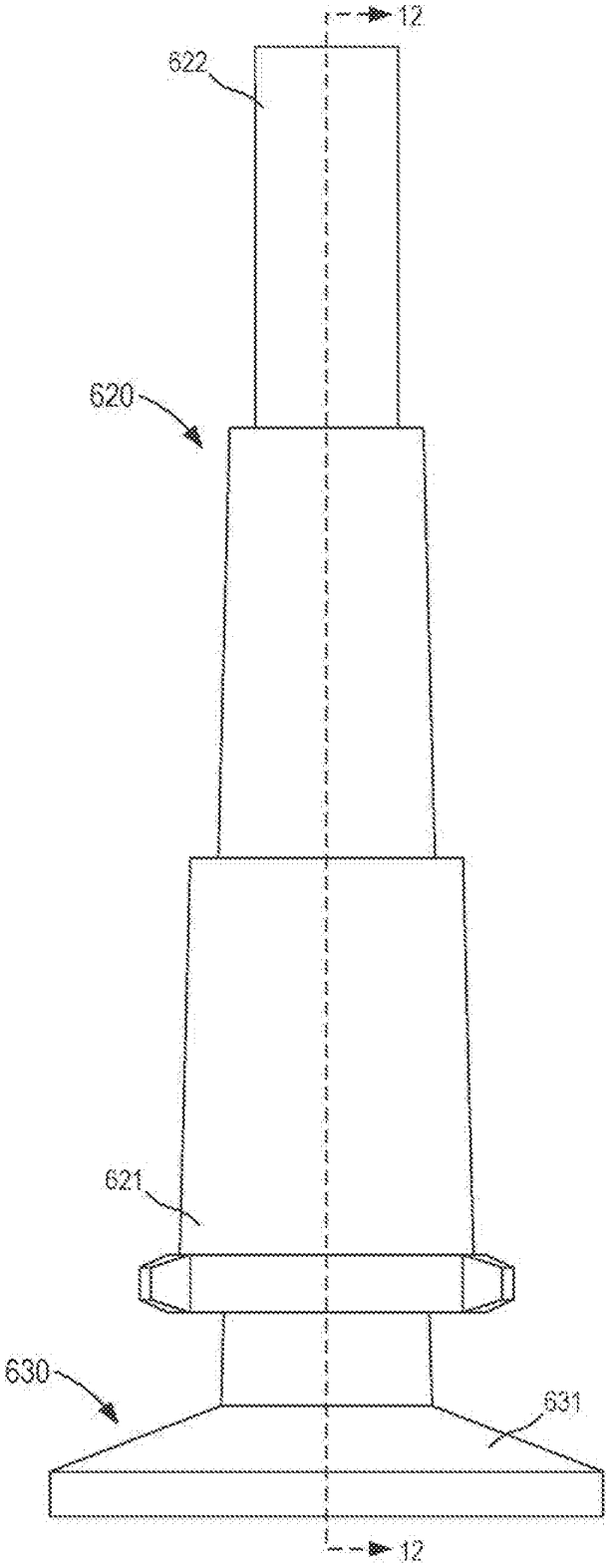


FIG. 11

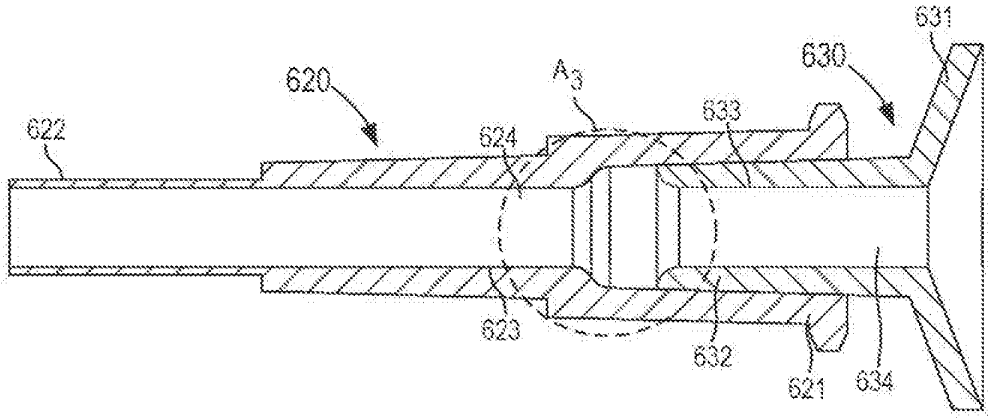

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FIG. 12

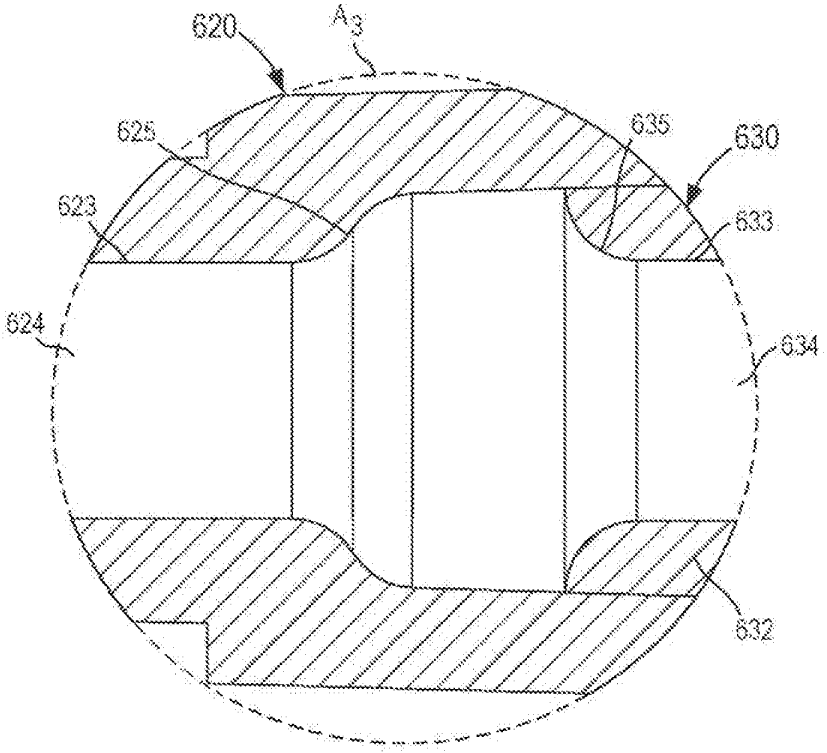

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FIG. 13

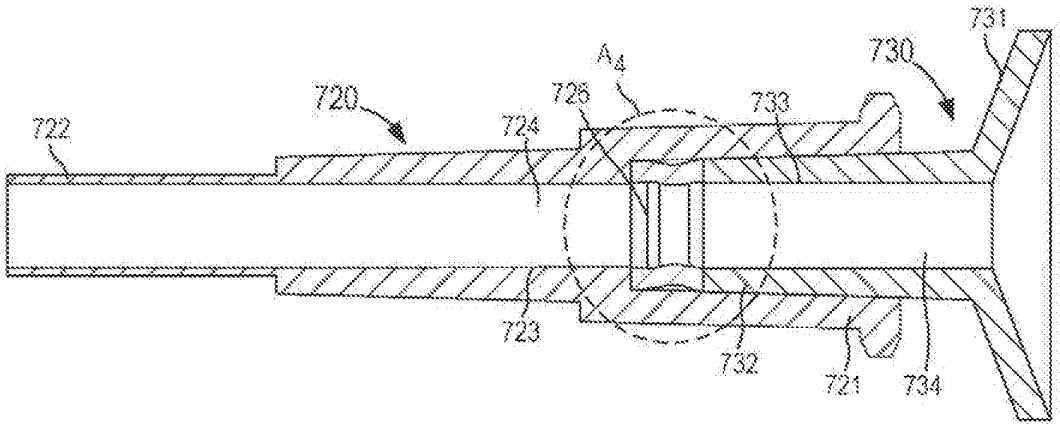

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FIG. 14

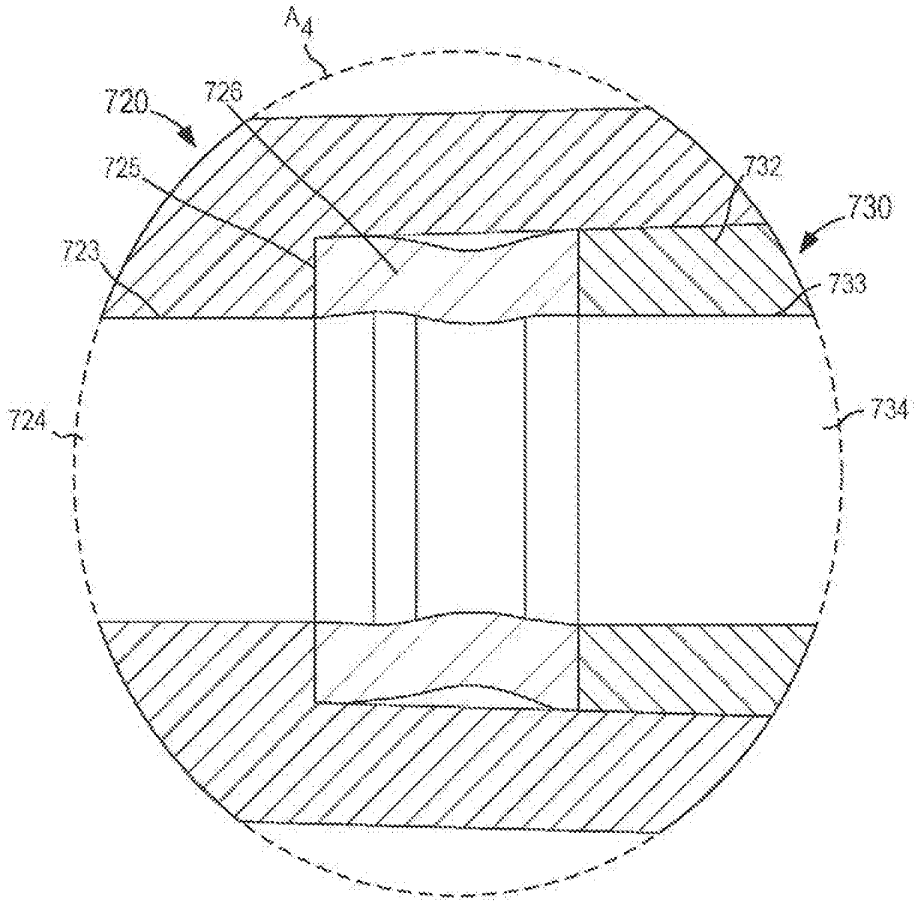

A_4
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FIG. 15

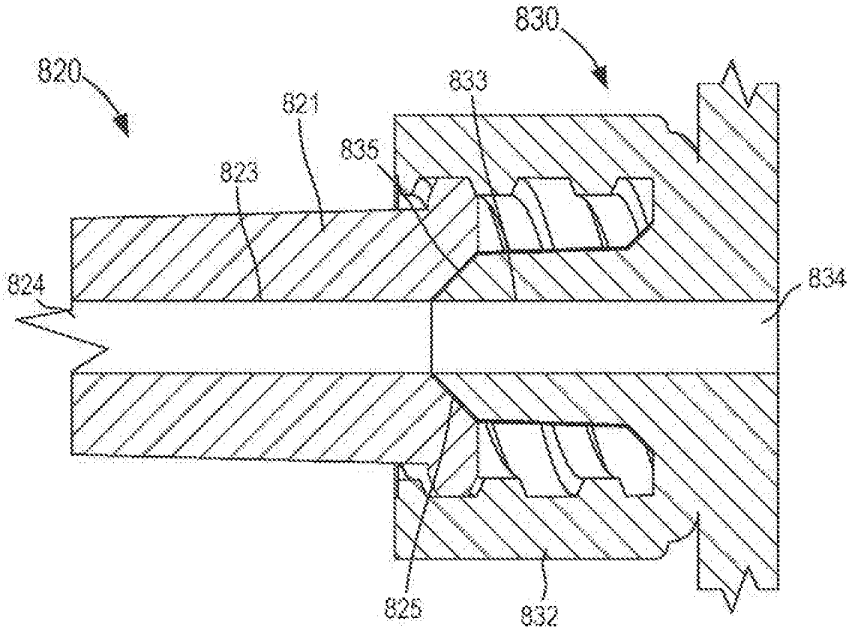

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FIG. 16

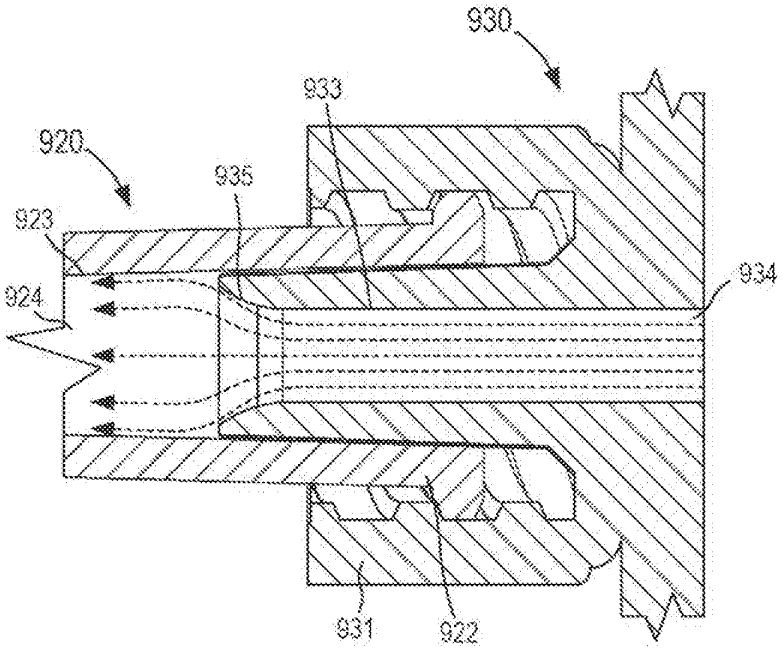

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FIG. 17

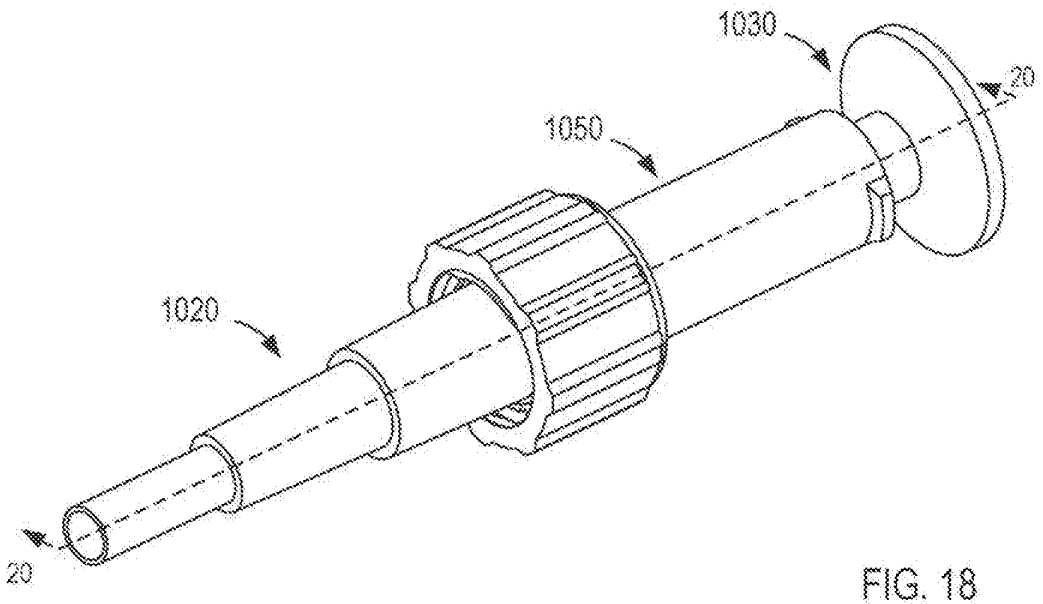

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FIG. 18

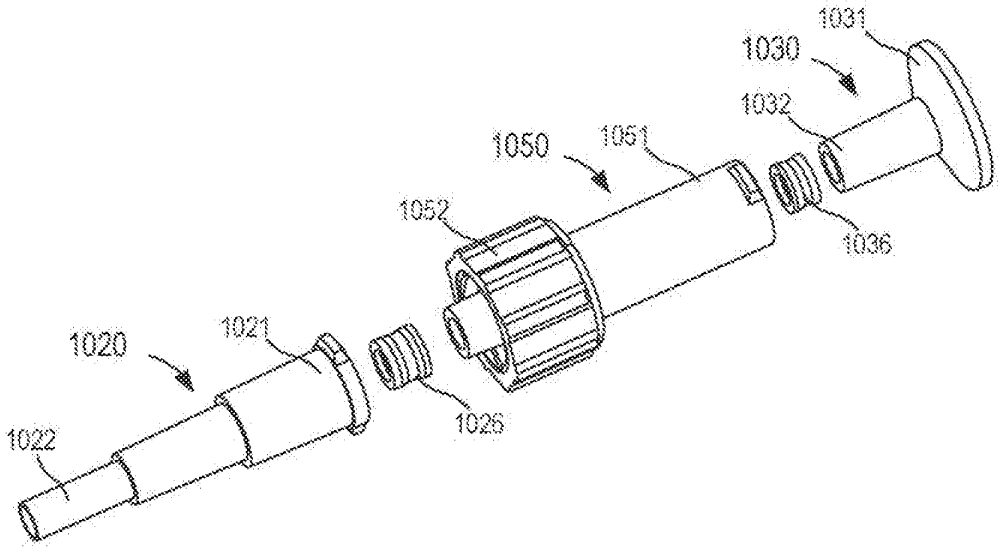

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FIG. 19

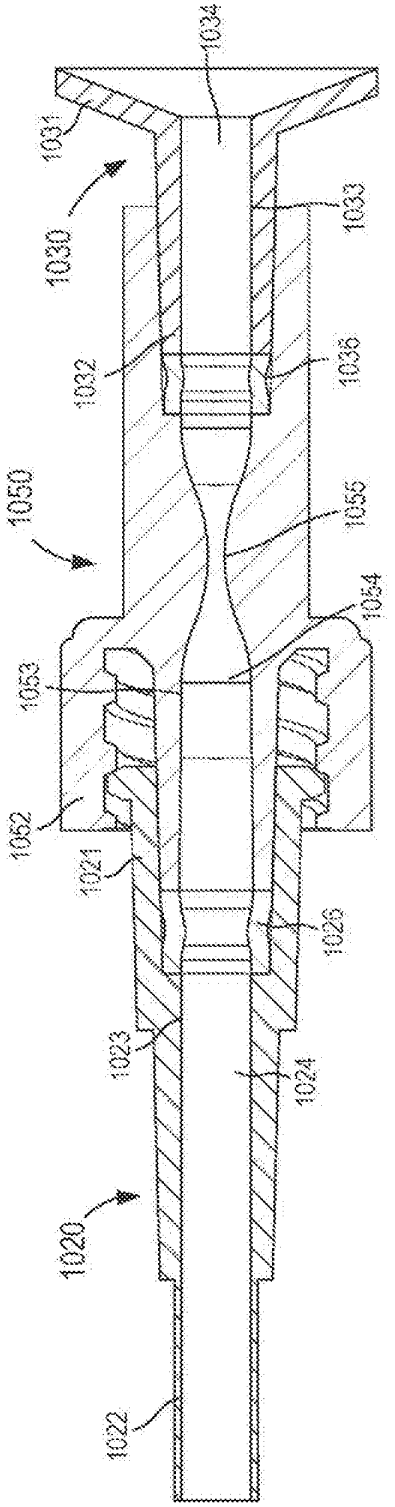

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FIG. 20

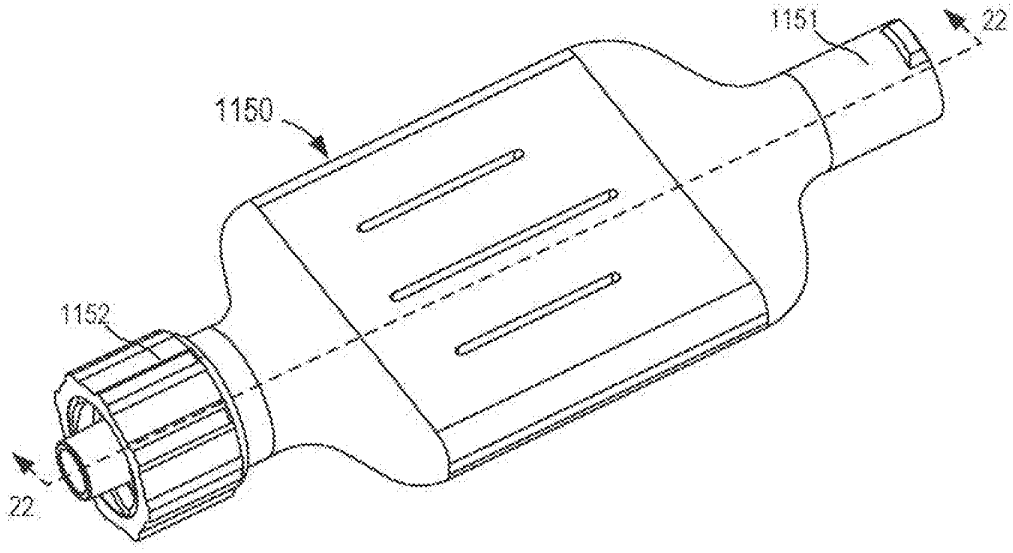


FIG. 21

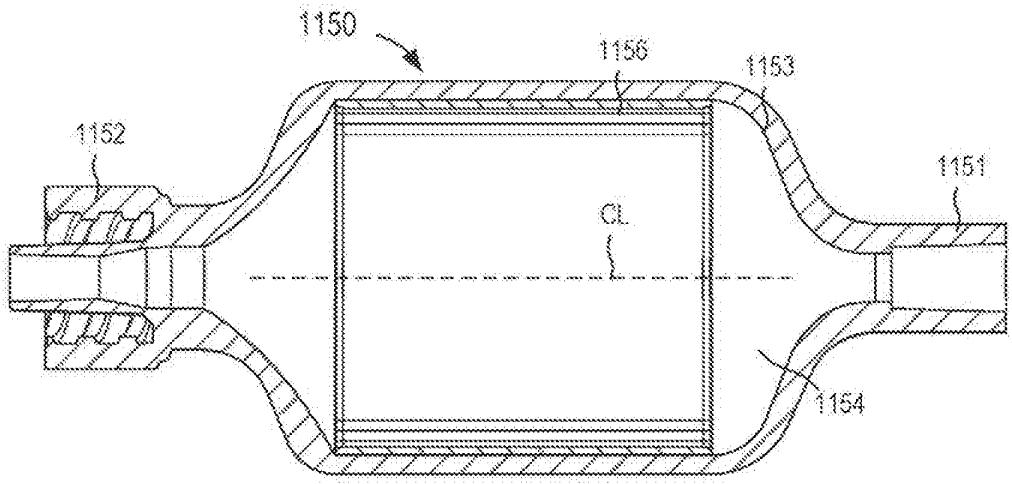


FIG. 22

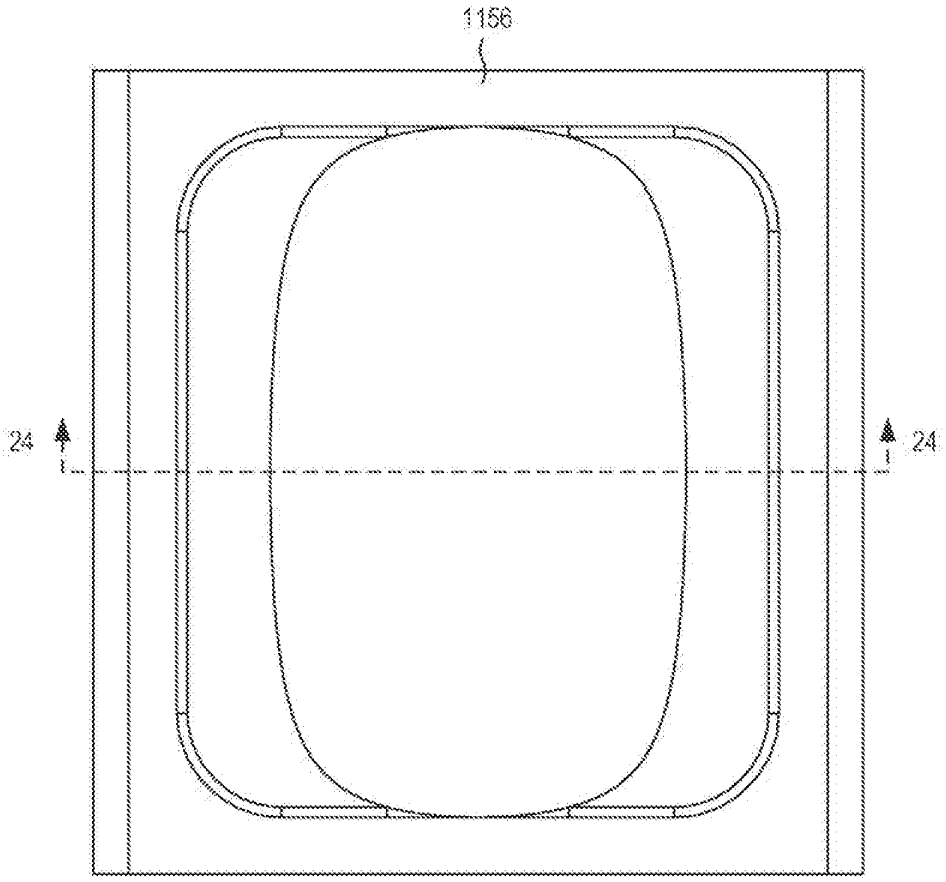


FIG. 23

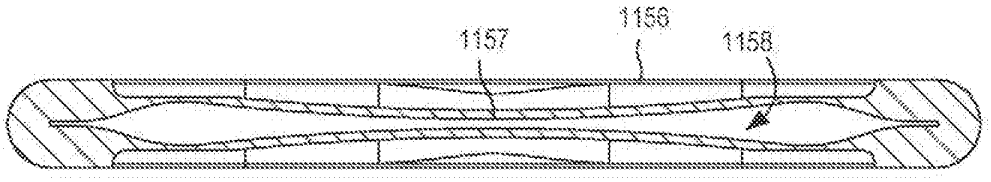


FIG. 24

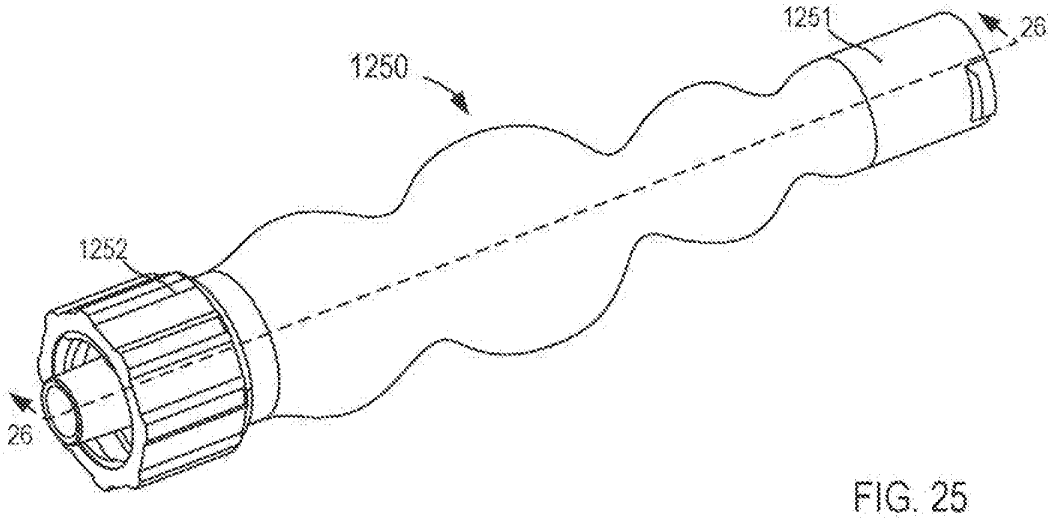

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FIG. 25

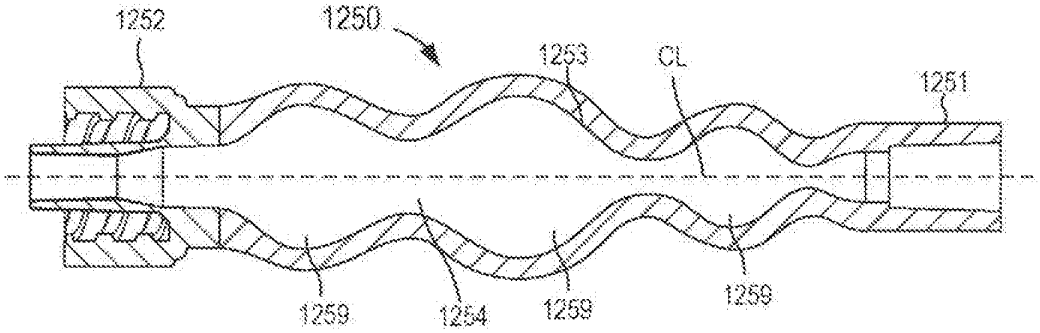

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FIG. 26

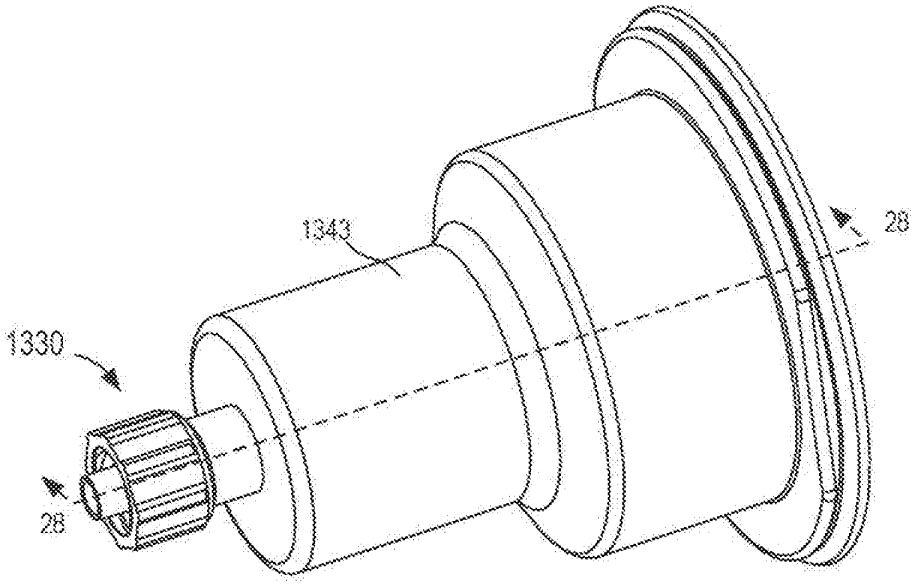


FIG. 27

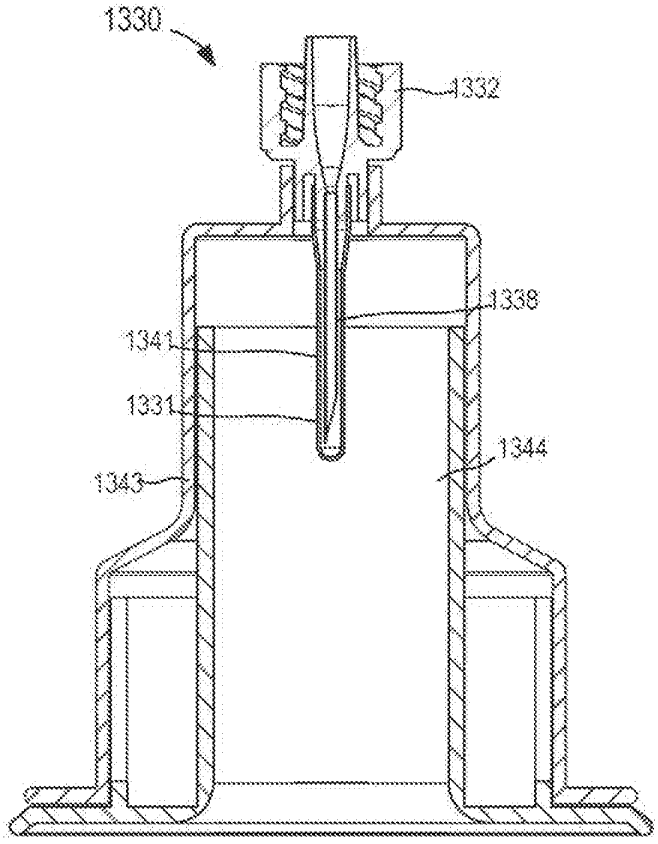


FIG. 28

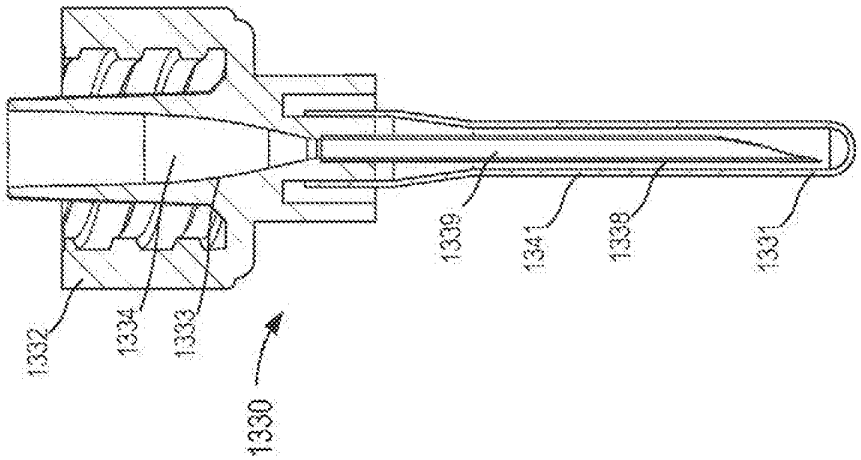


FIG. 30

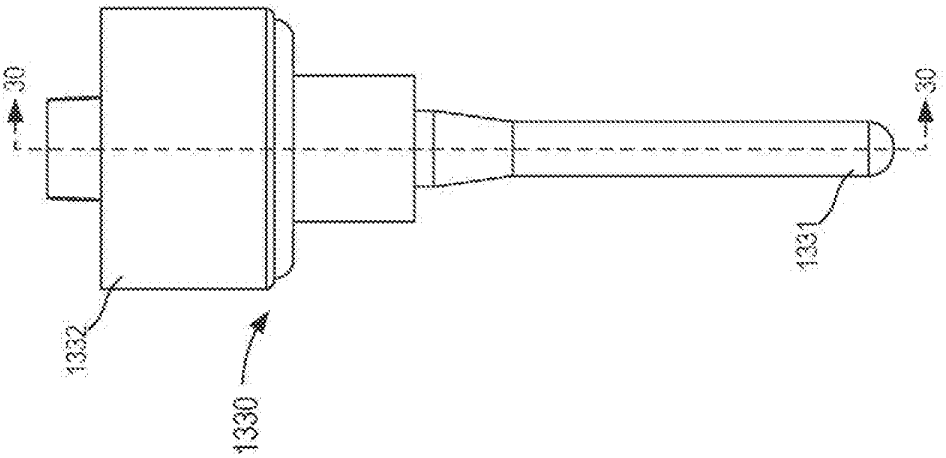


FIG. 29

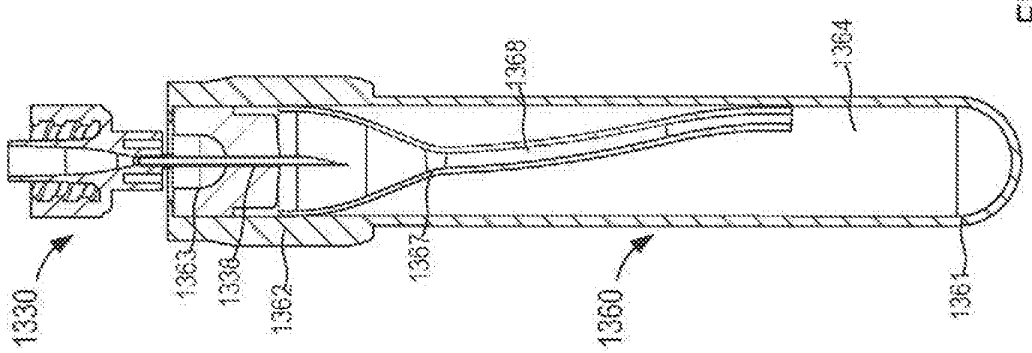


FIG. 33

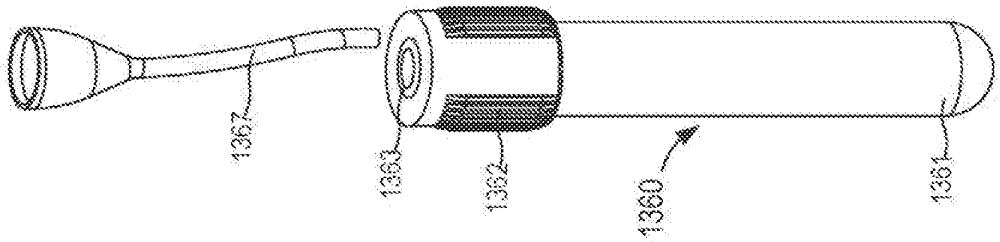


FIG. 32

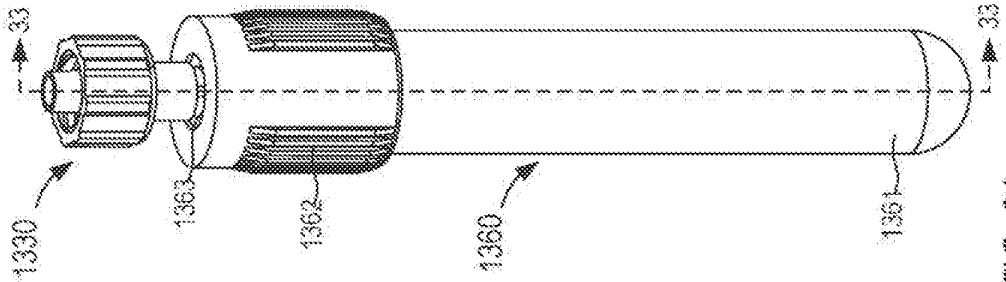


FIG. 31

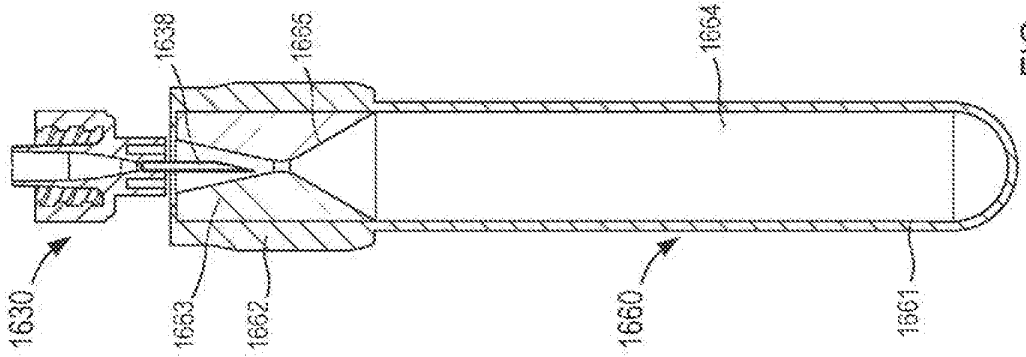


FIG. 36

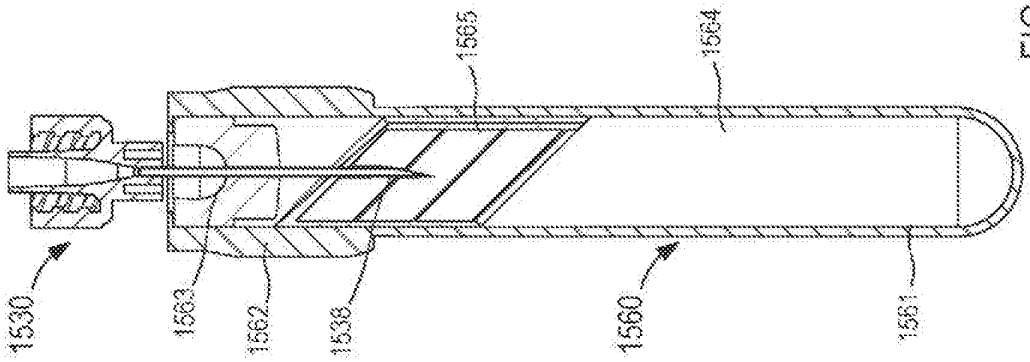


FIG. 35

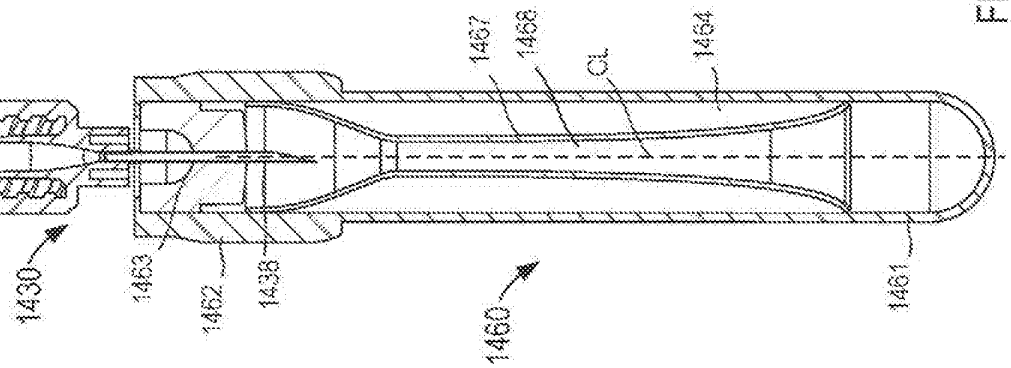


FIG. 34

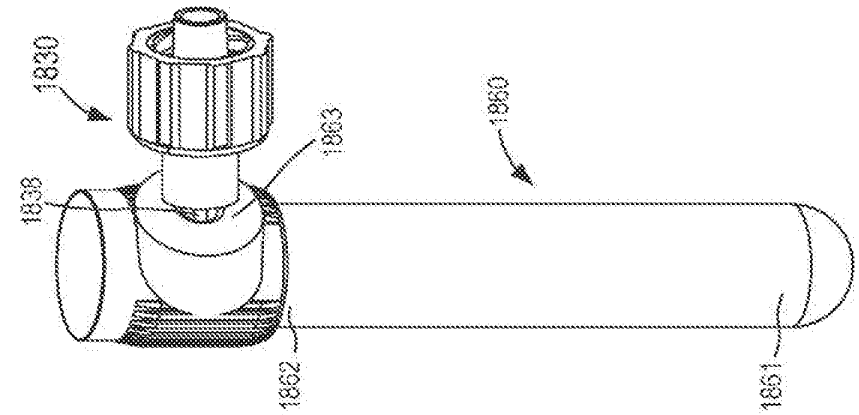


FIG. 39

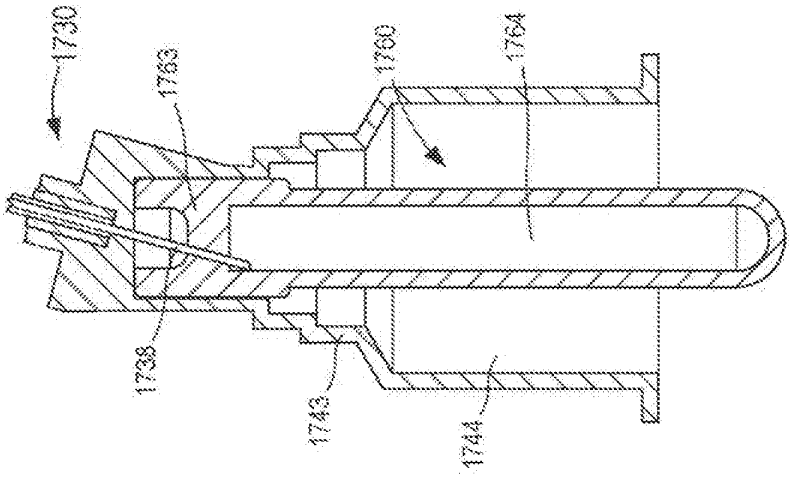


FIG. 38

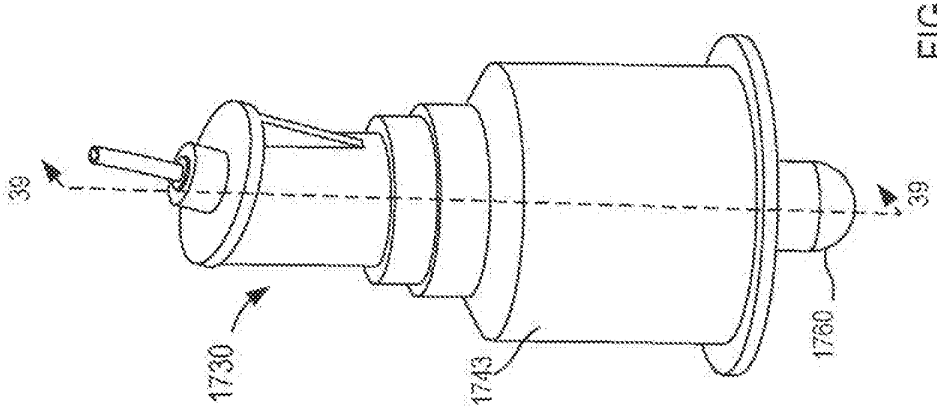


FIG. 37

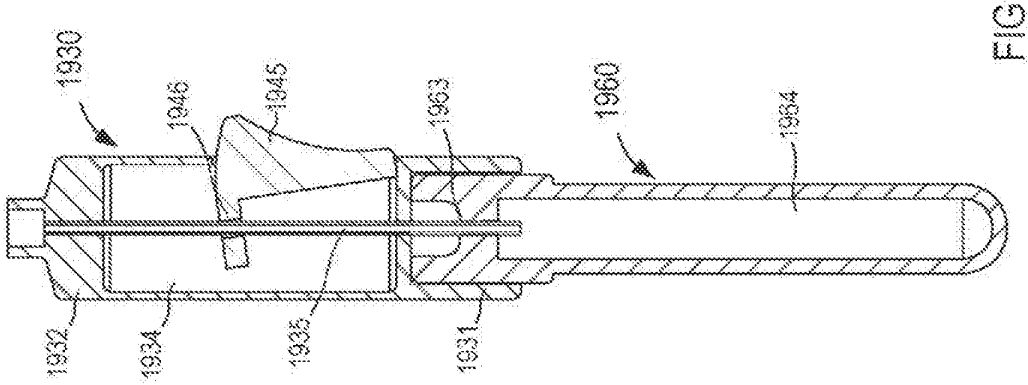


FIG. 42

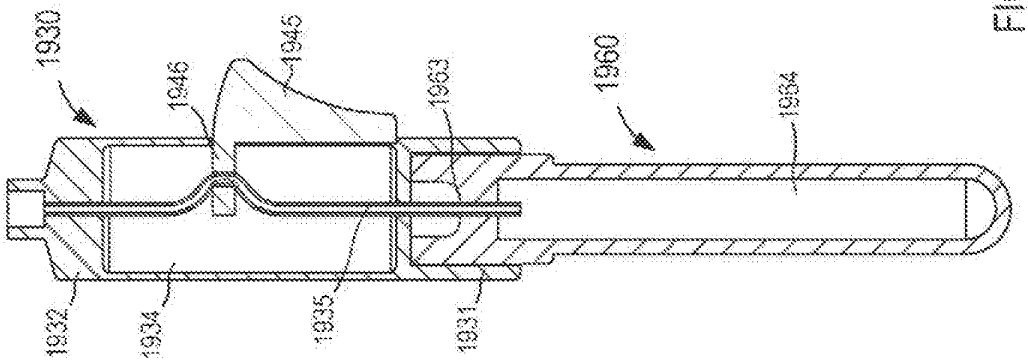


FIG. 41

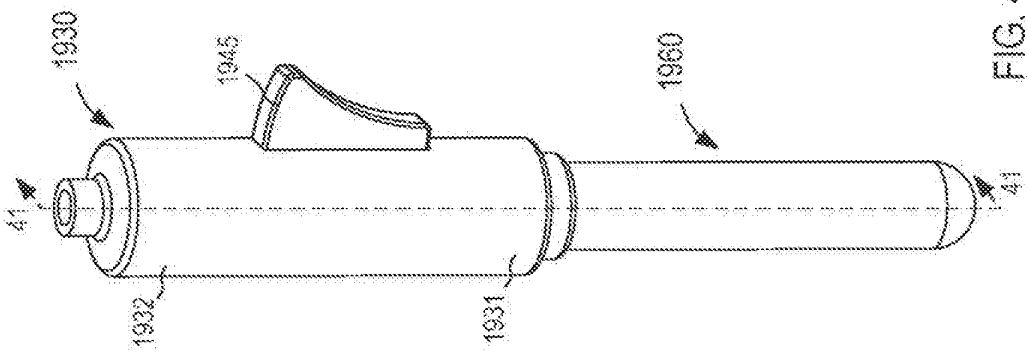


FIG. 40

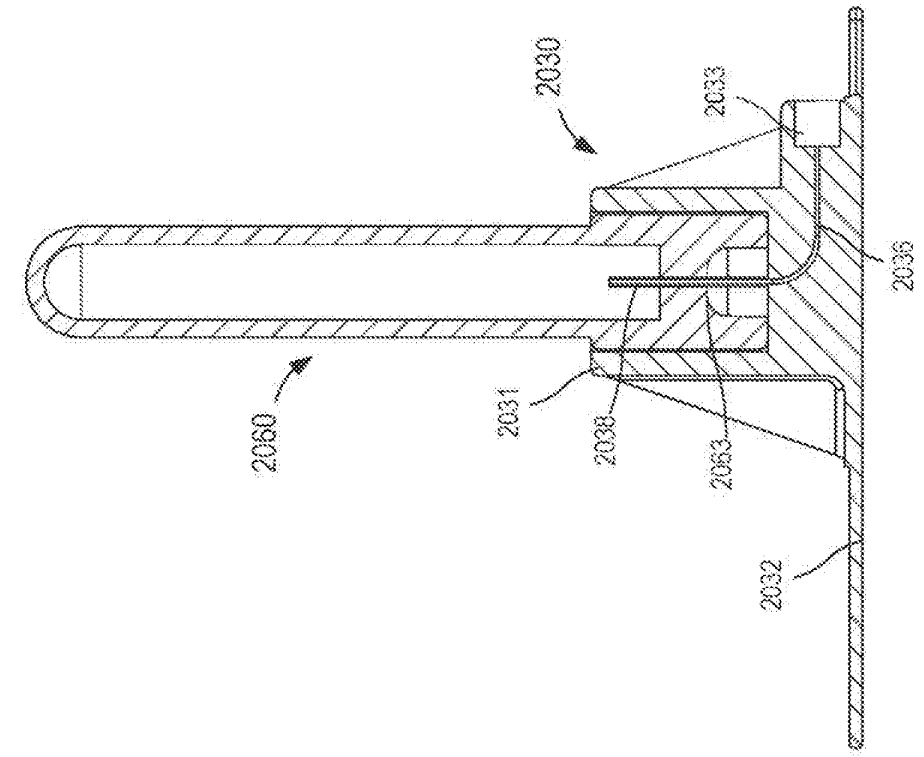

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FIG. 44

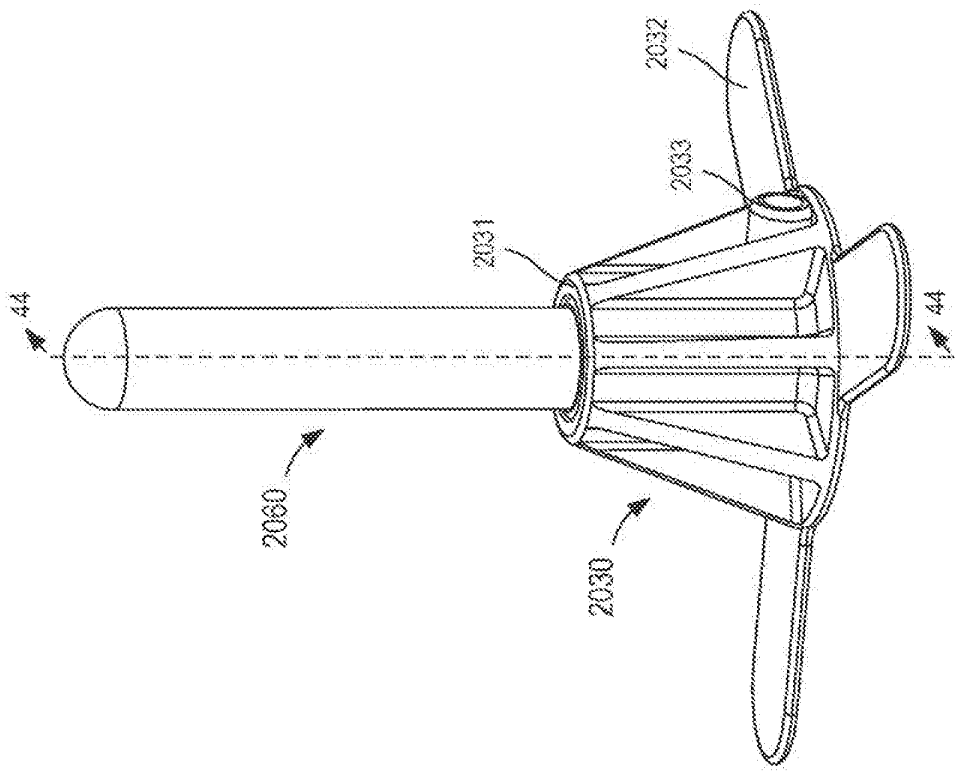

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FIG. 43

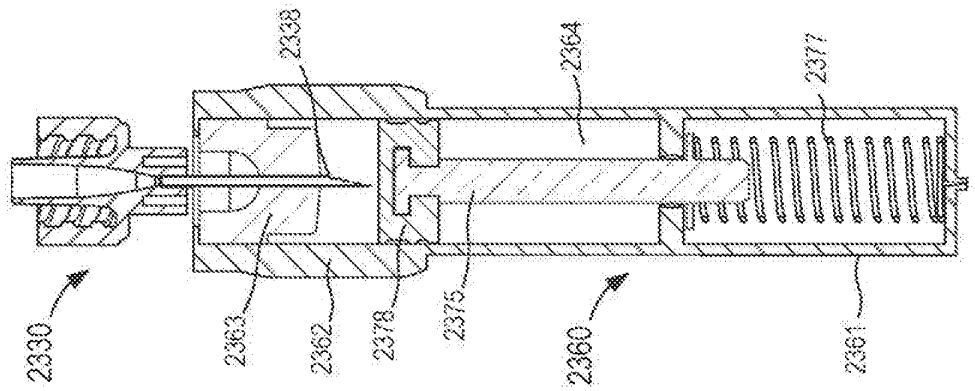


FIG. 47

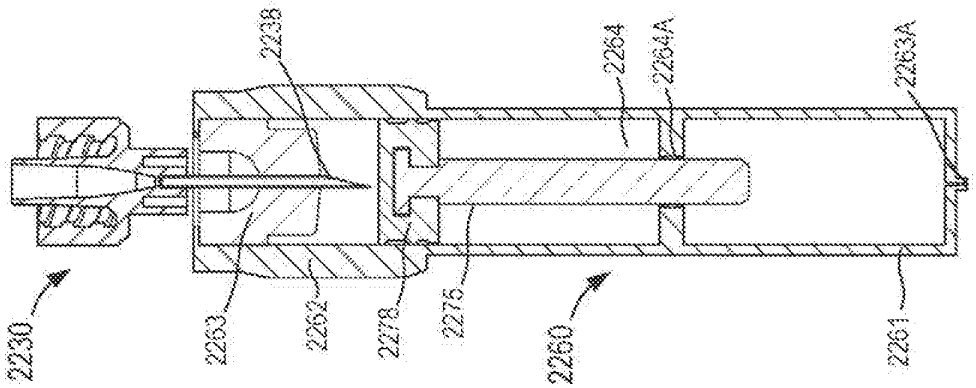


FIG. 46

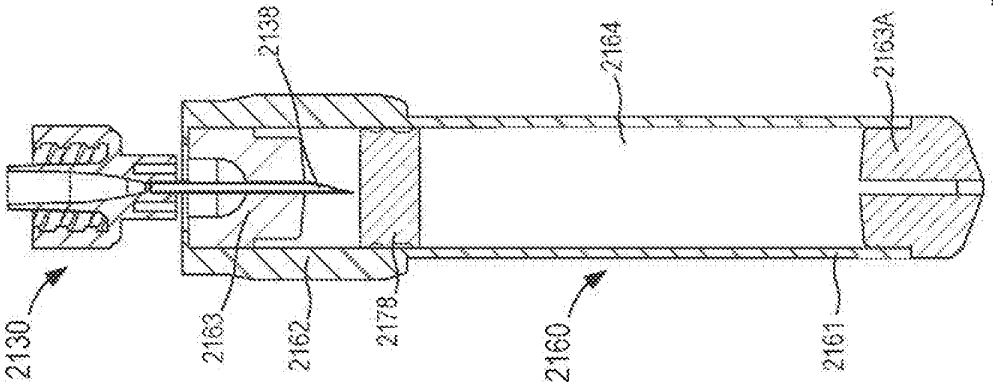


FIG. 45

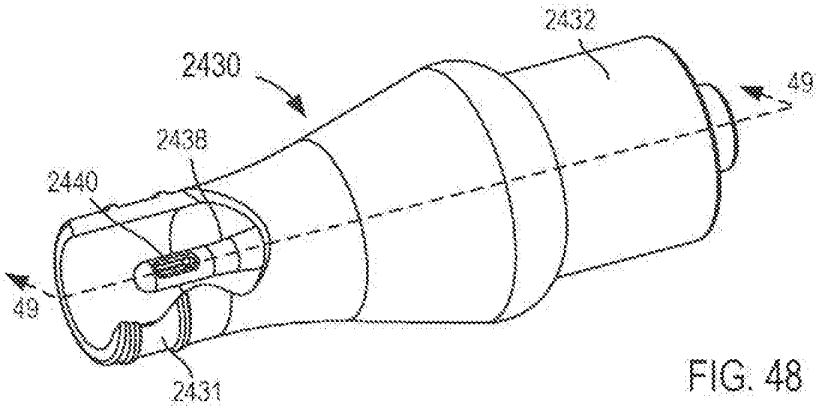


FIG. 48

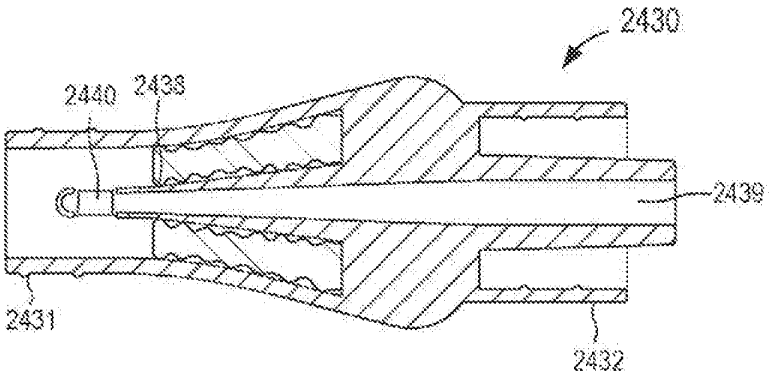


FIG. 49

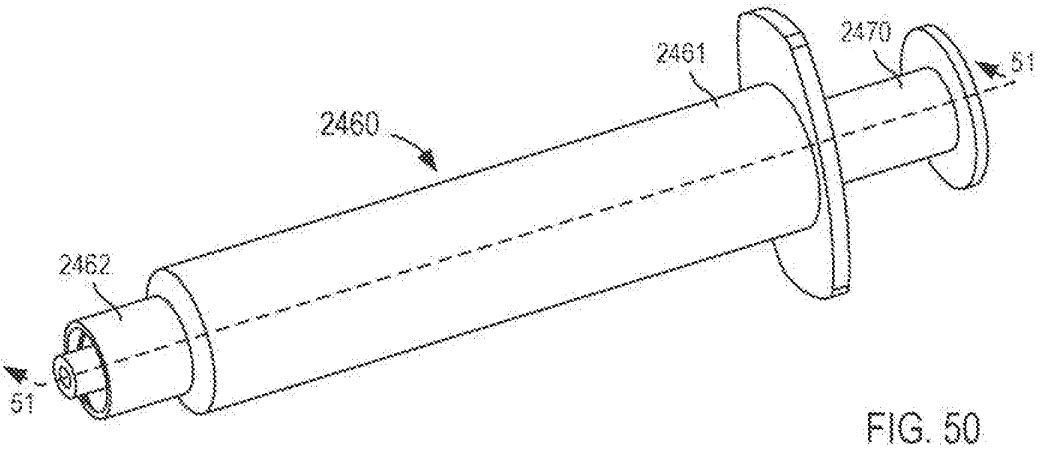


FIG. 50

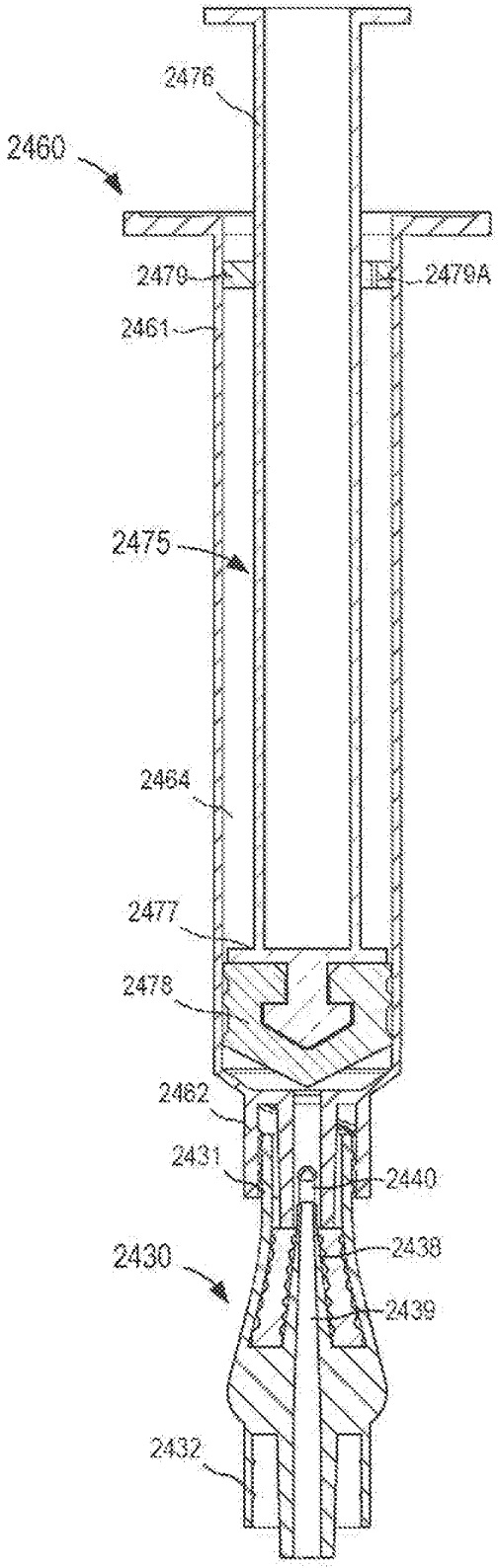

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FIG. 51

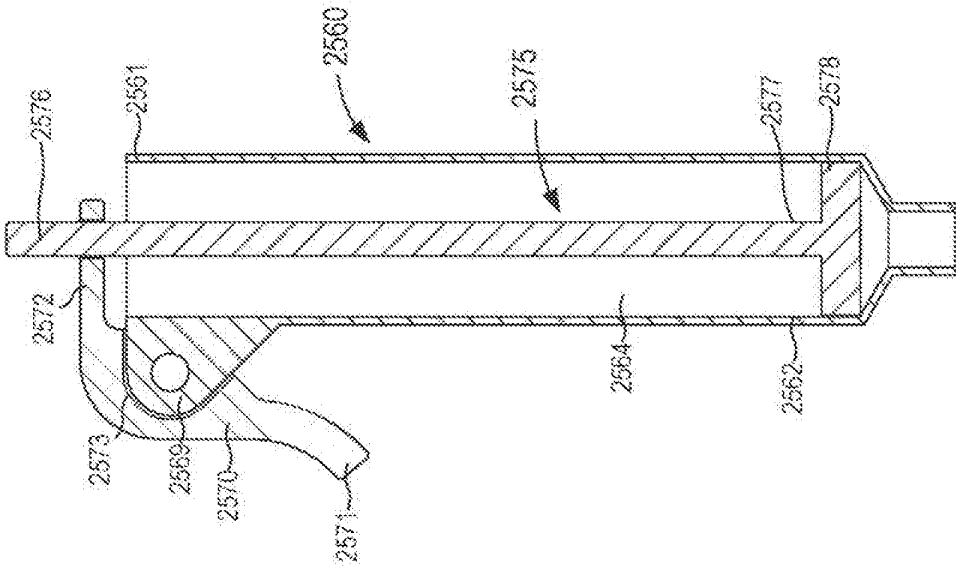

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FIG. 53

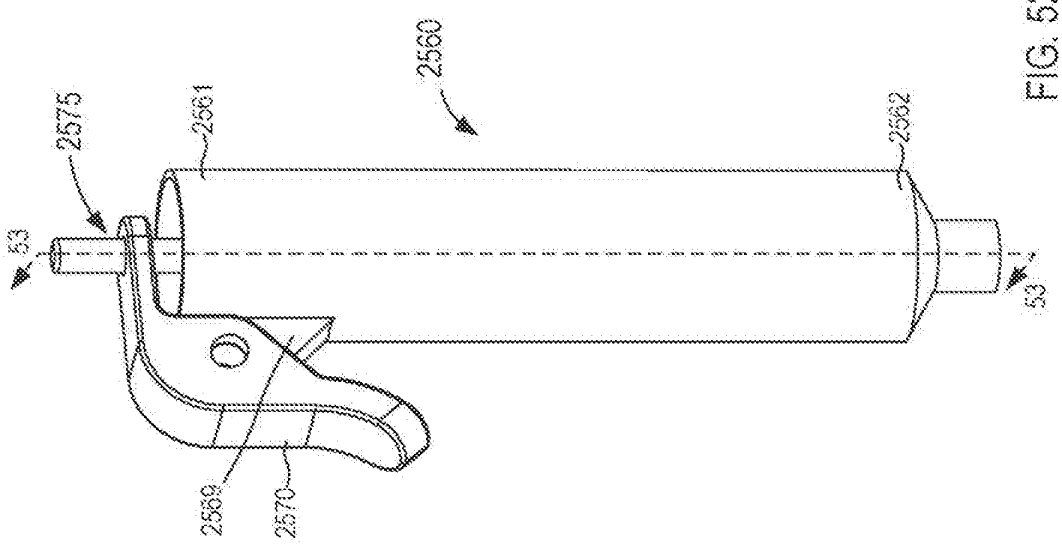

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FIG. 52

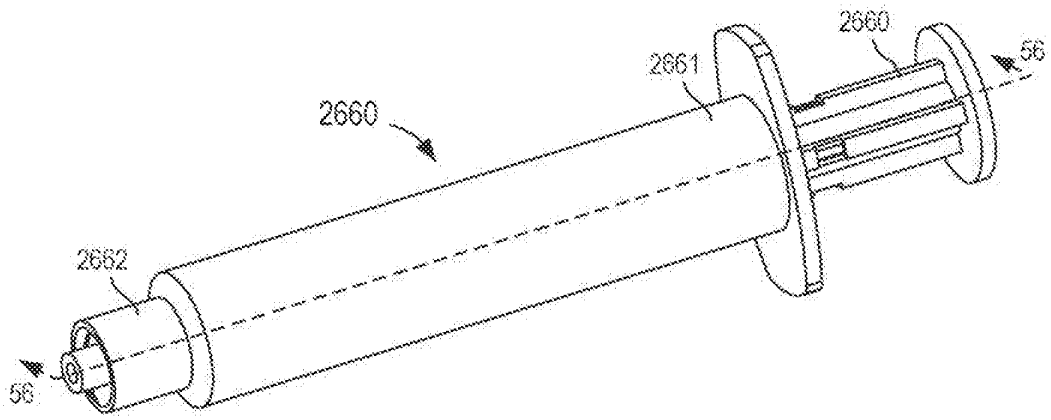

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FIG. 54

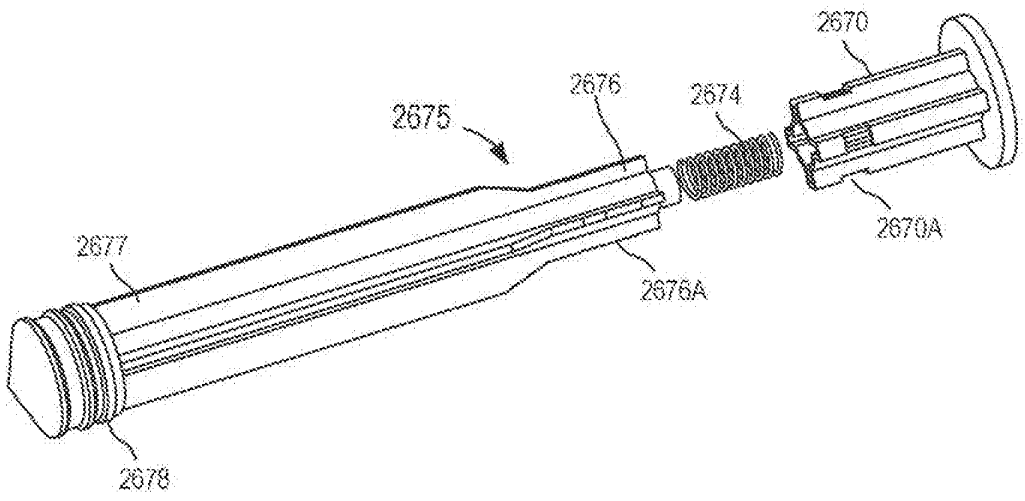

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FIG. 55

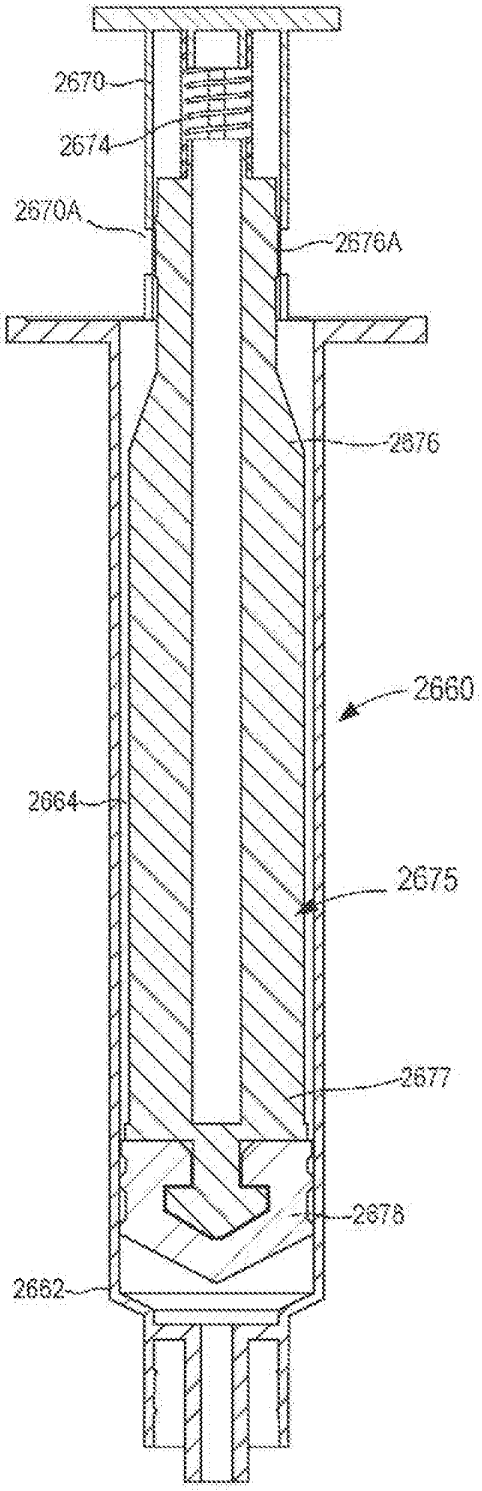


FIG. 56

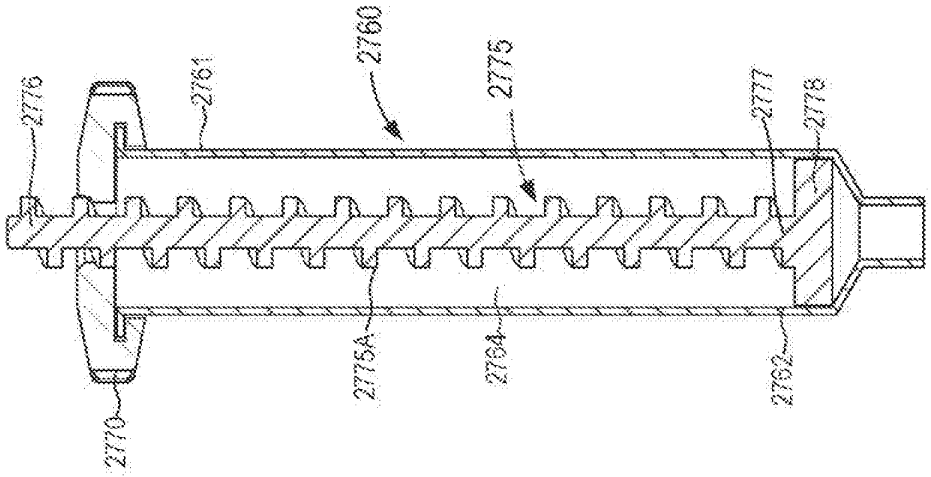

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FIG. 58

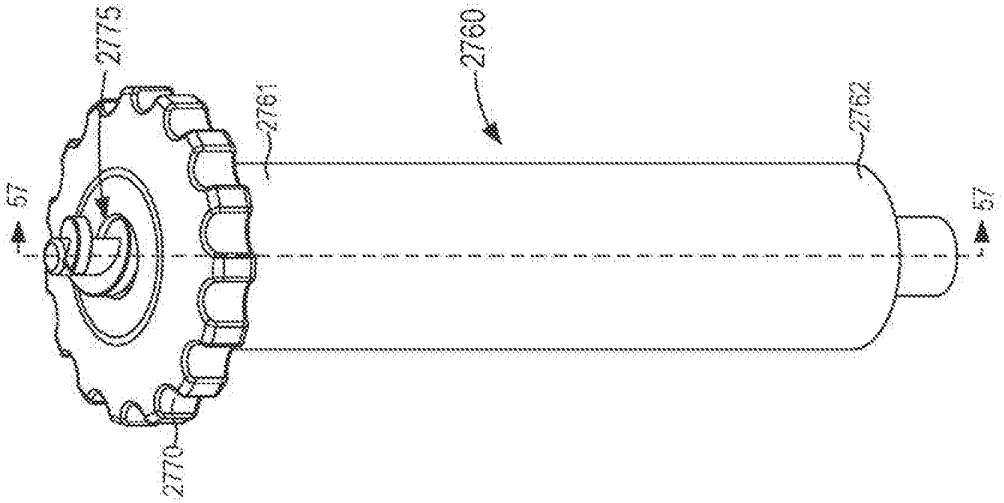

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FIG. 57

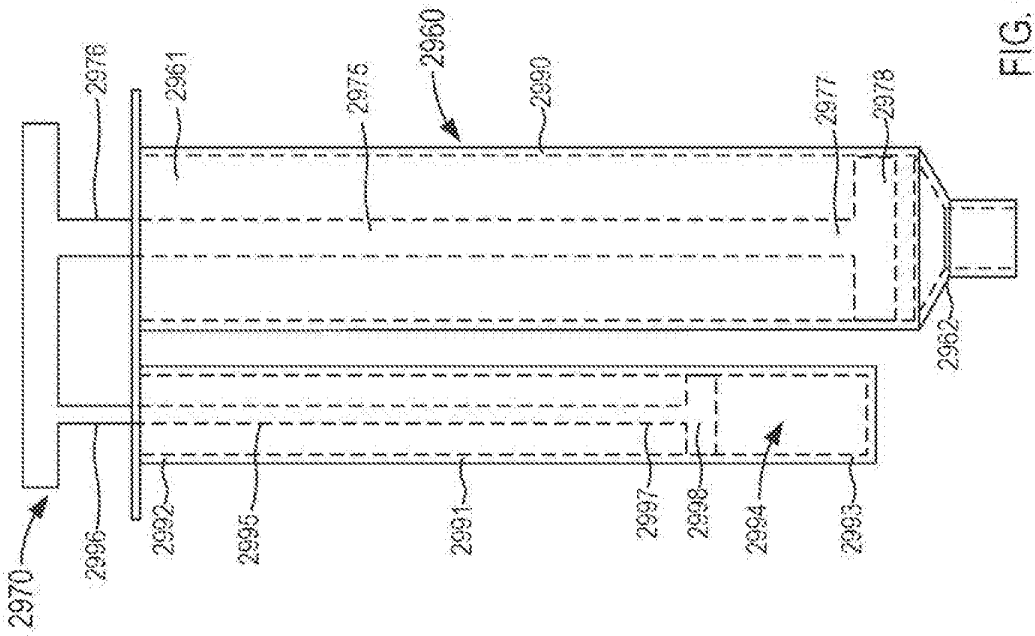

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FIG. 60

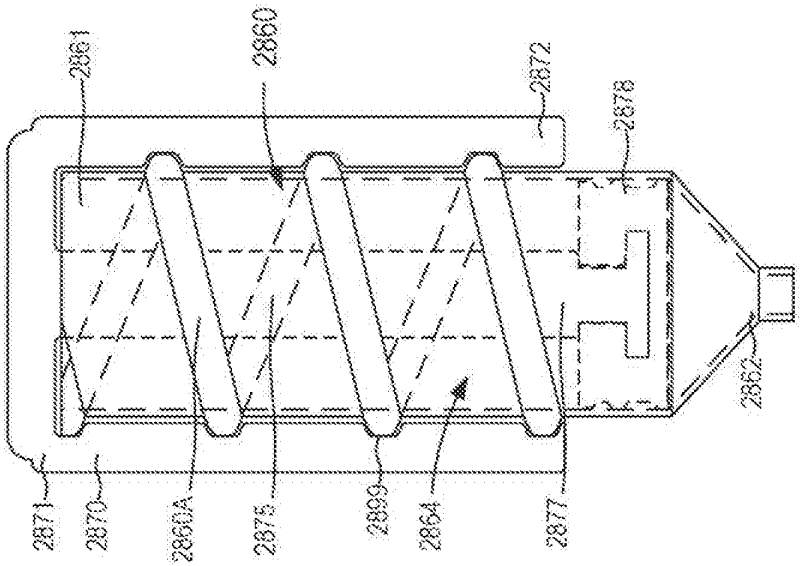

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FIG. 59

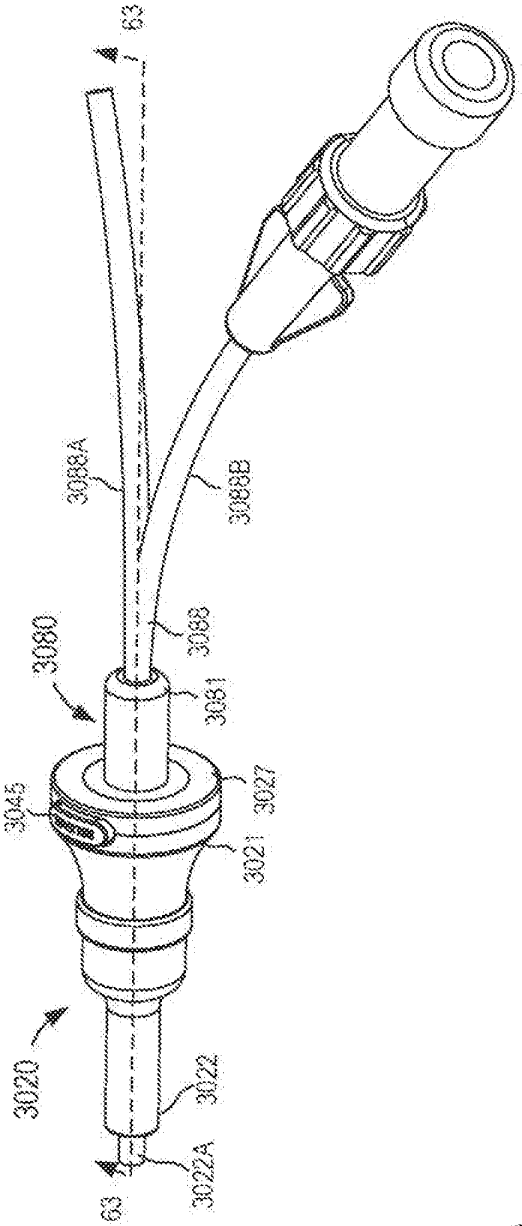

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FIG. 61

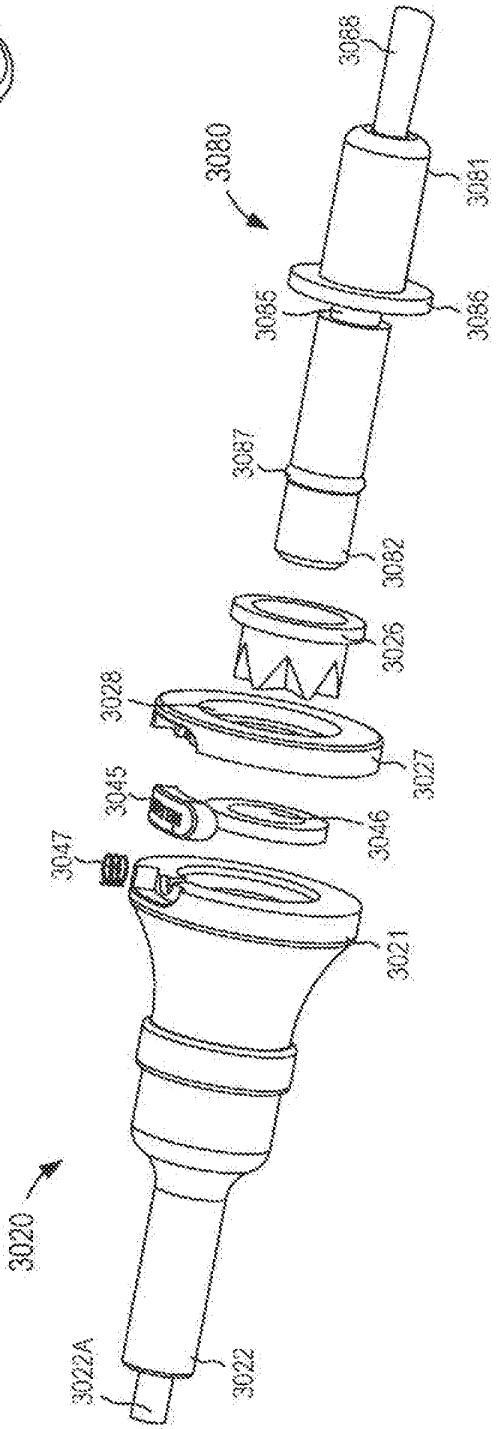

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FIG. 62

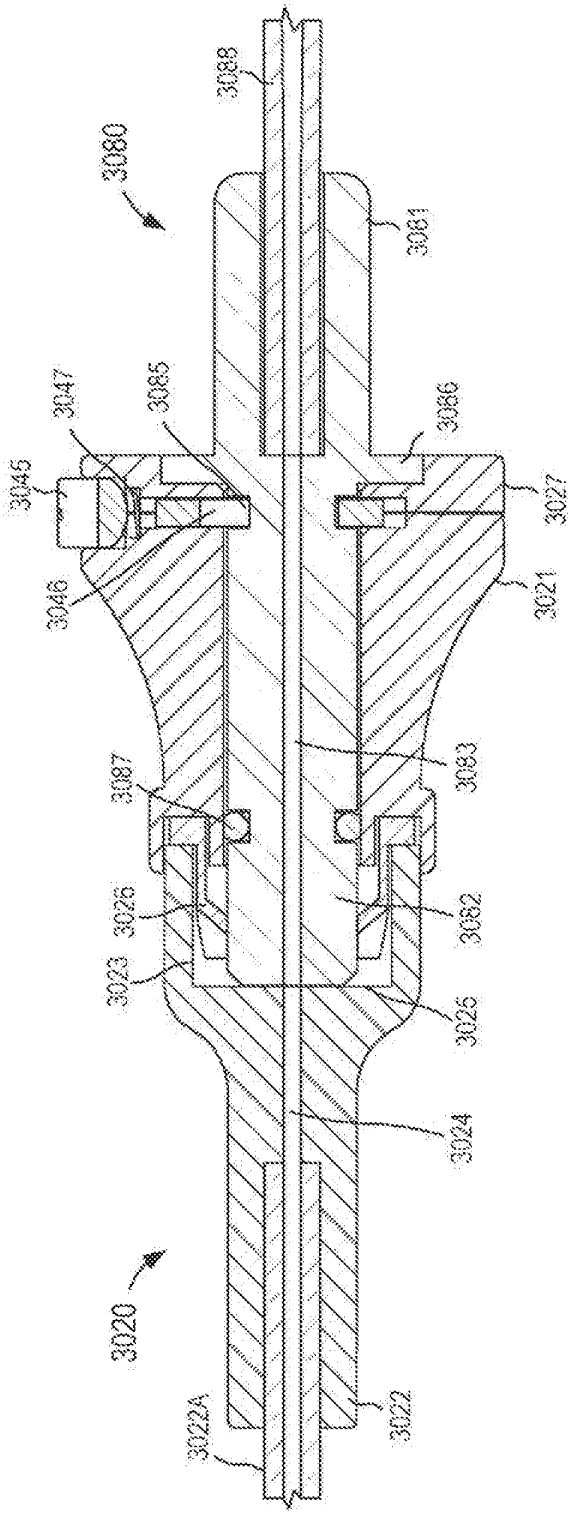

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FIG. 63

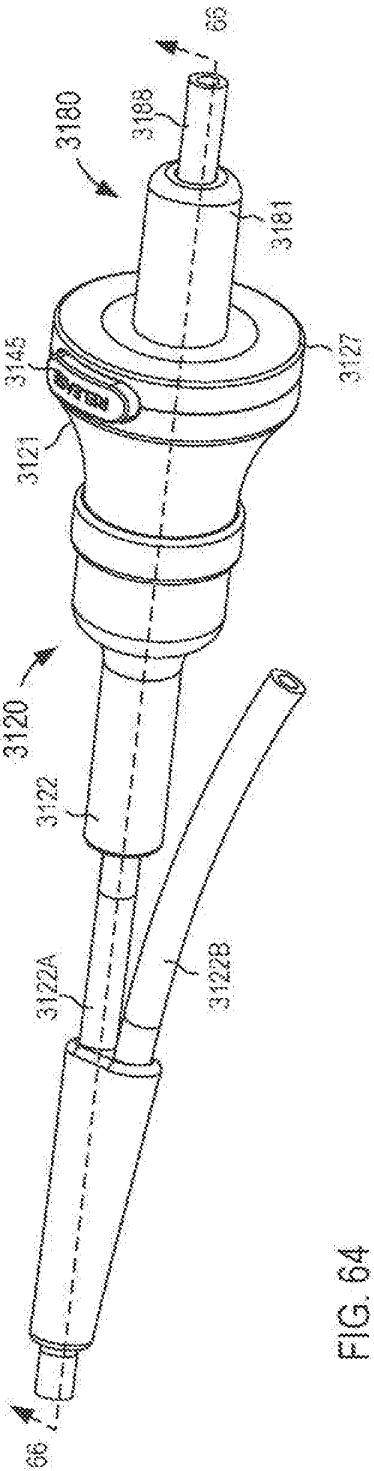

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FIG. 64

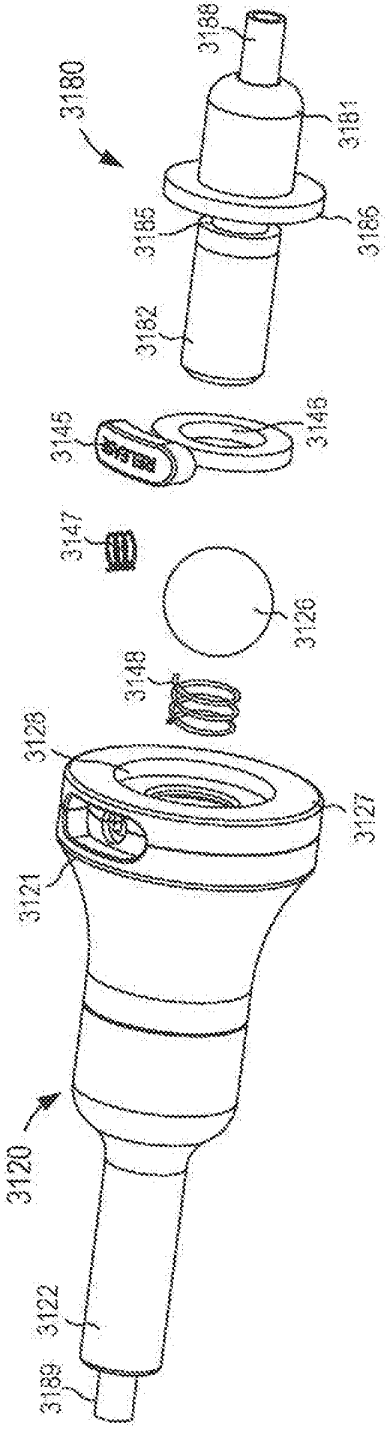

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FIG. 65

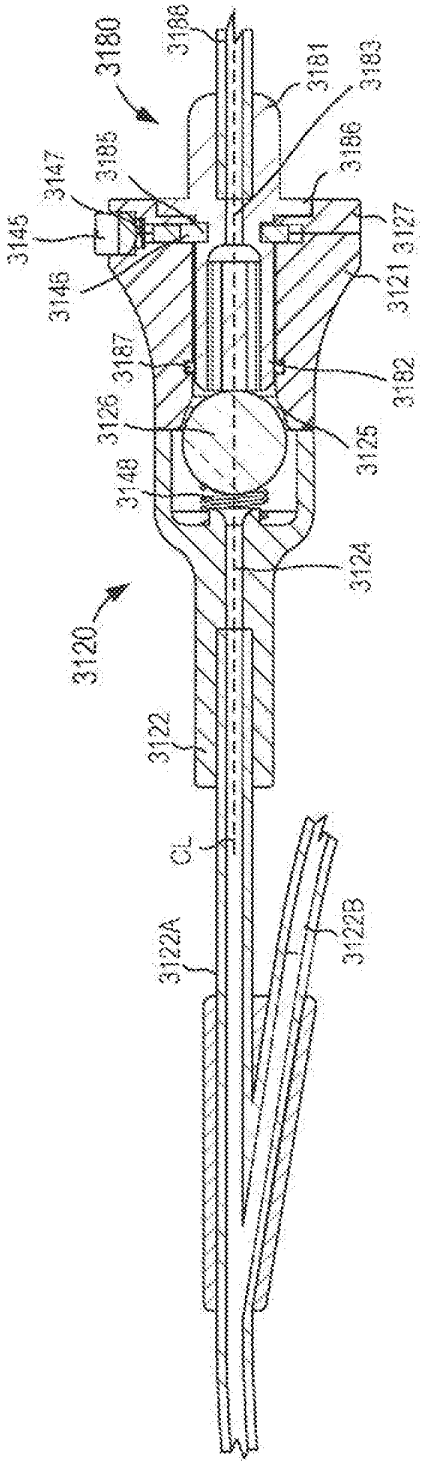

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FIG. 66

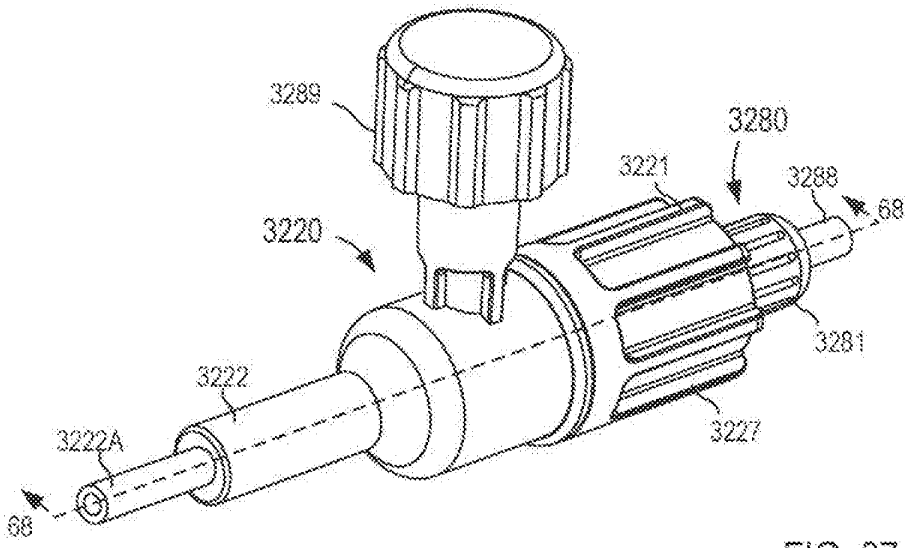

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FIG. 67

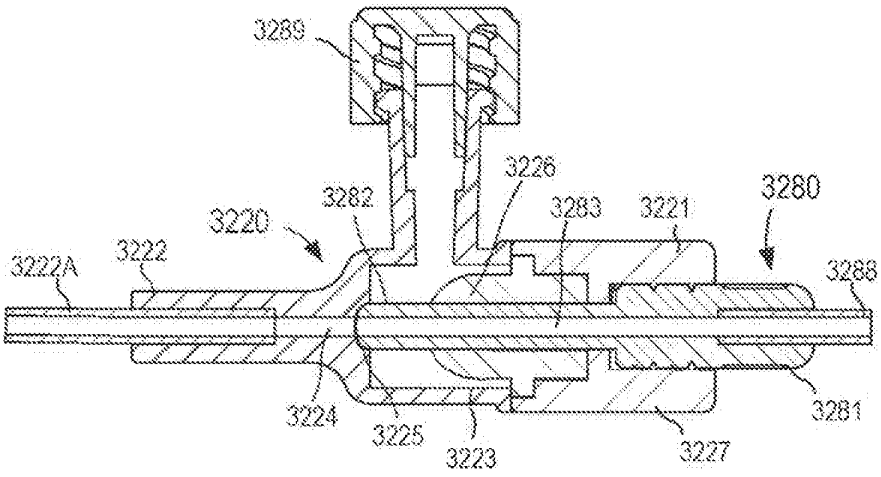

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3288
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3225
3223
3227
3281

FIG. 68

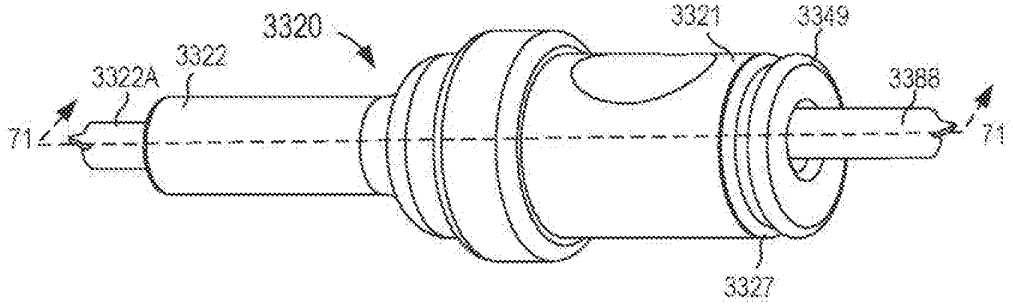

3320
3321
3349
3322
3322A
3388
71
71
3327

FIG. 69

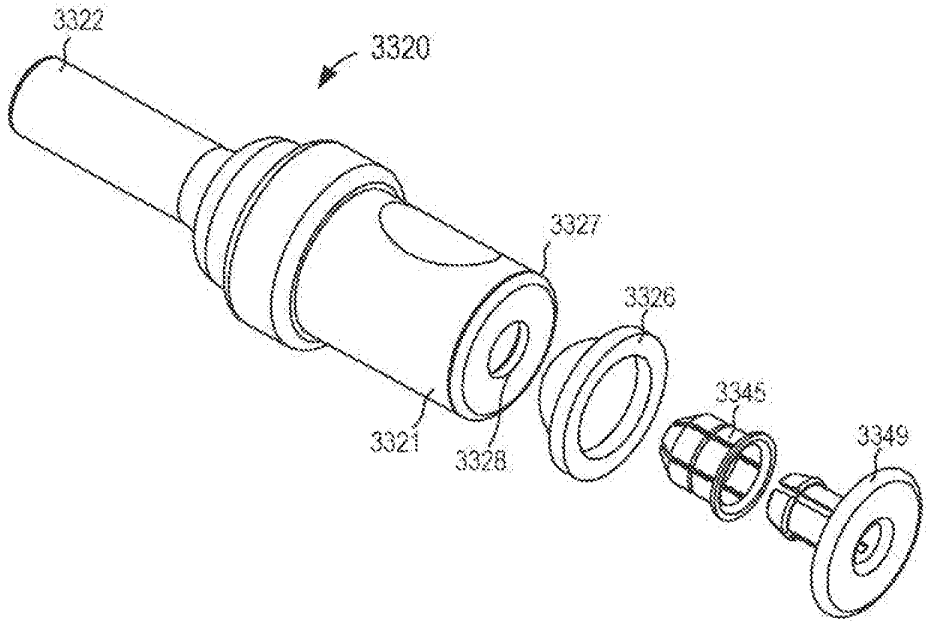

3322
3320
3327
3326
3345
3349
3321
3328

FIG. 70

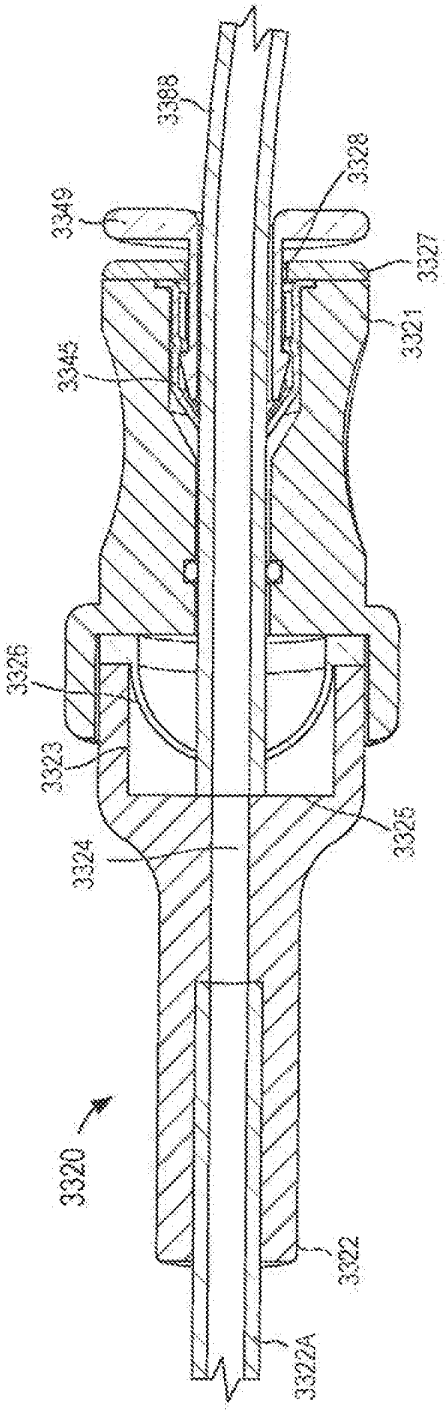

3308
3328
3349
3327
3321
3345
3326
3323
3325
3324
3320
3322
3322A

FIG. 71

PATENT SPECIFICATION (11) 1 378 602

1 378 602

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(72) Inventor WALDEMAR ALEXANDER AYRES

(54) IMPROVEMENTS IN NEEDLE ASSEMBLIES FOR USE WITH APPARATUS FOR COLLECTING SAMPLES OF BLO OD

(71) We, BECTON, DICKINSON & COMPANY, a Corporation organised and existing under a laws of the State of New Jersey, United States of America, and having a principle place of business at East Rutherford, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

In the blood sampling field, there are several well known systems. One of the commonly used systems collects blood from a vein through a needle assembly into an evacuated container. The evacuated container provides the pressure differential necessary to transfer the blood from the vein through the needle assembly into the container. The basic system and apparatus for collecting bleed in this manner is disclosed in U.S. Patent Specification No. 2,689,564 to Kleiner.

Improvements have been made in recent years to the basic evacuated container system for blood sampling such as by the provision of a valve on the assembly to automatically open and close the flow path through the assembly as the evacuated containers are coupled in succession with the assembly. In this manner, a multiplicity of samples can be collected in a multiplicity of containers with only one venapuncture being required. Needle assemblies with automatic valves are shown and described in British Patent Specification No. 1,132,197 to Nehring and U.S. Patent No. 3,494,352 to Russo et al.

Frequently the evacuated containers contain chemical materials, useful in the clinical laboratory tests to be conducted after mixing with the patient's blood. However, these chemical materials may be harmful to a patient if any were to flow from the evacuated container into the patient's blood system. This problem has been successfully eliminated by the use of a one-way valve as shown and described in our co-pending Application No. 20921/73 (Serial No. 1,378,603) filed on 2 May 1973.

In systems such as those referred to above, it has often been found that it is desirable to provide an indication means on the needle assembly to inform an operator that a venapuncture has been successfully accomplished. Consequently, it is desirable to provide a single device which includes a one-way valve for use in collecting multiple samples of blood from a single venapuncture into a multiplicity of collection containers whilst eliminating the danger of back flow of fluid into the patient and which includes a blood flow indication means which indicates that a venapuncture has successfully been accomplished so that the evacuated collection container can be coupled to the needle assembly to withdraw a blood sample from the patient.

According to our invention a needle assembly for use with apparatus for collecting blood samples from a patient has means for indicating when a venapuncture has been accomplished and then for transferring blood from the patient into an evacuated container, whilst preventing any back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing backflow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passage-way for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in com-

[P

munication with the evacuated container, a valve assembly mounted in the chamber and normally in an unarmed position in which passages therein permit blood to flow from the vein into the chamber upon venapuncture and being movable to an armed position in which the valve assembly forms a non-return valve and in which the passageway from the vein to the chamber is closed by means of a resilient elastomeric valve member in the chamber, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from the blood vessel to the rearward end and into the container, the valve member thereafter being responsive to an increase in pressure at the rearward end to automatically return to the closed position and thereby prevent the backflow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly.

Preferably the needle assembly also includes a second cannula which is slidably mounted in a bore in the rearward end of the housing, the second cannula having its forward end in the chamber and its rear end extending from the rear end of the housing for connection to the container.

The needle assembly may have the rear end of the first cannula extending into the chamber and have an elastomeric sleeve, having an open end and a closed end, slidably mounted on the rear end of the first cannula in sealing engagement therewith, the sleeve being movable between the unarmed position and the armed position on the first cannula, a transverse hole in the wall of the sleeve which permits communication between the rear end of the first cannula and the exterior of the sleeve when the sleeve is in the unarmed position and the hole being obscured when the sleeve is moved to the armed position, a slit in the wall of the sleeve, the slit normally being closed when the sleeve is in the armed and unarmed position but which opens automatically when there is a reduction in pressure at the rearward end as the container is coupled with the assembly and the slit thereafter automatically closing when there is an increase in pressure at the rearward end and when a predetermined pressure differential exists between the forward and reward end of the assembly, and an annular flange extending around the forward open end of the sleeve.

The invention also includes a method of transferring blood from a patient into an evacuated container whilst indicating that a venapuncture has been accomplished and preventing the back flow of fluid from the container into the patient during and after the collection of a blood sample with the use of a needle assembly having a forward end for penetration into the blood vessel of a patient, a rearward end adapted to be coupled in fluid communication with the evacuated container, a continuous passageway through the assembly, and a valve assembly including means for visually indicating a venapuncture and including a resilient elastomeric valve member on the assembly adapted to deform and open when subjected to pressure in one direction and adapted to close when the pressure in the one direction is relieved, the method comprising, inserting the forward penetrating end of the assembly into the blood vessel of a patient until the visual indicating means denotes a successful venapuncture, coupling the evacuated container to the rearward end of the needle assembly and initially shifting the resilient elastomeric valve member to an armed position in which the valve member prevents flow between the ends of the assembly and subsequently coupling the evacuated interior of the container to the passageway through the needle assembly so that the elastomeric valve is subjected to a pressure differential in one direction and automatically responds to the pressure differential to deform and open and permit blood to flow from the patient to the container, and removing the container from coupling engagement with the needle assembly after the pressure differential has been relieved so that the valve has automatically returned to the normally closed position thereby preventing flow between the ends of the needle assembly.

An example of a needle assembly in accordance with our invention will now be described with reference to the accompanying drawings in which:—

Figure 1 is a side elevation of a needle assembly attached to a holder and with an evacuated container in a position ready for coupling with the needle assembly;

Figure 2 is an enlarged fragmentary section of the apparatus shown in Figure 1 after it has been used to achieve a venapuncture prior to the initial closure of a valve member;

Figure 3 is an enlarged section of the needle assembly shown in Figure 2;

Figure 4 is a similar view to Figure 2 but showing the valve member in an armed position;

Figure 5 is an enlarged section of the needle assembly shown in Figure 4;

Figure 6 is a similar view to Figure 2 and Figure 4 but showing the evacuated container coupled to the needle assembly and the valve member in the opened position to

permit blood to flow from a vein to the container;

Figure 7 is an enlarged section of the needle assembly shown in Figure 6;

Figure 8 is a similar view to Figure 6 but showing the assembly after the container has been removed and showing a second valve member in a closed position preventing the flow of blood between the ends of the needle assembly;

Figure 9 is an enlarged section of the needle assembly shown in Figure 8; and

Figure 10 is an exploded fragmentary perspective view of the needle assembly.

The separate components of a needle assembly 20 are shown in Figure 10. The assembly includes a housing 21 which is in two parts, a forward part 22 and a rear part 23. Mounted in the forward part 22 is a cannula 24 and mounted in the rear part 23 is a second cannula 25. When the forward part 22 is engaged with the rear part 23 a chamber 26 is formed as shown in Figures 1 to 9. Housed within chamber 26 is an elastomeric sleeve 27, a rigid cage 28, a retaining disc 29, and an elastomeric sealing disc 30.

The forward part 22 has a frusto-conical surface 31 which fits into and engages with an inner cylindrical surface 32 of a tubular portion of the rear part 23. The engagement between parts 22 and 23 is tight enough to keep the parts of housing 21 together during operation of the assembly. If required, to ensure this engagement of the parts of housing 21, an epoxy resin adhesive may be employed between surfaces 31 and 32 to achieve a positive locking engagement.

A bore 33 in the forward part 22 provides communication between the space in front of the forward part 22 and the chamber 26. The cannula 24 is mounted in the bore 33 with a rear blunt end 34 extending into the chamber 26 and a forward end terminating in a tip 35 extending forward from the part 22 and fixed in the bore by an epoxy resin adhesive 51. The tip 35 is pointed to enable it to penetrate a patient's vein.

The rear part 23 of the housing 21 has a sleeve 36 for engagement with the forward part 22 and to provide the sidewalls of the chamber 26. The remainder of the part 23 is a reduced diameter cylinder having a screw thread 37 formed on its outer surface to connect the needle assembly 20 to a holder 38. The holder 38 forms a guide for an evacuated container 39. The container 39 is formed by a tube 40 which is evacuated and is closed at its open end by a self-sealing punctureable stopper 41.

The rear part 23 has an axial bore 42 providing communication between the rear end of the part 23 and chamber 26. The cannula 25 is slidably mounted in the bore 42.

The rear end of the cannula 25 extends rearwardly from the housing 21 and has a pointed tip 43 for penetration through the stopper 41 of the evacuated container 39. The cannula 25 is slidably mounted in the bore 42 and has a forward blunt end 44 extending into the chamber 26. Adjacent the forward end of the cannula 25 is a side opening 45 which is movable into and out of the chamber 26 as the cannula 25 slides through the bore 42. The elastomeric sealing disc 30 rests against a rear wall of the chamber 26 and has a central hole, the diameter of which is smaller than the external diameter of the cannula 25, so that the elastomeric sealing disc 30 maintains a seal with the external surface of the cannula 25 as it slides through the disc 30. Thus the chamber is liquid-tight so that liquid flow into and out of the chamber 26 only occurs through the cannulae 24 and 25. The sealing disc 30 is held in place by the rigid disc 29 which is a 'push fit' in the rear of the housing 21. The sealing disc 30 is sandwiched between the disc 29 and the rear wall of the housing 21. An annular bead 46 projecting from the rear wall of the housing engages with the under surface of the disc 30 to ensure a seal between the disc 30 and the rear wall of the chamber and prevent leakage from the chamber 26 through the bore 42 in the rear part 23.

The cage 28 is stuck on the end 44 of the cannula 25 with an epoxy resin adhesive 47. The cage 28 is constructed from a plastics material and it seals the open end of the end 44 of cannula 25. This means that the access from the chamber 26 into the bore of cannula 25 is solely by the side opening 45. The cage 28 is a hollow cylinder and has a closed end mounted on cannula 25 and an opposite open end. Adjacent to the closed end are four transverse side ports 48. The side ports are equi-spaced about the circumference of the cage 28. The external diameter of the cage 28 is less than the internal diameter of the housing 21 so the cage 28 is free to slide axially with the cannula 25. The hollow cage 28 receives the major portion of the sleeve 27 and there is a clearance between the cage 28 and the elastomeric sleeve 27 to enable the cage 28 to slide with respect to sleeve 27. A cylindrical rim at the open end of the cage 28 engages with a flange 50 formed at the open end of sleeve 27. The open end portion of sleeve 27 is slidably mounted on the rear, blunt end 34 of cannula 24. To achieve this the sleeve 27 has its open end expanded so that it surrounds and frictionally engages with the end 34 of the cannula 24 and seals with it. The sleeve 27 is movable to an armed position as shown in Figures 4 to 9 in contrast to its initial unarmed position as shown in Figures 2 and 3. The operational sequence of the needle assembly will be discussed in detail

below. The sleeve 27 is formed as a hollow cylinder having a closed end and an open end. As described above a flange 50 is formed about its open end and the bore 52 of the cylindrical sleeve receives the rear end 34 of the cannula 24.

Initially, in the unarmed position only the forward open end of the sleeve 27 is mounted on the cannula 24 and, rearwardly of blunt end 53 of the cannula 24, the sleeve 27 has one or more transverse holes 54 which pass from the interior to the exterior of the sleeve 27. Additionally, adjacent the rear, closed, end of the sleeve 27 is a slit 55 which is normally in the closed position due to the self-sealing elastomeric properties of the sleeve 27. Any well known elastomeric self-sealing material such as natural or synthetic rubber can be utilized for the sleeve 27.

The housing 21 and the cage 28 are made from a transparent plastics material so that the presence of blood within the chamber 26 is readily visible through them for indication purposes. The housing may not be wholly transparent, but may merely include a transparent portion and the presence of blood within the chamber 26 be observed through the transparent portion. Additionally, sleeve 27 may be constructed of a transparent elastomeric material, however, this is not generally utilized, since the blood will flow into the surrounding spaces provided and will be visible through the transparent portions of the housing during the indication procedures and this will be discussed in detail below. All of the components of the assembly with the exception of the cannula and the sleeve may be constructed of a standard low cost, transparent, plastics material or any readily available substitute.

The cannula 25 is slidable into and out of the housing 21 a predetermined distance, its travel being limited in the downward direction by the cage 28 engaging the disc 29 and in the opposite direction by the rim 49 engaging the flange 50 and pressing this against the face 57 of the part 22. The cannula 25 is moved as the evacuated tube 39 is reciprocated within holder 38 during the blood collection procedure since the cannula 25 when inserted through the stopper 41 is gripped tightly by the stopper 41 and thus caused to move by movement of the evacuated tube 39 and stopper 41.

Although slidable, the cannula 25 is continuously hermetically sealed relative to the bore 42 by the elastomeric sealing disc 30 which has been penetrated by the cannula 25.

Figure 1 shows the needle assembly ready for use having been screwed into the holder 38, the holder having the evacuated container 39 in a position ready for engagement with the assembly. The needle assembly 20 is in the initial position as shown in Figures 1 to 3, with the transverse holes 54 behind the end 34 of the cannula 24. In this manner, an open air way exists from the tip 35 of the cannula 24 through the assembly to the side opening 45 in the sliding cannula 25.

When sleeve 27 is pushed forward to encompass all of the rear portion 34 of cannula 24 so that the forward edge of flange 50 of the sleeve rests against inner wall of the housing, the cannula will be positioned so as to occlude transverse openings 54 and cannula 24 will be sealed by the sleeve 27.

Sliding cannula 25 supports valve cage 28. The tip of forward end 44 of cannula 25 is inserted into a recess in the rear end of the valve cage 28 and is sealed therein by epoxy 47 or any other common sealing means. The inner diameter of cylindrical cage 28 is substantially greater than the outer diameter of sleeve 27 so that blood or air can readily flow out of the valve sleeve 27 around the spaces between sleeve 27 and cage 28, and out through one or more of the ports 48 of cage 28.

As shown in Figure 10, portion 22 of housing 21 has a tapered exterior surface 31 which mechanically fits and supports and seals portion 32 of the cylindrical rear portion 23 of housing 21. Rear portion 23 supports sliding needle 25 which is mounted in a close sliding fit within passageway 42 through rear end portion 23. Rear end portion 23 also supports elastomeric sealing disc 30 and the retaining disc 29. Retaining disc 29 is a plastic moulded part. It may be constructed of any other common material for the purpose required. It has an outside diameter which has a push fit in a narrowed region of the inside of rear housing portion 23. In assembly of this seal, rear portion 23 is positioned vertically. Then the elastomeric sealing disc 30 is dropped inside. It is positioned to lie flat across the end of passageway 42. Then the sealing disc 29 is dropped in and stops at the narrowed portion 56 of rear end 23, then a small press or similar device is used to push disc 29 down as far as it will go. The annular bead 46 projecting from the inner surface of portion 23 bites into the elastomeric disc 30 under this pressure thereby assuring a continuous seal.

Then the cage 28 is joined to the tip of needle 25 by epoxy or any other common affixing means. Thereafter, the pointed end 43 of needle 25 is passed through the central hole of retainer disc 29 and pierces the elastomeric disc 30 and is then pushed into the position shown in Figures 1 to 3. The cylindrical member forming end portion 22 including cannula 24 is inserted into rear end portion 23 until the respective walls meet and seal. This action also inserts a partial amount of end portion 34 of cannula 24 into the open end of sleeve 27. The assembly is

then positioned for use as depicted in Figure 3.

In operation, threaded outer surface 37 of rear end 23 is screwed into the threaded receiving surface of holder 38 in a conventional manner. The evacuated container 39 is then positioned in the rear part of holder 38 in position for use. This arrangement is depicted in Figure 1 of the drawings. The operator should not couple any portion of the stopper 41 with the rear end of cannula 25 before inserting cannula 24 into the vein of a patient. In this manner, effectiveness of the blood flow indication portion of the needle assembly will be assured.

Then, as shown in Figures 2 and 3, the tip 35 of the cannula 24 is inserted into a patient's vein. Blood will start to flow from the patient's vein through the airway from the tip 35 to the side opening 45 as follows. The blood will pass through the cannula 24 and out through the transverse holes 54 in the sleeve 27. It will then flow through the space between the outside of the sleeve 27 and the inside of the cage 28 until it passes out through the ports 48 in the wall of the cage 28. The blood will then begin to fill the annular space between the outside of the cage 28 and the inside of the chamber 26. If the blood is allowed to continue to flow from the vein, it will pass through the side opening 45 in the sliding cannula 25 and out through the tip 43 of the cannula 25. The pressure in the patient's blood vessels causes the blood to flow through this series of open passageways. When blood is present in the chamber 26, it will be visible to an operator, who will be watching for this indication. The operator will then push the evacuated container 39 further into the holder 38 so that the cannula 25 penetrates through the stopper 41. The action of pushing the tube 39 into holder 38 forces the cannula 25, firstly to slide forward so that the sleeve 27 is forced further onto the end 34 of the cannula 24 until the flange 50 abuts the interior surface 57 of the housing 21 which acts as a positive stop. In this position the transverse openings 54 will be occluded by the wall of the cannula 24. The only restriction to the sliding of the cannula 25 is the friction acting between the sealing disc 30 and the external surface of the cannula 25. This friction is considerably less than the friction between the cannula 25 and the stopper 41 when the cannula 25 penetrates the stopper 41. Thus the sleeve 27 will be moved forward to its position in which it operates as a valve member before the cannula 25 enters the evacuated space in the container 29. The sleeve 27 stays in its forward position and operates as a valve member thereafter. Figures 4 and 5 show the assembly after the sleeve 27 has been transferred to its forward position just prior to the penetration of the stopper 41 by the cannula 25.

As the evacuated container 39 is pushed further into the holder 38 the cannula 25 pierces the stopper 41 and the cannula 25 enters the evacuated space within the container 39. Figures 6 and 7 show the evacuated container after the forward movement has been completed and with the cannula 25 in the interior of the tube 40. The slit 55 opens because of the large pressure differential that exists between the vacuum within the container 39 and the blood pressure within the patient's vein, thus blood flows into the tube 40 via the path shown by the arrows in Figure 7. As blood flows into the tube 40 the pressure differential across the slit 55 is reduced and eventually the slit 55 closes when a predetermined pressure differential is reached. After the tube 40 is filled with blood, and it is desired to fill one or more additional tubes, the operator pulls the container 39 out of the holder 38. In doing this, because the friction between the stopper 41 and the cannula 25 is greater than the friction between the cannula 25 and the sealing disc 30, the cannula 25 is moved rearwardly until the rear end of the cage 28 abuts the retaining disc 29 which provides a positive stop. This action is completed before the cannula 25 is pulled out of the stopper 41. In this position, the side opening 45 of the cannula 25 is behind the sealing disc 30 and is no longer in communication with the chamber 26. Therefore, no more blood can flow out of the cannula 25. However when another container is inserted this will once again force the cannula 25 and the cage 28 forward exposing the opening 45 to the chamber 26 and thus permitting blood to flow into the container when the cannula 25 has pierced the stopper on this other container. The closed position at the end of the collection of the first sample of blood and prior to the insertion of a second collection container is shown in Figures 8 and 9 of the drawings. It should be noted that the tip 35 remains in the vein thereby enabling multiple samples to be taken in a succession of collecting containers with only a single venapuncture. After the desired number of samples have been taken, the assembly is discarded.

Thus, the needle assembly 20 performs a combination of functions. It provides a one-way valve which is normally closed and alleviates the danger of the back flow during blood sampling procedures whilst at the same time providing an indication to notify the operator when a proper venapuncture has been accomplished as well as providing a multiple sampling device.

WHAT WE CLAIM IS:—

1. A needle assembly for use with appar-

atus for collecting blood samples from a patient, the needle assembly having means for indicating when a venauncture has been accomplished and then for transferring blood from the patient into an evacuated container, whilst preventing back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing backflow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passageway for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in communication with the evacuated container, a valve assembly mounted in the chamber and normally in an unarmed position in which passages therein permit blood to flow from the vein into the chamber upon venapuncture and being movable to an armed position in which the valve assembly forms a non-return valve and in which the passageway from the vein to the chamber is closed by means of a resilient elastomeric valve member in the chamber, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from the blood vessel to the rearward end and into the container, the valve member thereafter, being responsive to an increase in pressure at the rearward end to automatically return to the closed position and thereby prevent the back flow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly.

2. A needle assembly according to claim 1, in which a second cannula is slidably mounted in a bore in the rearward end of the housing, the cannula having its forward end in the chamber and its rear end extending from the rear end of the housing for connection to the container.

3. A needle assembly according to claim 2, in which an elastomeric sealing member is in sealing engagement with the external surface of the second cannula and the wall of the rear end of the housing to thereby eliminate leakage between the wall of the rear end of the housing and the second, sliding cannula.

4. A needle assembly according to claim 3, in which a retaining disc is frictionally mounted in the chamber so that the elastomeric sealing disc is sandwiched between the retaining disc and the housing, the retaining disc having a bore through which the sliding cannula passes.

5. A needle assembly according to claim 3 or claim 4, in which an annular bead projects from the inner surface of the housing into the chamber and engages with the elastomeric sealing disc to provide the seal at the rear end of the housing.

6. A needle assembly according to any one of the preceding claims, in which the rear end of the first cannula mounted in the forward penetrating end of the housing extends rearwardly into the chamber, an elastomeric sleeve having an open end and a closed end is slidably mounted on the rear end of the first cannula in sealing engagement therewith, the sleeve being movable between the unarmed position and the armed position on the cannula, a transverse hole in the wall of the sleeve which permits the communication between the rear end of the first cannula and the exterior of the sleeve when the sleeve is in the unarmed position and the hole being obscured when the sleeve is moved to the armed position, a slit in the wall of the sleeve, the slit normally being closed when the sleeve is in the armed and unarmed posision but which opens automatically when there is a reduction in pressure at the rearward end as the container is coupled with the assembly and the slit thereafter automatically closing when there is an increase in pressure at the rearward end and when there is a predetermined pressure differential between the forward and rearward end of the assembly, and an annular flange extending around the forward open end of the sleeve.

7. A needle assembly according to claim 6 when dependent on any of claims 2 to claim 5, in which a tubular hollow cage is mounted in the chamber, on the forward end of the sliding cannula and surrounding the elastomeric sleeve, the cage being in engagement with the flange on the sleeve so that moving the sliding cannula will move the cage and the engaged sleeve from the unarmed to the armed position when the cannula is moved towards the sleeve and will disengage the cage from the sleeve when the sliding cannula is moved away from the sleeve.

8. A needle assembly according to claim 7, in which there is a transverse opening in the side wall of the cage so that when the sleeve is in the unarmed position and a venapuncture is accomplished, blood will flow through the penetration cannula, through the

transverse opening in the sleeve and through the transverse opening in the cage into the chamber where its presence can be seen and this provides an indication that the venapuncture has been accomplished.

9. A needle assembly according to claim 7 or claim 8, in which the cage is mounted on the forward end of the sliding cannula to seal the end thereof and the sliding cannula has a side opening therein adjacent its forward end, the side opening being positioned within the chamber when the sliding cannula is in its forward position and outside the chamber and being sealed therefrom by the elastomeric sealing disc when the sliding cannula is in its rearmost position in which a surface on the cage engages with a surface on the housing to provide a stop and limit the further withdrawal of the sliding cannula.

10. A needle assembly according to any one of the preceding claims in which the housing is formed in two separate parts a forward end portion and a rearward end portion, the two portions being held together in frictional engagement.

11. A needle assembly according to any one of the preceding claims having a holder coupled to it, the holder being of a hollow cylindrical configuration so that, in use, it receives the evacuated container within and directs the container to couple with the needle assembly.

12. A needle assembly according to any one of claims 2 to claim 10 or claim 11 when dependent on any one of claims 2 to claim 10, having an evacuated container coupled with it, the container including a punctureable self-sealing stopper pierced by and engaged with the sliding cannula.

13. A method of transferring blood from a patient into an evacuated container whilst indicating that a venapuncture has been accomplished and preventing the back flow of fluid from the container into the patient during and after the collection of a blood sample with the use of a needle assembly having a forward end for penetration into the blood vessel of a patient, a rearward end adapted to be coupled in fluid communication with the evacuated container, a continuous passaway through the assembly, and a valve assembly including means for visually indicating a venapuncture and including a resilient elastomeric valve member in the assembly adapted to deform and open when subjected to pressure in one direction and adapted to close when the pressure in the one direction is relieved, the method comprising, inserting the forward penetrating end of the assembly into the blood vessel of a patient until the visual indicating means denotes a successful venapuncture, coupling the evacuated container to the rearward end of the needle assembly and initially shifting the resilient elastomeric valve member to an armed position in which the valve member prevents flow between the ends of the assembly and subsequently coupling the evacuated interior of the container to the passageway through the needle assembly so that the elastomeric valve is subjected to a pressure differential in the one direction and automatically responds to the pressure differential to deform and open and permit blood to flow from the patient to the container, and removing the container from coupling engagement with the needle assembly after the pressure differential has been delivered so that the valve has automatically returned to the normally closed position thereby preventing flow between the ends of the needle assembly.

14. A method according to claim 13, in which a multiplicity of evacuated containers are coupled successively with the needle assembly to thereby collect a multiplicity of successive blood samples without leakage of blood from the needle assembly and without back flow of fluid from the rear end of the assembly into the patient.

15. A needle assembly for use with apparatus for collecting blood samples from a patient, the needle assembly having means for indicating when a venapuncture has been accomplished and then transferring blood from the patient into an evacuated container, whilst preventing back flow from the container into the patient, and means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container to be filled from the same venapuncture, the means for indicating when a venapuncture has been accomplished and for preventing back flow comprising an at least partly transparent housing having a chamber therein, a forward penetrating end including a cannula extending from the housing for penetration into the blood vessel of a patient, a rearward end extending from the housing and adapted to be coupled in fluid communication with the interior of the evacuated container, a passageway for directing blood from the blood vessel through the housing to the container when the forward end is in the blood vessel and the rearward end is in communication with the evacuated container, a resilient elastomeric valve member in the chamber forming a non-return valve which closes the passageway, the valve member being responsive to a reduction in pressure at the rearward end of the assembly upon coupling with the evacuated container to deform the valve member and automatically open the passageway to permit blood to flow from a blood vessel to the rearward end and into the container, the valve member thereafter being responsive to an increase in pressure at the rearward end to automatically return to the

closed position and thereby prevent the back flow of fluid from the rear end of the assembly to the blood vessel when a predetermined pressure differential exists between the forward and rearward end of the assembly, the means for automatically blocking the blood flow due to venous pressure while changing from one container to a successive container including a second valve means adapted to permit or prevent the flow of blood through the rearward end and into the evacuated container as successive containers are filled with successive blood samples.

16. A needle assembly according to claim 1 constructed substantially as described with reference to the accompanying drawings.

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Sheet 1

Fig. 1

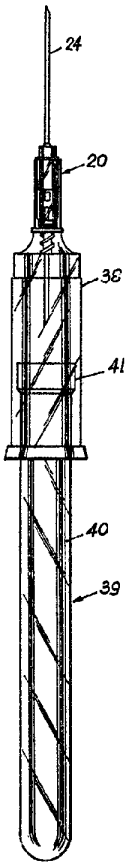


Fig. 2

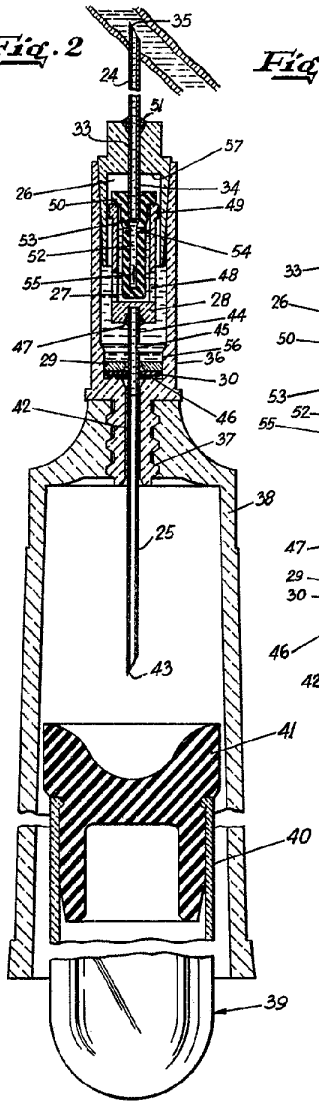


Fig. 3

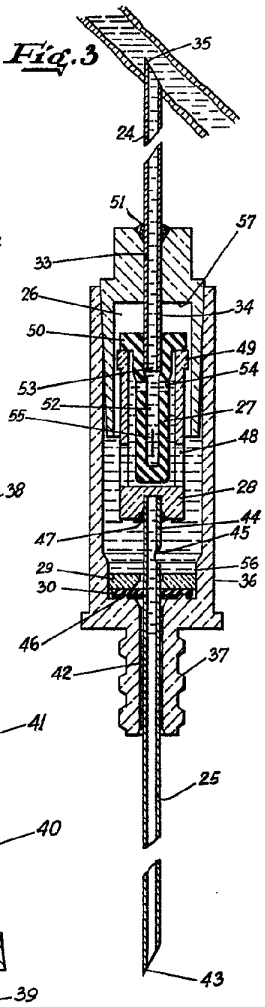


Fig. 4

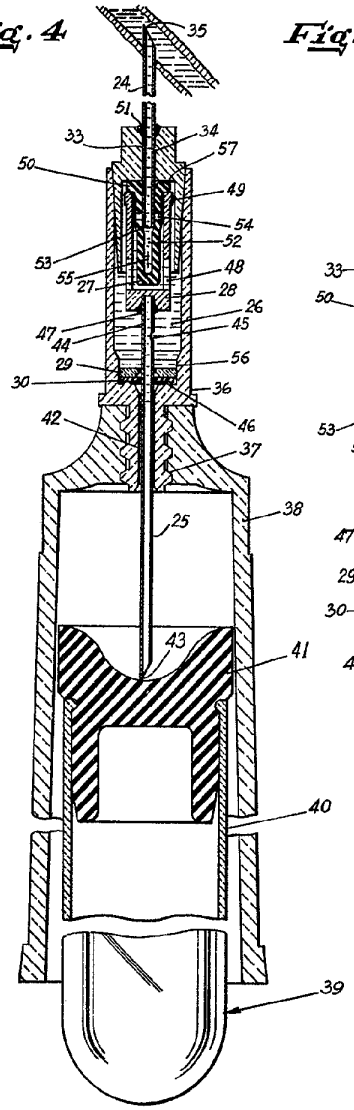

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Fig. 5

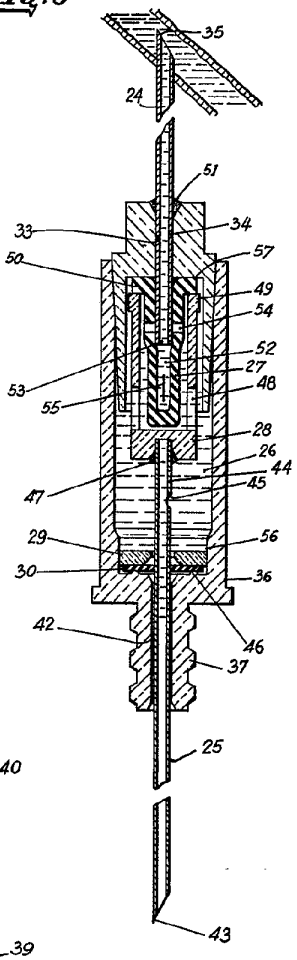

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Fig. 6

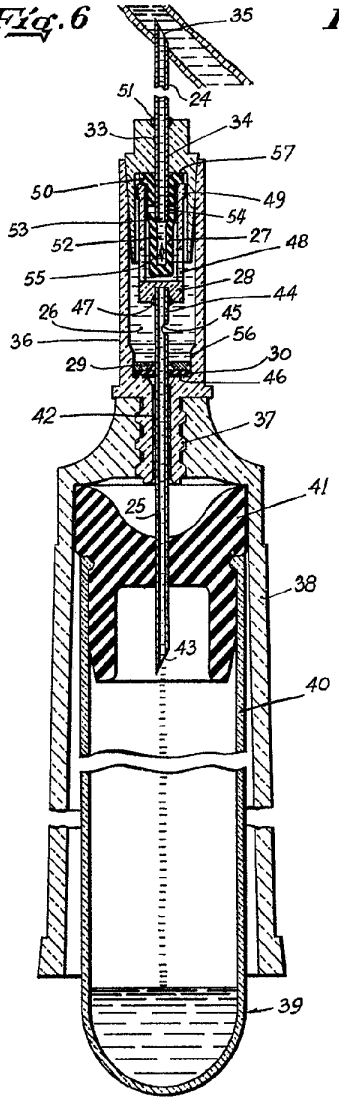

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Fig. 7

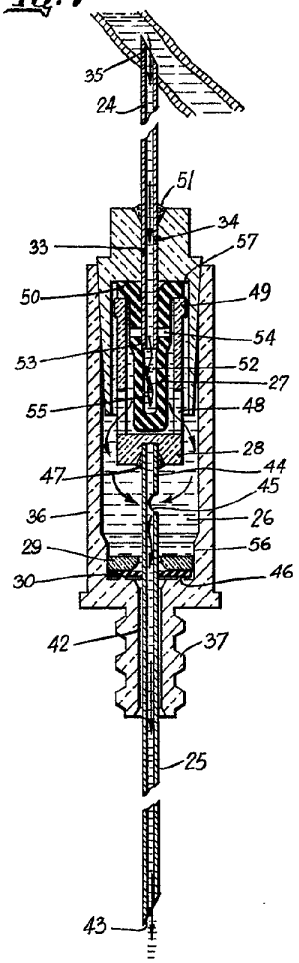

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Fig. 8

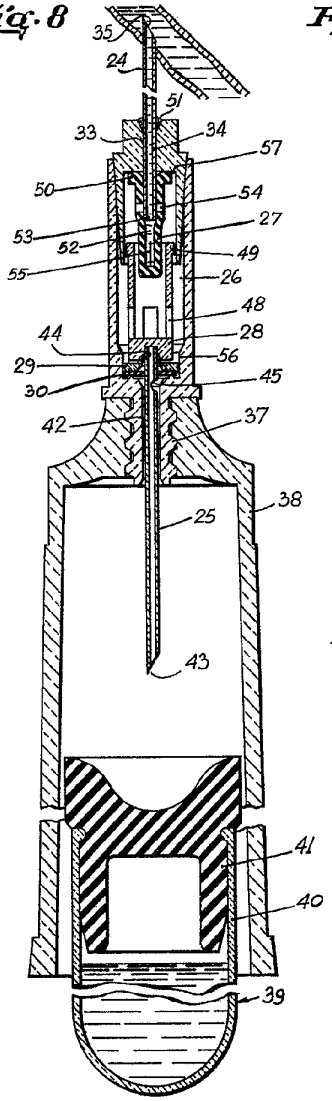
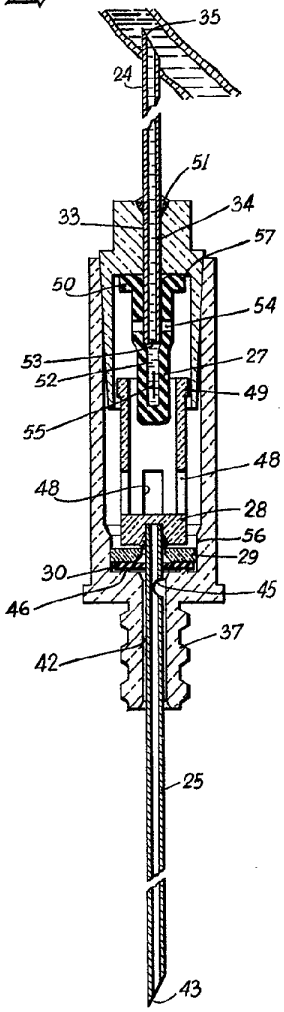

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Fig. 9


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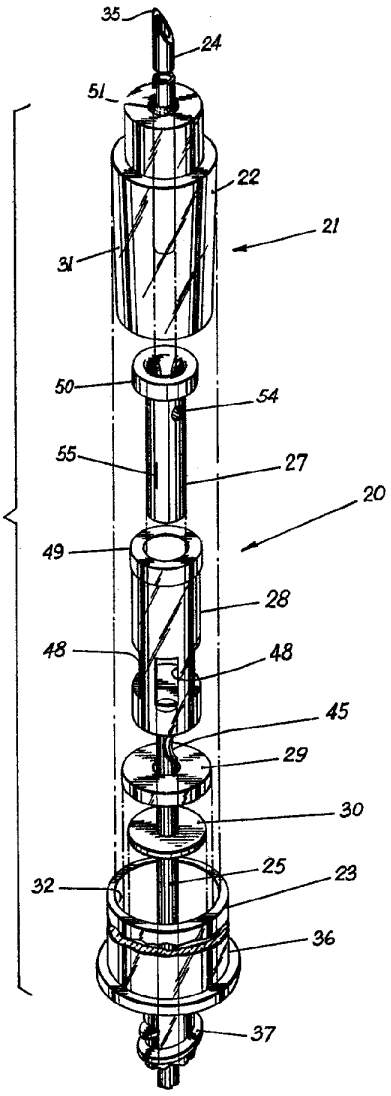


Fig. 10

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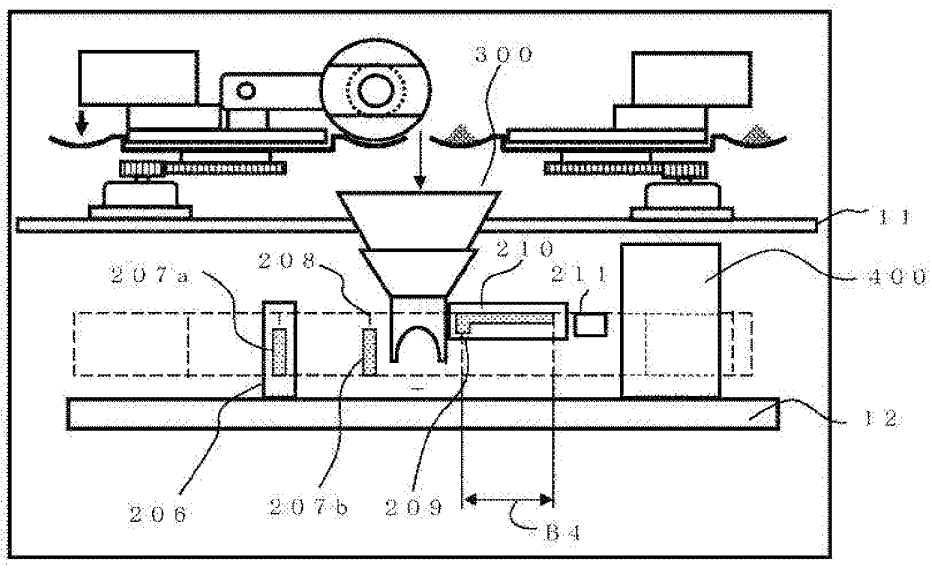
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[Request for examination] Unclaimed
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[Theme code (reference)]
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wrap up close

(57) [Summary]
[Problem] To provide a drug packaging device and a method for manufacturing a packaged dr ug that does not break at the perforated portion of the packaging paper during transportation. A packaging paper storage unit in which V-shaped packaging paper is wound, a transport path for pulling out and transporting the packaging paper from the packaging paper storage unit, a nd a transport path provided in the middle of the transportation path. a heat sealing unit that forms a heat seal for dividing the packaging paper into individual packages; and a drive roller for sandwiching and driving the packaging paper containing the medicine supplied by the med icine supply unit, and a driving roller provided downstream in the transportation direction of t he packaging paper from the driving roller, and the heat seal a perforation forming part for for ming perforations in the portion heat-sealed by the part.
[Selection drawing] Fig. 4



The scope of the claims open —

Claims:

1.

A packaging paper storage unit around which V-shaped packaging paper is wound, a transport path for pulling out and transporting the packaging paper from the packaging paper storage unit,

A heat seal portion provided in the middle of the transport path for forming a heat seal for dividing the packaging paper into individual packages

; A drug supply unit that supplies each package,

a drive roller that sandwiches and drives the packaging paper containing the drug supplied by the drug supply unit, and a downstream downstream of the drive roller in the transportation direction of the packaging paper

. and a perforation forming section provided in the heat-sealing section for forming perforations in the portion heat-sealed by the heat-sealing section

.

2.

The perforation forming section is

provided on one side of the transportation path for the packaging paper, and includes a blade storage section in which a perforation blade is retractably stored, and the transportation path for the packaging paper

. a blade receiving portion provided opposite to the blade housing portion on the other side of the blade housing portion and forming perforations in the packaging paper between the perf

orating blade protruding from the blade housing portion

; a first drive unit for moving the unit and the blade receiving portion toward the packing pa per to sandwich the packing paper

; and a second driving section for forming perforations in the packaging paper by driving the perforating blade of the blade accommodating section so as to protrude toward the blade rece iving section while holding

the A drug packaging device as described.

[Claim 3]

The perforating blade includes

a base portion and a

cutting edge portion including a plurality of blade pieces protruding from the base portion an d having a chevron-shaped cutting edge formed at the tip thereof, with a predetermined inter val between adjacent blade pieces. and

the second drive unit

forms perforations in the packaging paper by projecting partway of the blade piece of the pe rforation blade toward the blade receiving portion, and the base portion

of the perforation blade.

3. The medicine packaging device according to claim 2 , wherein the packaging paper is cut by protruding up to the blade receiving portion side .

4.

The perforating blade

is formed such that the width of the blades at both ends in the direction perpendicular to the conveying direction of the packing paper is larger than the width of the blades of the inner bla des,

4. The drug packaging device according to claim 3 , wherein the cutting start portions are fo rmed at both ends of the packaging paper in a direction orthogonal to the conveying direction of the packaging paper .

5.

The perforating blade

is formed so that each of the blade pieces has the longest length from the base of the centra l blade piece, and the length gradually decreases toward the end.

5. The medicine packaging device according to claim 3 or 4, characterized in that:

6.

The perforating blade has a horizontal blade having

a blade width larger than the thickness of said blade and inserted between said plurality of b lades.

By forming a plurality of cross-shaped blades, the cross-shaped blades form a perforation for med in the packaging paper to form a cutting start portion when separated along the perforati on

. The drug packaging device according to any one of claims 3 to 5.

7. A

pre-stored V-folded packaging sheet is pulled out to a conveying path, a

heat-sealed portion is formed on the pulled-out packaging sheet for dividing into individual p ackages, and the

heat-sealed portion is formed. The medicine is supplied and stored one by one between the packaging papers on which is formed, and the

packaging paper containing the medicine is nipped by the driving roller and driven to convey one by one, and the driving

roller

A method for manufacturing a packaged medicine , comprising: forming perforations in the heat-sealed portion of the packaging paper downstream of the packaging paper in the conveyi ng direction of the packaging paper.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to a medicine packaging device for suppl ying and packaging medicines one by one and to a method for manufacturing divided medicin es. 2. Description of the Related Art A drug packaging device has been developed and put int o practical use for automating drug dispensing work. As an example of such a medicine packa ging device, there is one described in Patent Document 1. [0003] That is, the ends of the pa ckaging paper are pulled out from a roll around which the V-folded packaging paper is wound, and the end portion of the packaging paper is pulled through a plurality of support shafts onto a conveying path inclined downward in the conveying direction. and fed to a funnel-shaped dr ug hopper. A thermal pressure contact portion is provided downstream of the drug hopper, an d the thermal pressure contact portion is provided with a heat seal and a perforation forming portion. Then, a T-shaped heat seal for separating the individual packages is formed by heat s ealing, and perforations for separating the individual packages are formed. After heat-sealing, one packet of medicine is supplied from the medicine hopper to the space between the packa ging papers. [0004] When the drug is supplied, the packaging paper is nipped by driving roll ers provided downstream of the thermal pressure contact portion and pulled out by the length of one package to prepare for the next individual package. Heat sealing and perforation are p erformed. By repeating such an individual packaging operation, a single prescription of a pack aged drug is created. [Prior Art Document] [Patent Document] [Patent Document 1] Japanese Unexamined Patent Application Publication No. 2012-131551 [Summary of the Invention] [Pro

blems to be Solved by the Invention]

[0006]

In the apparatus disclosed in Patent Document 1, the driving rollers for conveying the packaging paper are provided downstream of the perforation forming section. Therefore, when the packaging paper is pulled out by the drive roller, if an excessive load is applied to the packaging paper, there is a risk that the packaging paper will be torn at the perforations. In addition, since the drug is enclosed in the lower portion between the packaging papers, the driving rollers must inevitably hold the upper side of the packaging papers to convey them. In order to prevent the packing paper from tearing during transportation, the upper edge of the packing paper cannot be perforated (cut). As a result, there is also the problem that it is difficult for an elderly person or a person with weakened muscles to cut along the perforations from the upper end side.

[0007]

Therefore, in some conventional packing machines, perforations (cuts) are made at the lower end of the paper so that the paper is cut from the lower side. then
In addition, the printing direction is reversed and the visibility is poor, and after cutting it off, it is necessary to turn it upside down again and cut it horizontally by hand to open it, which is inconvenient.

[0008]

An object of the present invention is to provide a drug packaging device and a method for manufacturing a packaged drug, in which paper for packaging is not cut at perforations (cuts) during transportation. aim. The second problem is that perforations (cuts) can be made on the upper end side of the packaging paper so that the patient can easily cut the single package along the perforations. An object of the present invention is to provide a highly convenient drug

packaging device and a method for manufacturing a packaged drug.

[0009]

Furthermore, as a secondary effect, by providing perforations (cuts) at the upper and lower ends of the packaging paper in this way, long packaging paper can be packed three times a d ay (morning, noon, evening), for example. I would also like to raise the point that the appear ance is neat when everything is folded because it is easy to make the creases firmly when fold ing it for storage.

Means for Solving the Problems

[0010]

A medicine packaging device of the present invention comprises a packaging paper storing s ection in which a V-folded packaging paper is wound, and a packaging paper from the packagi ng paper storing section. a transport path for pulling out and transporting paper, a heat seal p ortion provided in the middle of the transport path for forming a heat seal that separates the packaging paper into individual packages, and a heat seal portion provided in the middle of th e transport path. , a medicine supply unit for supplying the medicine one package at a time b etween the packaging papers; a driving roller for pinching and driving the packaging paper co ntaining the medicine supplied by the medicine supply unit; and the driving roller. a perforatio n creating section provided downstream in the conveying direction of the packaging paper and forming perforations in the portion heat-sealed by the heat-sealing section.

[0011]

Further, in the method for manufacturing a packaged medicine of the present invention, a pr e-stored V-folded packaging sheet is pulled out to a conveying path, and the pulled-out packa ging sheet is divided into individual packages by a heat-sealing section. is formed, and the me dicine is supplied and stored one by one between the packaging papers on which the heat-sea led portion is formed, and the packaging paper containing the medicine is sandwiched by the driving rollers to make one package. The perforations are formed in the heat-sealed portion of the packaging paper downstream of the drive roller in the transportation direction of the pack aging paper.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

FIG. 1 is a plane cross-sectional view of a disc distribution unit of an automatic powder medici ne packaging machine according to an embodiment;

FIG. 2 is a front cross-sectional view showing the raised position of the drop hopper of the aut omatic powder medicine packaging machine of the embodiment;

FIG. 3 is a diagram showing the structure and operation outline of a drop hopper;

FIG. 4 is a front cross-sectional view showing the lowered position of the drop hopper of the a utomatic powder medicine packaging machine of the embodiment;

FIG. 5 is a cross-sectional plan view of the printing and packaging machine section of the auto matic powder medicine packaging machine of the embodiment;

FIG. 6 is a perspective view of the perforation forming device of the embodiment, showing a s tate in which the blade storage section and the blade receiving section are opened;
FIG. 7 is a perspective view of the perforation forming device of the embodiment, showing a s tate in which the packaging paper is being conveyed between the blade storage section and th e blade receiving section;
FIG. 8 is a perspective view of the perforation forming device of the embodiment, with the bla de housing portion and the blade receiving portion opened and the cover of the blade housing portion removed;
FIG. 9 is a perspective view of the perforation forming device of the embodiment, showing a s tate in which perforations are being formed with the blade storage section and the blade recei ving section closed;
FIG. 10 is a perspective view of the perforation forming device of the embodiment, with the c over of the blade housing section removed in a state where the blade housing section and the blade receiving section are closed to form perforations;
FIG. 11 is a perspective view of the perforation forming device of the embodiment, showing a state in which the blade storage section and the blade receiving section are closed to cut the packaging paper;
FIG. 12 is a perspective view of the perforation creating device of the embodiment, in which t he blade housing portion and the blade receiving portion are closed and the packaging is perf ormed;
FIG. 10 is a view of the blade storage section with the cover removed, in a state where the pa per is being cut;
13A and 13B are diagrams for explaining the shape and movement distance of the perforation blade of the perforation creating device according to the embodiment; FIG.
14A and 14B are diagrams for explaining the shape of a perforation blade of the perforation cr eating device according to the embodiment; FIG.
FIG. 15 is a diagram for explaining the relationship between the shape of the perforation blad e of the perforation creating device of the embodiment and the packaging paper;
FIG. 16 is a diagram showing an example of a packaged medicine manufactured by the autom atic powder medicine packaging machine of the embodiment;
17 is a plan view for explaining a printing packaging machine according to a second embodim ent; FIG.
FIG. 18 is a front view for explaining a printing packaging machine according to a second emb odiment; FIG.
BEST MODE FOR CARRYING OUT THE INVENTION
[0013]
An automatic powder medicine packaging machine according to an embodiment will be descr ibed below with reference to the drawings.
In the following description, an automatic powder medicine packing machine will be taken as

an example, but the present invention is not limited to the automatic powder medicine packin g machine, and can also be applied to an automatic tablet packing machine. Further, it is need less to say that the present invention can also be applied to a medicine packaging device for p ackaging a plurality of medicines into one individual package as described in Japanese Patent No. 6255528 and Japanese Patent Application Laid-Open No. 2000-24087.

FIG .

1 is a plan view of an automatic powder medicine packing machine of this embodiment, and FIG. 2 is a front view of the automatic powder medicine packing machine. Above the intermed iate table 11 of the housing 10 is arranged a disk distribution section 100 as a drug supply sec tion, and below the intermediate table 11 is arranged a printing packaging machine 200 as a drug packaging section. A drop hopper 300 serves to introduce the powdered medicine discha rged from the disc distribution unit 100 through the inner surface of the drop hopper 300 into the printing packaging machine 200 side.

[0015]

The disc distributor 100 is provided with two sets of distributors. In the disc distribution unit 100, 101 is a detachable powdered medicine cassette, which is loaded with powdered medicin e in the amount necessary for the prescription at another place in advance, and manually ope rated by a staff member or by an automatic device such as a robot arm (not shown). It is plac ed on the vibration table 102 from another shelf. The vibration table 102 generates vibration by an electromagnet (not shown) or the like, and by transmitting the vibration force to the po wdered medicine cassette 101, the powdered medicine in the powdered medicine cassette 10 1 is transported by vibration, and the powdered medicine is dropped little by little in the direct ion of the arrow 103. It is.

Reference

numeral 104 denotes a horizontally arranged distribution disk, a large wheel of which is rotat ed by a stepping motor 105 via a gear 106 in the direction of an arrow 104a. Further, an arc-s haped concave surface 107 is formed on the upper surface of the distribution disk 104 in the outer peripheral direction. Here, when the vibrating table 102 is driven while the stepping mot or 105 is continuously rotated, the powdered medicine falls little by little onto the arcuate con cave surface 107 of the distribution disc 104 to form a doughnut-shaped powdered medicine mountain P1. can be done. This operation is called a "circumferential scattering operation".

Reference numeral

108 denotes a scraping disk portion, and a lever 108a can rotate up and down around a shaf t 109. As shown in FIG. A disc 110 whose circumference is made of silicone rubber is attached to the tip of the lever 108a, and can be rotated in the direction of an arrow 110a by a motor 1 11. As shown in FIG. This disc 110 has a waterwheel-like shape in which blades are provided between two discs. It should be noted that the disk diameter of the disk 110 is the same as th e diameter of the concave surface of the arcuate concave surface 107 .

[0018]

In the case of the above-mentioned "circumferential scattering operation", the disk 110 is rotated upward and retracted, and does not interfere with the formation of the donut-shaped powdered drug pile P1. Next, during the "one-pack distribution operation", the disk 110 of the scraping disk portion 108 rotates downward, and the disk 110 comes into close contact with the arc-shaped concave surface 107 without any gap. In this state, when the motor 111 is driven, the blades provided on the disk of the disk 110 scrape the powdered medicine on the arcuate concave surface 107 onto the drop hopper 300 . Then, when the stepping motor 105 is rotated by a predetermined angle R, the amount of powdered medicine corresponding to that angle is dispensed to the drop hopper 300 side. Here, the predetermined angle R is not specified separately.

This is the angle for the dose to be packaged in one package specified by the label. For example, in the case of making a prescription for 36 packets of a powdered medicine of 1g per packet, 36g of powdered medicine is loaded in the powdered medicine cassette 101 in advance, and this is referred to as a "circumferential spreading operation"

.

", spread the entire amount evenly in a donut shape. Next, in the "single package distribution operation", when the stepping motor 105 is rotated by 10 degrees while the disc 110 is being rotated, one package of 1 g of powdered medicine can be correctly dispensed to the drop hopper 300. be. The disc distribution unit 100 and the drop hopper 300 constitute a medicine supply unit.

Two pairs of discs 112a and

112b are arranged in the disc distribution unit 100 in a symmetrical manner. is for enabling the other disk portion 112b to perform a "single package dispensing operation" so that a plurality of consecutive prescriptions can be continuously packaged without wasting time.

[0021]

FIG. 3 outlines the shape and operation of the drop hopper 300 . The drop hopper 300 has a double structure of an upper hopper 301 and a lower hopper 302, and a lower opening 303 of the upper hopper 301 is closed by a shutter 304 that can be opened and closed. The upper end of the upper hopper 301 is formed with an upper opening 300a for receiving the powdered medicine from the disc distribution unit 100 . The lower end of the lower hopper 302 is formed in a wedge shape as shown in FIGS.) 305c are formed. The drop hopper 300 can move up and down as a whole. Then, at the timing of dispensing the powdered medicine from the disc distribution unit 100 in the "one packet dispensing operation", it is positioned at the upper position in FIGS. 3(a) and 3(b). At this time, the shutter 304 is closed as shown in the side view of FIG. At this time, the left and right claws 305a and 305b at the lower end of the drop hopper 300 are inserted into the open end B1 of the packaging paper B folded in two to be conveyed

. When the powdered medicine is discharged, as shown in FIG . 3(c), the entire drop hopper 300 moves downward. It acts as a guide when entering the When the shutter is opened as sh

own in 304a in this state, the powdered medicine is stored inside the packaging paper B. FIG. After that, the drop hopper 300 rises to the position shown in FIG. 3(b). [0024]

Next, the configuration and operation of the printing packaging machine 200 will be described with reference to FIGS. 4 and 5. FIG. FIG. 4 is a cross-sectional view of the front of the powder medicine packaging machine, showing a state in which the drop hopper 300 positioned above in FIG. 2 has moved downward. FIG. 5 is a top cross-sectional view of the printing and packaging machine 200. As shown in FIG. Reference numeral 201 denotes a packing paper roll as a packing paper storage unit, which is formed by winding a double-folded paper having thermal adhesiveness on a reel with the valley-fold side facing downward, and is placed on the lower stage 12. It is The packaging paper pulled out from the leading end of the paper on the outer peripheral side of the reel is conveyed along the conveying path along a route such as the one-dotted chain line B2 to B3. A printing unit 202 is composed of an ink ribbon 203, a thermal printing head 204, a platen roller 205, etc., and prints prescription information on the surface of the packaging paper B for each package.

Reference numeral

206 denotes a vertical sealing mechanism, which is a heat sealing portion provided on the lower table 12. By pressing the packing paper B from the front and back (top and bottom in FIG. 5) with a hot plate, the vertical sealing mechanism 207a is classified into individual packages by performing the sealing. 207b shows vertical sealing at a position moved by one package, but the upper open end 208 of the packaging paper B is not sealed. This is so that the packing sheets B can be transported in a state in which the claw portions 305a and 305b of the drop hopper 300 are inserted between the packing sheets B as shown in FIG. 3(a). The drop hook to be placed next

A drop hopper cleaning device 310 is attached to the back side of the hopper 300 . Since the drop hopper cleaning device 310 is not directly related to the present invention, detailed description thereof will be omitted.

Next , reference

numeral 209 denotes a horizontal sealing mechanism, which presses the packing paper B from the front and back with a hot plate to seal the unsealed portions in the horizontal direction and the vertical direction, as indicated by 210 . With the vertical seal 207 and the horizontal seal 210, the packaging paper B is sealed as a single package. Although not shown in the drawing, the vertical seal 7 does not seal the perforated portion but seals both sides of the perforated portion, which will be described in detail later.

A driving roller 211

is driven synchronously with the platen roller 205 of the printing unit 202, and rotates while

nipping the upper end portion of the packaging paper B from both sides to cover the distance of the one-packing pitch B4. , is driven as one step. Reference numeral 400 denotes a perfora tion forming device, which forms vertical perforations in the non-sealed portion provided in th e middle of the vertically sealed portion, thereby facilitating the separation of individual packe ts by the patient. 2 and 4 do not indicate perforations, but indicate boundaries between single packages. Also, in FIGS. 2 and 4, the description of the vertical seal downstream of the drop h opper 300 is omitted for the sake of clarity of explanation. As auxiliary equipment for the dr op hopper cleaning device 310, a dust collection blower 320 and a compressed air generating compressor 330 are arranged at the rear of the housing and used as air sources for the drop hopper cleaning device 310

.

.

[0029]

The configuration and operation of the perforation forming apparatus 400 will be described b elow with reference to FIGS. 6 to 15. FIG. FIG. 6 is a perspective view of the perforation formi ng device, showing a standby state in which the blade housing portion 402 and the blade rece iving portion 404 are open, and FIG. 4 is a diagram showing a state in which packing paper B is inserted. FIG. For the packaging paper B, the blade housing portion 402 and the blade recei ving portion 404 are arranged so as to be positioned between the blade housing portion 402 a nd the blade receiving portion 404 . FIG. 8 is a diagram showing a state in which the cover of the blade housing portion 402 is removed. A motor base 406 is fixed to the lower stage 12 s hown in FIGS. 4 and 5, and a stepping motor 408 is fixed to the motor base 406. As shown in FIG

.

A base 410 of a perforating blade unit 401 is fixed to the lower table 12 .

The base 410 of the perforating blade unit 401 is slidably provided with a supporting portion 4 28 to

which the blade housing portion 402 is fixed. A support portion 424 to which the blade recei ving portion 404 is fixed is slidably provided on the base 410, and slides integrally with a slide shaft 422 fixed to the support portion 424. As shown in FIG. The support portion 424 and the support portion 428 are slidable in the directions of contacting and separating from each othe r. A spring 426 is provided between the supporting portion 424 and the supporting portion 42 8 to bias them away from each other.

A shaft 434 is slidably provided inside the support portion 428 of the blade housing portion 40 2 , and

a sewing machine blade 432 is fixed to the left end of the shaft 434 . The perforating blade 4 32 is slidably provided between the two covers of the blade housing portion 402 in a direction in which the perforating blade 432 protrudes from the blade housing portion 402 .

[0033]

A timing belt is stretched between a shaft (not shown) of the stepping motor 408 and a pulle y 414 fixed to the camshaft 412, so that the camshaft 412 is rotated by the rotation of the ste pping motor 408. .

Three cam plates 416 ,

418 and 420 are fixed to the camshaft 412 . The lowermost first cam plate 416 drives the bl ade receiving portion 404, and the first cam plate 416

By rotating , the slide shaft 422 is pulled rightward in the figure by a cam follower (not show n). Since the supporting portion 424 to which the blade receiving portion 404 is fixed is conne cted to the slide shaft 422, the blade receiving portion 404 is also drawn rightward in the figur e. A second cam plate 418 on the second stage from the bottom drives the blade housing po rtion 402. By rotating the cam plate 418, a cam follower attached to a support portion 428 to which the blade housing portion 402 is fixed is driven

.

430 is driven leftward in the figure. Therefore, by rotating the stepping motor 408, the blade accommodating portion 402 and the blade receiving portion 404 are moved in the direction of coming into contact with each other, and the packing paper B is sandwiched. The shape of the cam plates 416 and 418 keeps the packaging paper B sandwiched between the blade accomm odating portion 402 and the blade receiving portion 404 even if the cam plates 416 and 418 r otate further. Thus, the drive mechanism for the blade receiving portion 404 by the cam plate 416 and the drive mechanism for the blade housing portion 402 by the cam plate 418 constitu te a first drive portion. Further, the third cam plate 420 on the uppermost stage is for driving a perforating blade 432, and a cam follower 436 fixed to a shaft 434 is in contact with the thir d cam plate 420. As shown in FIG

.

As the stepping motor 408 rotates, the third cam plate 420 rotates and pushes the cam follow er 436 to drive the shaft 434 to the left in the figure. As a result, the perforating blade 432 fix ed to the shaft 434 protrudes from the blade accommodating portion 402 toward the blade re ceiving portion 404 to form perforations in the packing paper B. As shown in FIG. A mechanis m for driving the perforating blade by the cam plate 420 constitutes a second driving section.

[0037]

FIG. 8 shows the standby state of the perforating blade unit 401 . As shown in FIG. 8A, whe n the perforating blade unit 401 is in the standby state, the perforating blade 432 is sunk insi de the cover of the blade housing portion 402 . The state of cam plate 420 and cam follower 4 36 at this time is shown in FIG.

Next, FIGS

. 9 and 10 show a state in which the stepping motor 408 rotates to form perforations on the packaging paper B. FIG. As shown in FIGS. 9 and 10, by rotating the first cam plate 416 and t he second cam plate 418, the blade housing portion 402 and the blade receiving portion 404 c ome into contact with each other to sandwich the packing paper B. becomes. 9 and 10, illustr

ation of the packaging paper B is omitted. When perforations are formed on the packaging pa per B, the cam plate 420 pushes the cam follower 436 as shown in FIG. It will be in a protrud ed state. After the perforations are formed on the packaging paper B, the stepping motor 40 8 rotates in reverse, so that the cam plate 420 reverses from the state shown in FIG. 9(b) to t he standby position shown in FIG. 8(b)

.

back to After the perforations are formed in the packaging paper B by such an operation, the packaging paper B is conveyed by the drive roller 211 to form the next individual package. Fo rmation of vertical seals, supply of medicine, and formation of horizontal seals are performed i n synchronism with the formation of perforations. When the perforations are formed, the pack aging paper B is stopped, and the vertical seal formation, drug supply, and horizontal seal for mation are performed while the packaging paper B is stopped. be. The above operation compl etes the cycle for one package.

[0040]

Here, the medicine is prescribed to the person taking the medicine, for example, 42 doses fo r two weeks in the morning, afternoon and evening. Perforations are made between 42 individ ual packages for one drug taker, and when individual packages for one drug taker are complet ed, the prescription drug is released by cutting the packaging paper B instead of the perforati ons. There is a need to. Therefore, in this embodiment, the perforation forming device 400 a lso cuts the packaging paper B. As shown in FIG

.

As shown in FIGS. 11 and 12, the cam plate 420 is shown in FIG. 9(b).

After the formation of the stitches, the stepping motor 408 is further rotated to rotate the ca m plate 420 to the position shown in FIG. 11(b). Cam follower 436 is then pushed to the farth est position from camshaft 412 . As a result, the perforating blade 432 further protrudes into t he blade receiving portion 404 to the base of the perforating blade 432 . As a result, the pack aging paper B is cut by the perforating blade 432 . When cutting the packaging paper B, the r otation of the camshaft 412 need only be rotated once without returning. Next, FIG. 13 sho ws the shape and amount of movement of the perforating blade 432. As shown in FIG . The perforating blade 432 is composed of a fixed portion 432a to the shaft 434, a blad e base portion 432b, and a cutting edge portion 432c protruding from the blade base portion 432b. A plurality of blades 432d each having a chevron-shaped blade edge formed at the tip o f the blade edge portion 432c are formed at predetermined intervals between adjacent blades 432d. Between the blades 432d and 432d, there are three horizontal blades having a blade wi dth wider than the thickness t of the blade edge, but they are omitted in FIGS. ing. As for the length to the tip of each blade 432d, the blade at the center is the longest, and the length gra dually decreases toward the ends. The angle θ between the straight line L1 connecting the tip s of the blades 432d and the straight line L2 parallel to the tips of the bases is set to about 4 degrees. As a result, when perforations are formed on the packaging paper B, the cutting port

ion gradually shifts from the central blade 432d to the end blade 432d, so that the driving force required to move the perforating blade 432 is small. done. [0043]

In addition, the lengthwise ends of the perforating blade 432, that is, the blade widths of the blade pieces 432e, 432e at the ends in the direction orthogonal to the transport direction of the packaging paper B are formed larger than the blade width of the inner blade piece 432d. It is 13(b), the width of the packaging paper B is configured so that the ends of the packaging paper B are located at the positions of the edge pieces 432e, 432e of the perforating blade 432. It is Therefore, even if the transportation position of the packaging paper B is shifted, a cutting start portion (cut) can be reliably formed at the end of the packaging paper B when the patient cuts off the individual package, and the patient can easily separate. You can separate the package.

FIG.

13(b) shows the projection distance of the perforation blade 432 when the perforation is formed by the perforation blade 432 and the packing paper B is cut. When forming perforations, the perforation blade 432 protrudes from the blade receiving portion 404 to the position M, which is the intermediate portion of the blade tip portion 432c of the perforation blade 432. As shown in FIG. When cutting the packaging paper B, the perforating blade 432 protrudes from the blade receiving portion 404 to the position C of the base portion 432b of the blade beyond the position of the blade tip portion 432c. With this configuration, the formation of perforations between individual packages of the packaging paper B and the cutting of the packaging paper B between one prescription can be achieved by changing the protruding amount of the perforation blade 432. It is. Next, a cross-cut blade by inserting a horizontal blade piece between the blade pieces 432d of the perforating blade 432 will be described with reference to FIGS. 14 and 15. FIG

.

14(a) is a perspective view, (b) is a left side view, (c) is a front view, and (d) is a top view. [0046]

That is, three horizontal blades are provided between the fifth and sixth blades, between the eighth and ninth blades, and between the eleventh and twelfth blades from the top in FIG. 432g is inserted. The horizontal blade 432g has a blade width larger than the thickness t of the blade 432d, and is press-fitted between the blades 432d. The base 432b of the blade 432 is press-fitted and held. By using the perforation blade 432 configured in this manner, perforations are formed, and a cutting start portion (cut) is formed when opening each individual package when the packaging paper B is separated into individual packages. It is something to do. The insertion position and the number of horizontal blades 432g are not limited to the above examples, and they can be inserted at any position between blades 432d

.

Especially when the amount of powdered medicine stored in each individual packet is small, it is better to open it at the cross-cut position at the bottom of each individual packet to reduce the amount of leftovers.

Therefore, the insertion position and the number of sheets can be selected in consideration of this.

FIG .

15(a) illustrates the relationship between the perforating blade 432 and the packaging pape r. As shown in FIG. 15(a), the sealed portion (shaded portion) of the packing paper is formed by the vertical sealing mechanism 206 leaving a perforated portion (non-sealed portion) of, fo r example, 4 mm. It is formed in the sealing portion. Assuming that the width of the packagin g paper B, that is, the width in the direction perpendicular to the transport direction is, for exa mple, 70 mm, the length of the perforating blade 432 is set to 75 mm, which is larger than th e width of the packaging paper B. As a result, the ends of the packing paper B can be oppose d to the edge pieces 432e of the perforating blades 432, and as a result, the cutting start port ions (cuts) B1 are formed at both ends of the packing paper B. can be done. Further, as sho wn in FIG. 15(b), by setting the width of the horizontal blade to about 4 mm, which is larger t han the thickness t of the perforating blade 432 (=1 mm), the width of the unsealed portion o f the packing paper B is reduced

.

A cross cut portion B2 can be formed over 4 mm, which serves as a cutting start portion when opening the individual package. Therefore, it is possible to provide a packaged drug that can be easily opened by a patient/user.

FIG .

16 shows an example of a cross-sectional view of a manufactured packaged medicine, showi ng an example in which three cross-cut portions are formed at intervals of 9 mm from a positi on 20 mm from the upper end, for example. In the first embodiment, the packing paper B is conveyed in the horizontal direction, and along the conveying direction, the vertical sealing po rtion 206, the drop hopper 300 serving as the medicine supply portion, the horizontal sealing portion 209, and the conveying rollers

.

211 and the perforation creating unit 400 are arranged, but if the packaging paper B is config ured to be conveyed along the conveying path inclined downward in the conveying direction, t he vertical seal portion is located downstream of the medicine supply unit. It is also possible t o provide

Next ,

a printing packaging machine 500 of a second embodiment will be described with reference t o FIGS. 17 and 18. FIG. 17 is a plan view, and FIG. 18 is a front view of the same. The base p late 515 is provided with a packaging paper storage unit 533 in which the V-folded packaging

paper B is wound into a roll. , is conveyed upward via a plurality of support rolls 534 and 535, the conveying direction is changed by the twist roller 531, and conveyed to a conveying path i nclined downward by 45 degrees along the conveying direction. On the upper surface of the base plate 515, a conveying base 516 for the packaging paper B having an inclination of 45 d egrees with respect to the horizontal plane is provided

.

The sheet B is transported along the transport path. A drop hopper 518 having a lower exit en tered from the upper opening side of the valley-folded packaging paper B is provided substant ially vertically in the center of this transport path, and a drug supply hopper 519 is provided a bove it. The lower part of the medicine supply hopper 519 is open, and the shutter mechanis m 520 that blocks this opening temporarily holds the medicine to be put in one sachet, and op ens the medicine like 520a by an actuator (not shown), thereby lowering the medicine. Via th e drop hopper 518, the drug is dropped into the inner space of the folded packaging paper B a nd supplied.

[0054]

This space is blocked on the left and right by a paper holding plate 521 arranged on the upp er left upstream side of the transport and an inverted L-shaped heat seal portion 522 arrange d on the downstream lower right side. The paper pressing plate 521 is opened and closed by a rotating actuator 523, and is controlled to open when the packing paper B is being conveyed and to close when it is stopped. The heat seal portion 522 has a surface heating element 524 held by a carriage 525a. The carriage 525a is pivotally supported by a guide rod 526 and confi gured to be movable forward and backward by a feed screw 528 directly connected to a motor 527 . When the carriage 525a advances, the upper end of the packaging paper B is pressed a gainst the receiving plate 525b, and the packaging paper B is sealed by heating.

[0055]

With the packaging paper B stationary, the carriage 525a is advanced for a predetermined ti me, and the shutter mechanism 520 is opened as indicated by 520a at the timing when the p aper pressing plate 521 is closed. to fall. Next, when the packaging paper B is conveyed by a predetermined distance P and the carriage 525a is moved forward again, the portion containin g the medicine that has just dropped is sealed all at once. By repeating this operation, the pac kaging paper B is continuously sealed. At this time, if the types and amounts of the medicines to be put in sequentially are controlled according to the prescription and the dosing order, for example, two weeks' worth of medicine can be taken. , One dose is divided into each package and completed. The pair of rubber rollers 529 is means for pinching and conveying the packin g paper B, and by installing them at a plurality of locations on the continuous packing paper B, the paper can be conveyed without slack. The drive roller pair 529 is controlled by a pulse motor 530 to stop the conveyance of a predetermined distance. A perforation forming device 540 similar to the perforation forming device 400 described as the first embodiment is provide d downstream of the driving roller 529 on the downstream side

. [0057] In the operation of creating a medicine package, the transported packaging paper B is longitudinally sealed by the heat seal portion 522 to separate one package. At this time, the previous individual package is laterally sealed at the same time. Next, one package of medicin e is supplied between the packaging sheets B from the medicine supply 519 via the drop hopp er 518 . The packaging paper B to which the medicine is supplied is conveyed by the drive roll er 529 by the length of one package. [0058]

Next, the second medicine is supplied between the packaging papers B, and the packaging p apers B are further conveyed by the driving roller 529 . At this stage, the first vertical seal por tion comes to the perforation forming device 540, so the perforation forming device 540 forms a perforation in the central portion of the vertical seal portion. After this operation is repeated to complete one prescription of packaged medicine, the perforated line forming device 540 cut s the vertically sealed portion to manufacture the packaged medicine.
[0059]

Thus, the position of the heat seal portion is not limited to the upstream side of the drug sup ply section, but may be the downstream side of the drug supply section. While several embo diments and variations of the invention have been described, these embodiments and variatio ns are provided by way of example and are not intended to limit the scope of the invention
.

These novel embodiments and modifications can be implemented in various other forms, and various omissions, replacements, and modifications can be made without departing from the s cope of the invention. These embodiments and modifications thereof are included in the scope and gist of the invention, and are included in the scope of the invention described in the claim s and equivalents thereof.

[Description of Reference Numerals]

100
... Disk distribution section (medicine supply section)
200... Printing and packaging machine
201... Packaging paper roll (packaging paper storage section)
206... Vertical sealing mechanism
209 ... Horizontal sealing mechanism
211 ... Driving roller
300 ... Dropping hopper (medicine supply section)
400 ... Perforation creating device
402 ... Blade storage section
404... Blade receiving portions

416, 418... Cam plate

420... Cam plate

432 Perforating blade

432b Perforating blade base

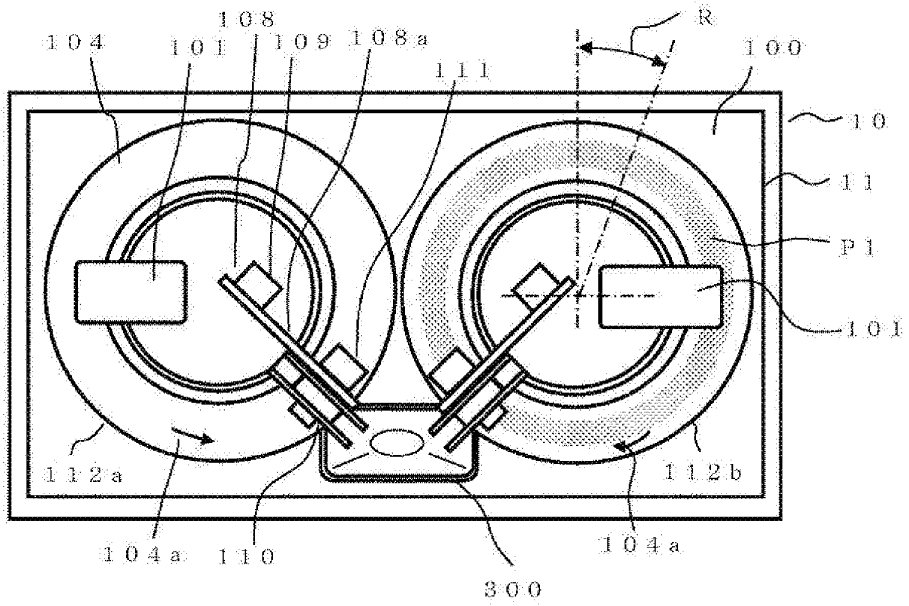
432c Perforating blade tip

B Packaging paper

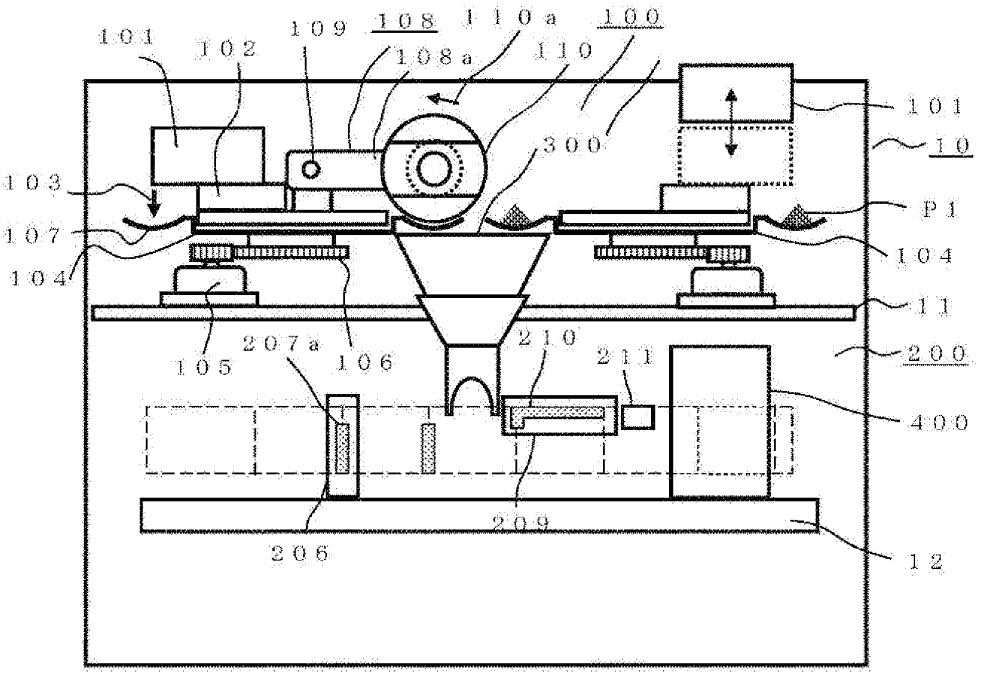
B2, B3 Conveyance path (conveyance path)

drawing open —

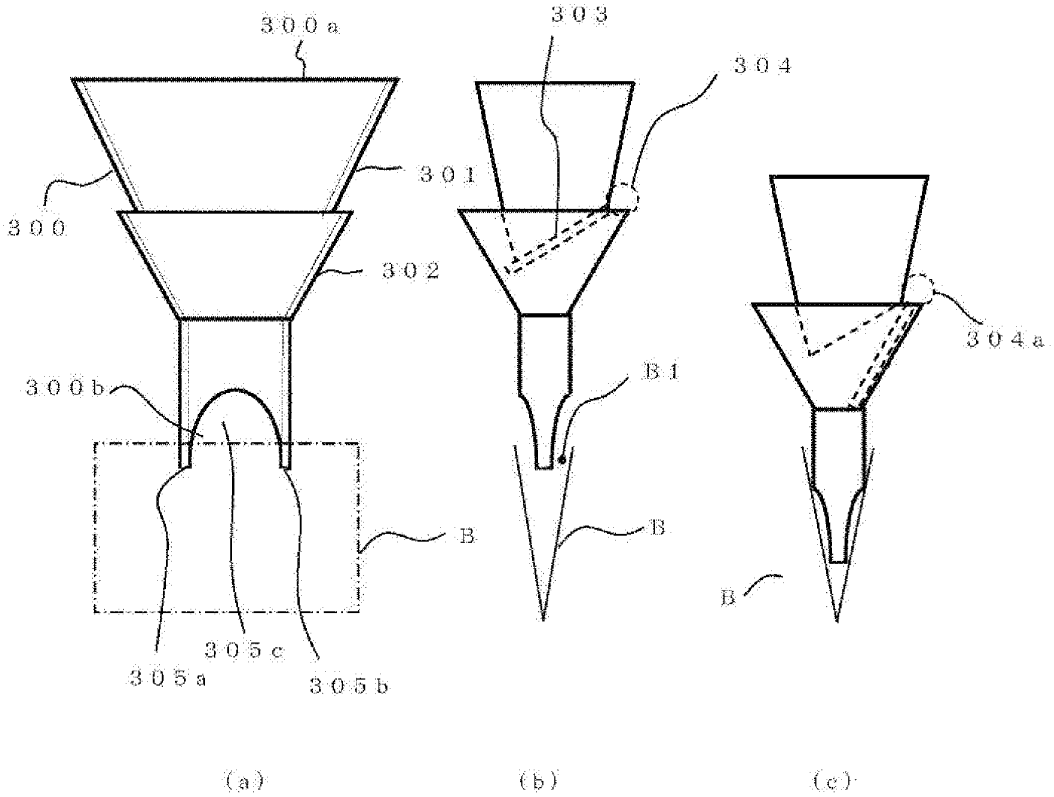
[Fig. 1]



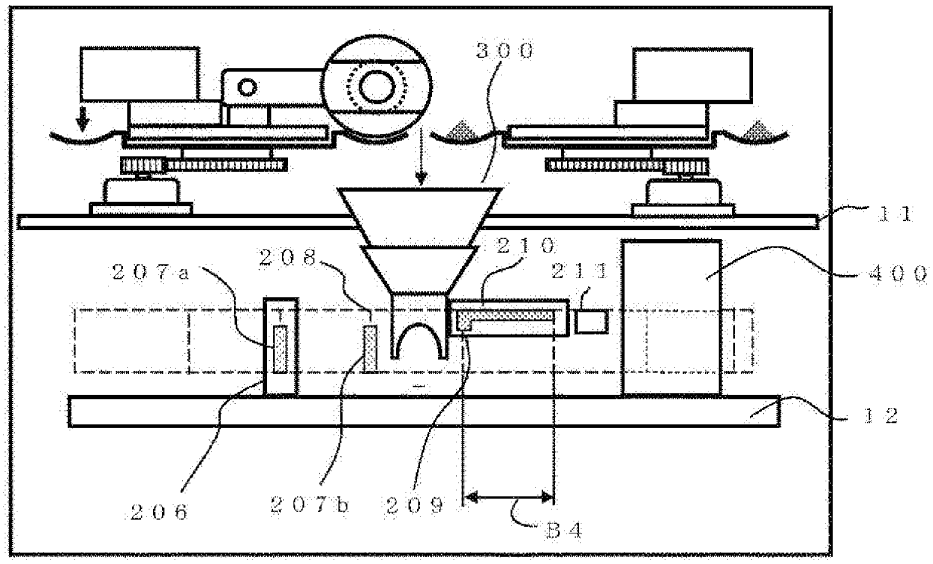
[Figure 2]



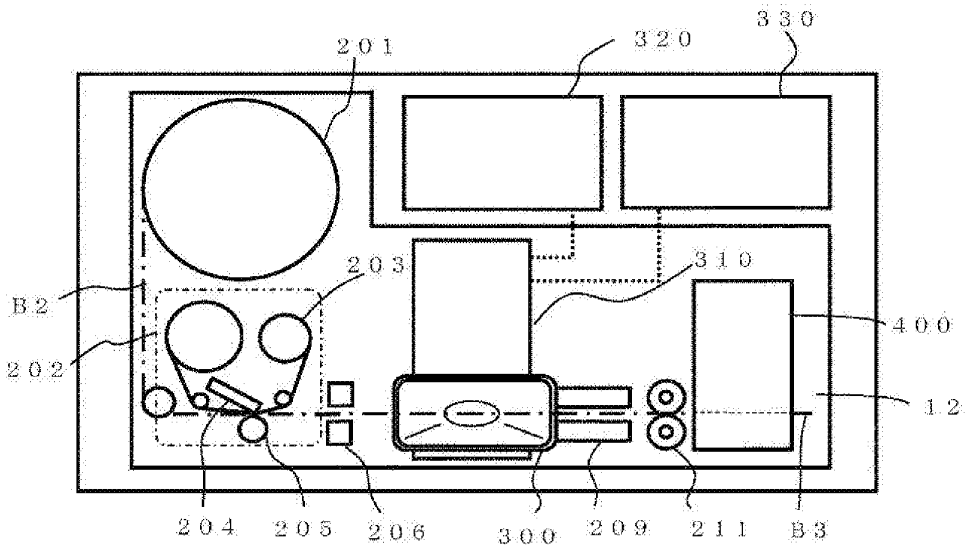
[Figure 3]



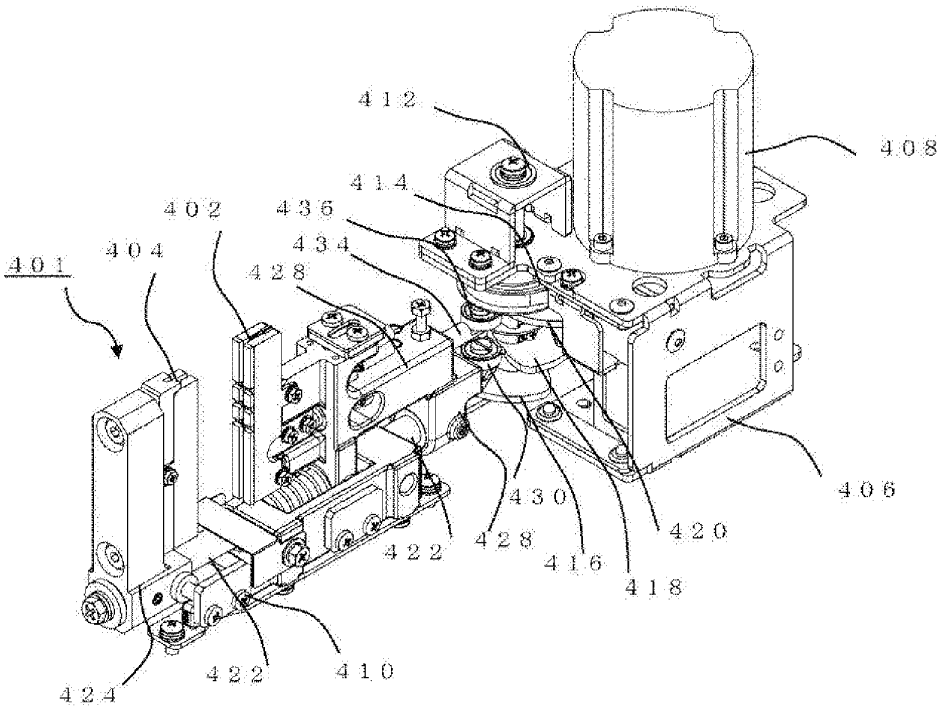
[Figure 4]



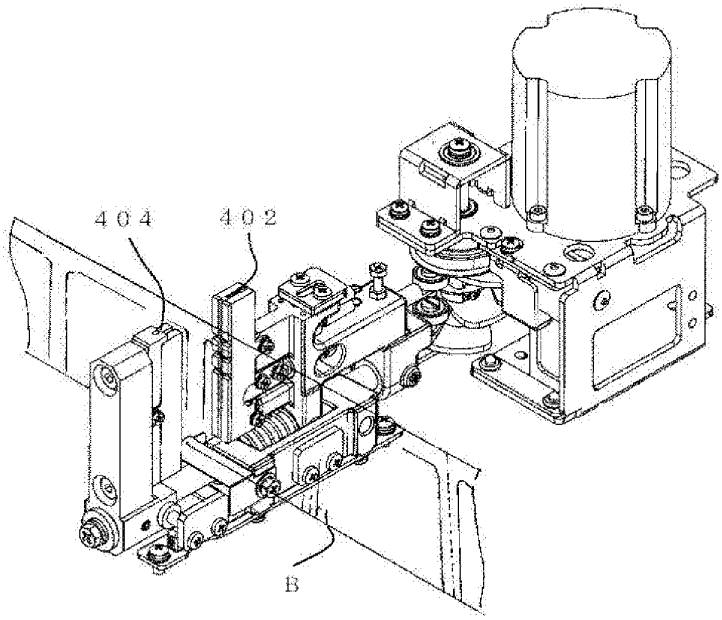
[Figure 5]



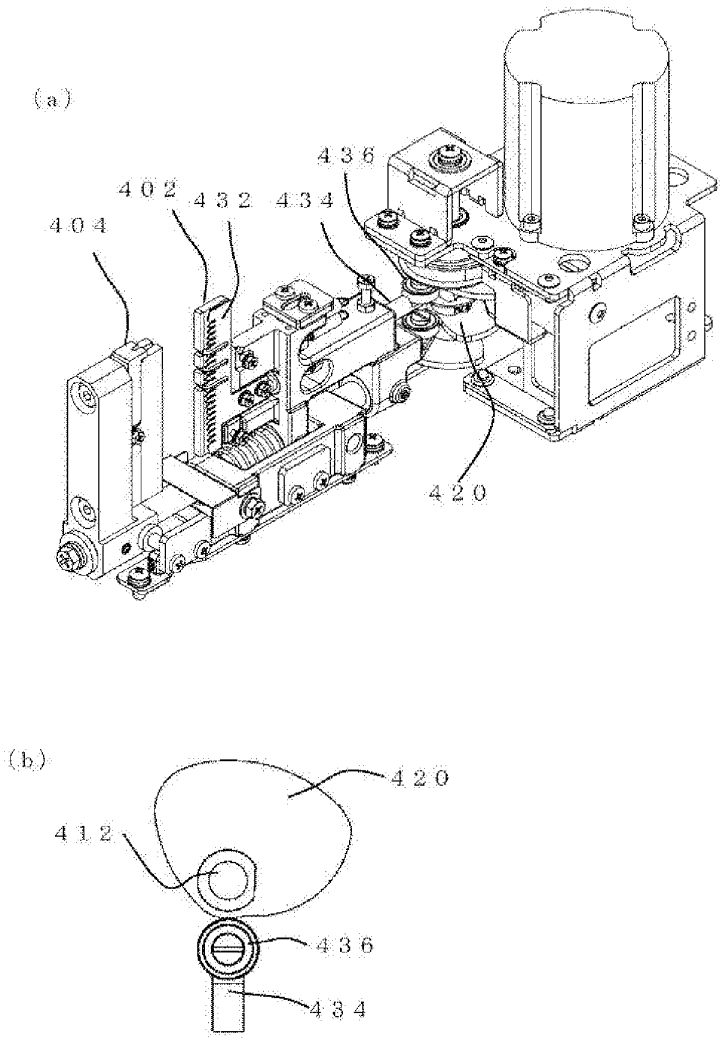
[Fig. 6]


412
408
414
402
436
434
401
404
428
406
430
420
422
428
416
418
422
410
424

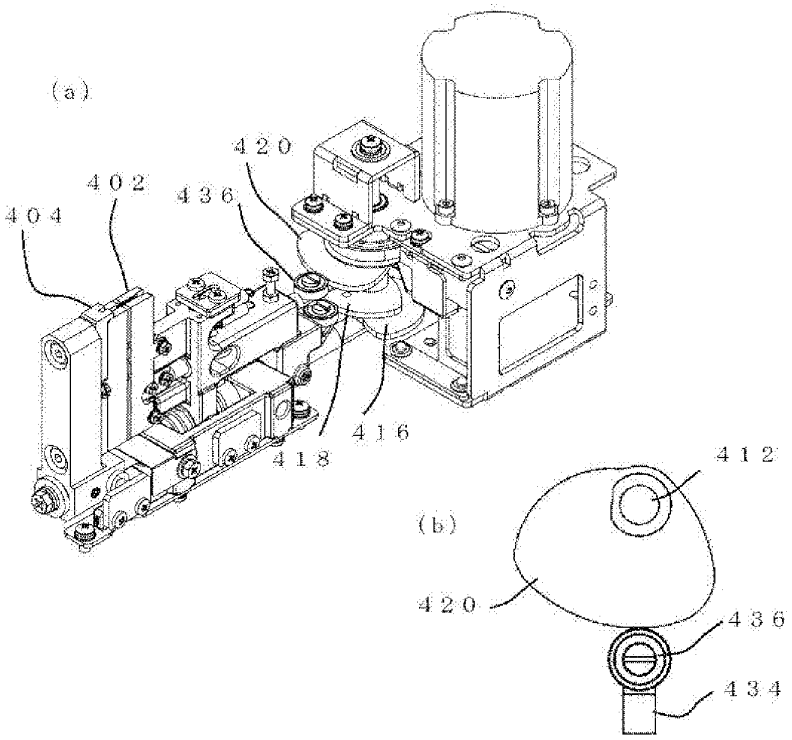
[Fig. 7]


404
402
B

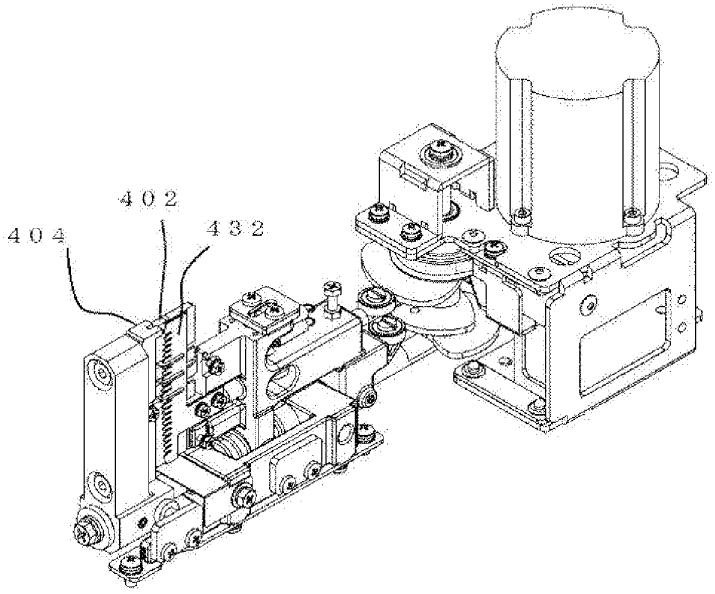
[Fig. 8]



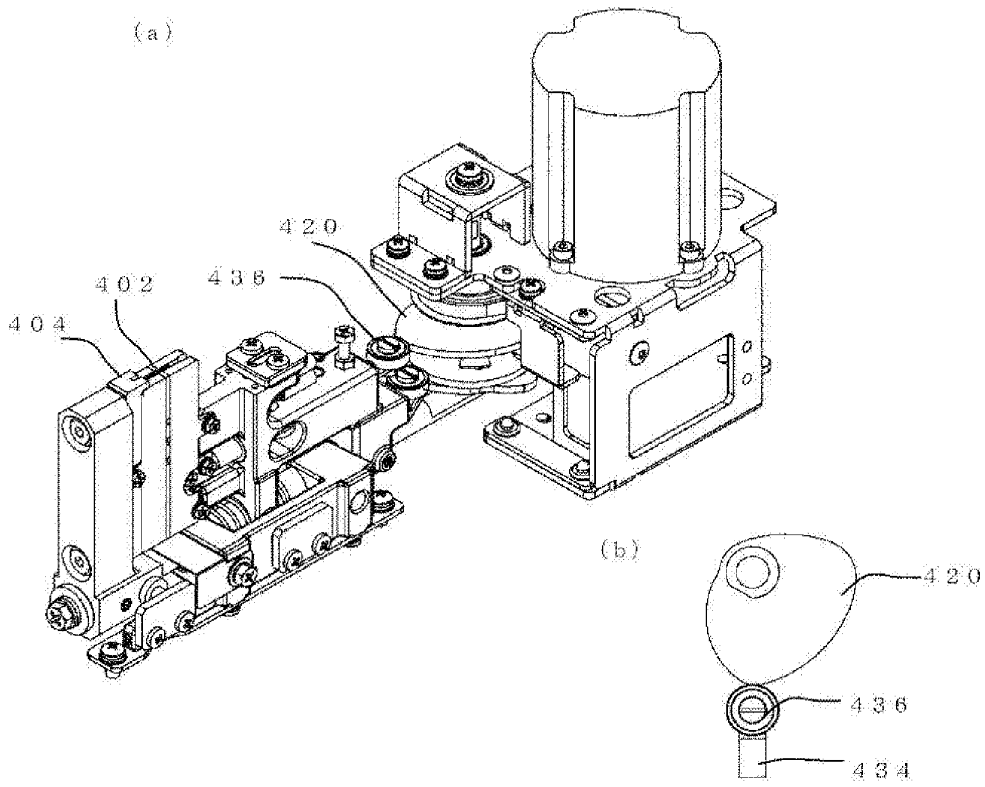
[Fig. 9]



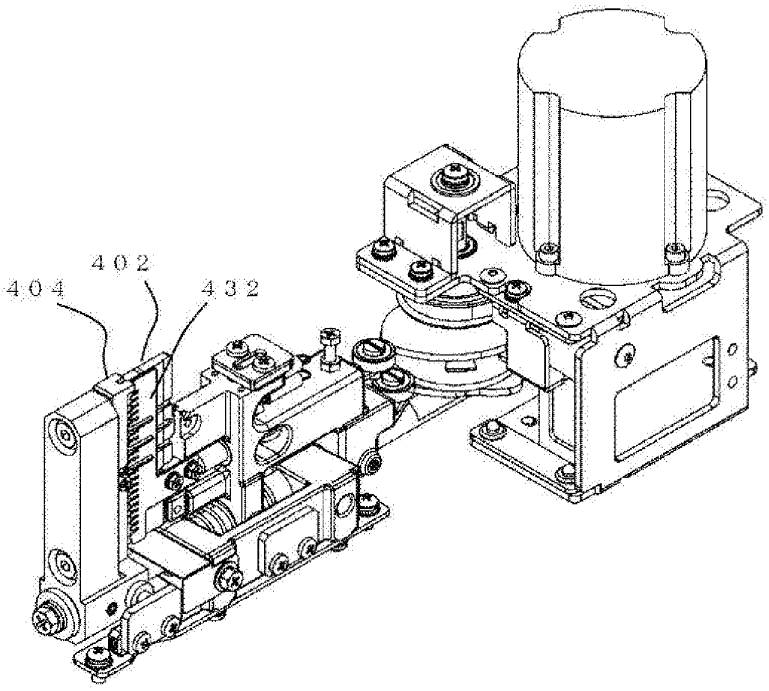
[Fig. 10]



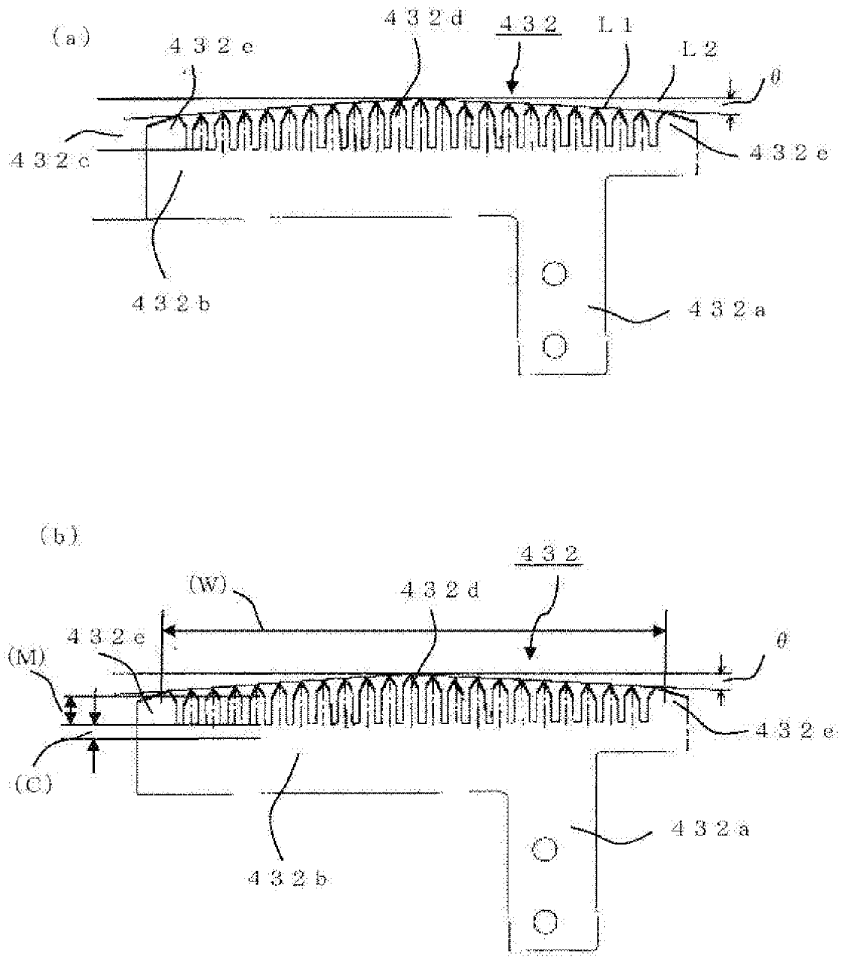
[Fig. 11]



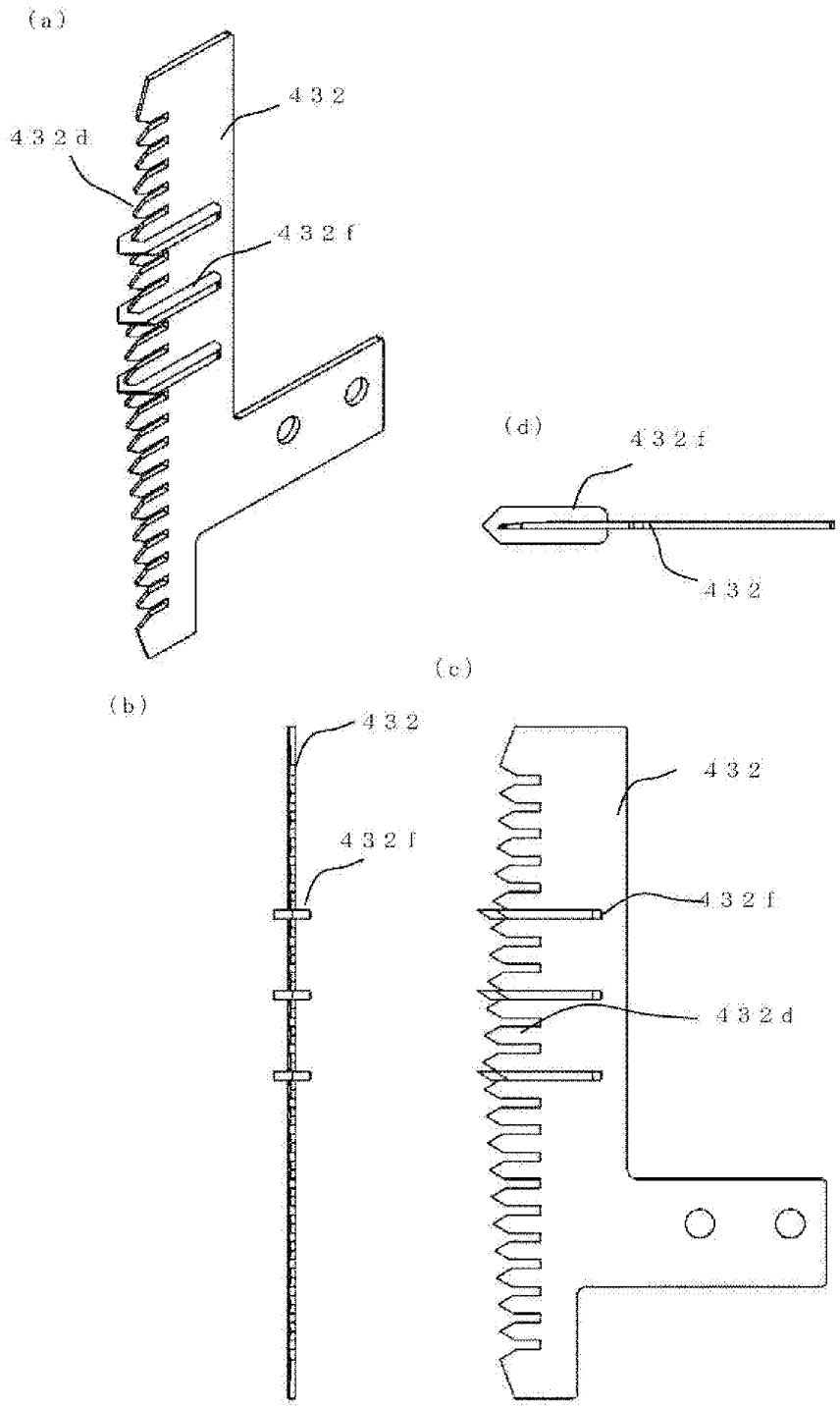
[Fig. 12]



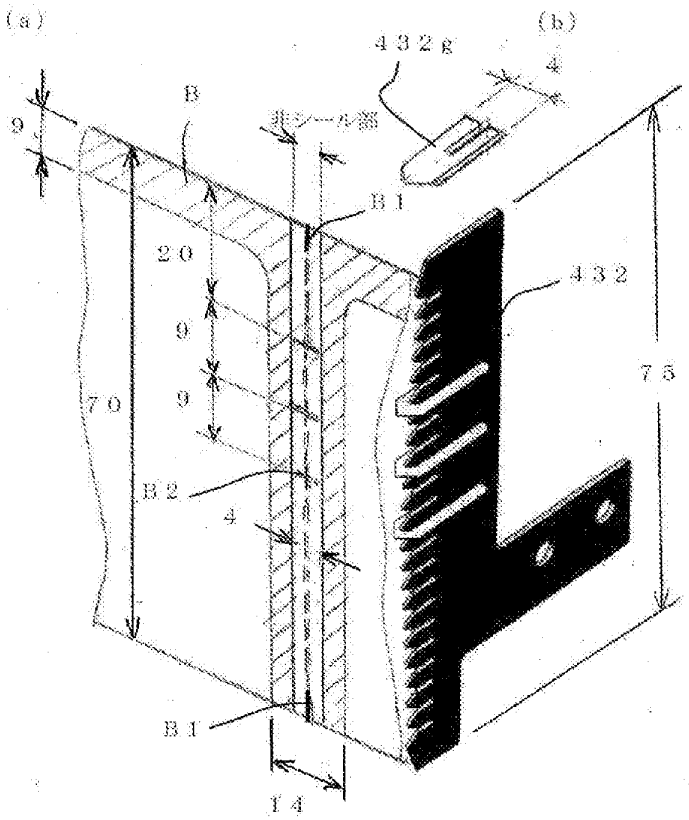
[Fig. 13]


(a)
432e
432d
432
L1
L2
θ
432c
432e
432b
432a
(b)
432
(W)
432d
432e
θ
(M)
432e
(C)
432a
432b

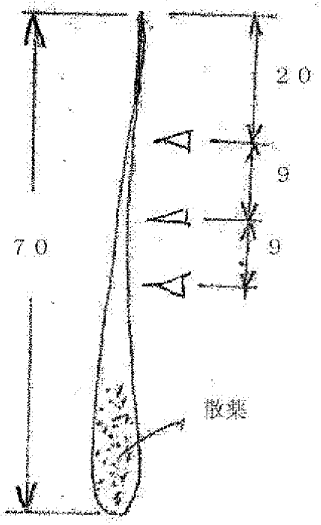
[Fig. 14]



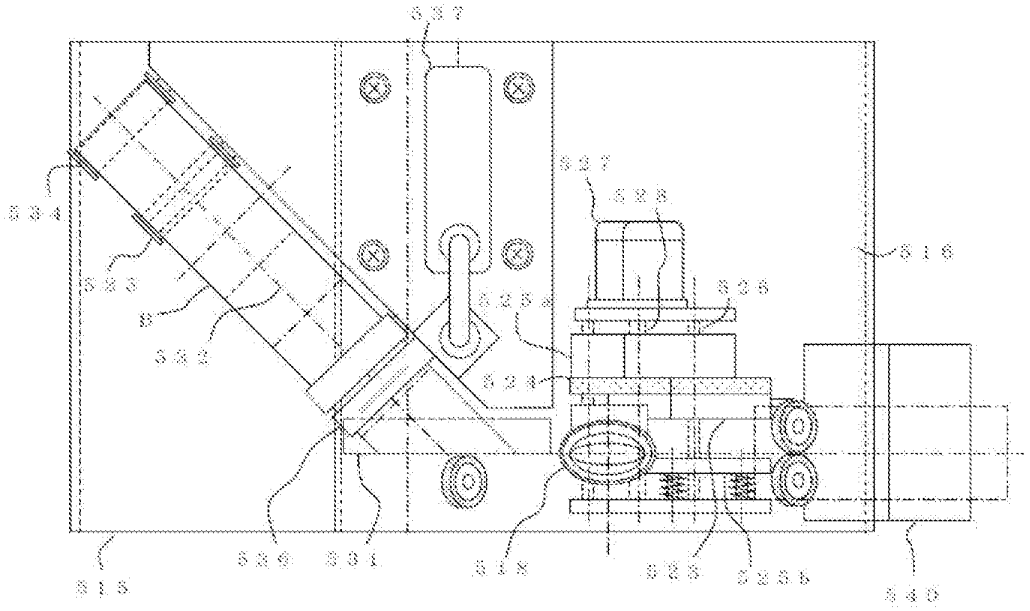
[Fig. 15]



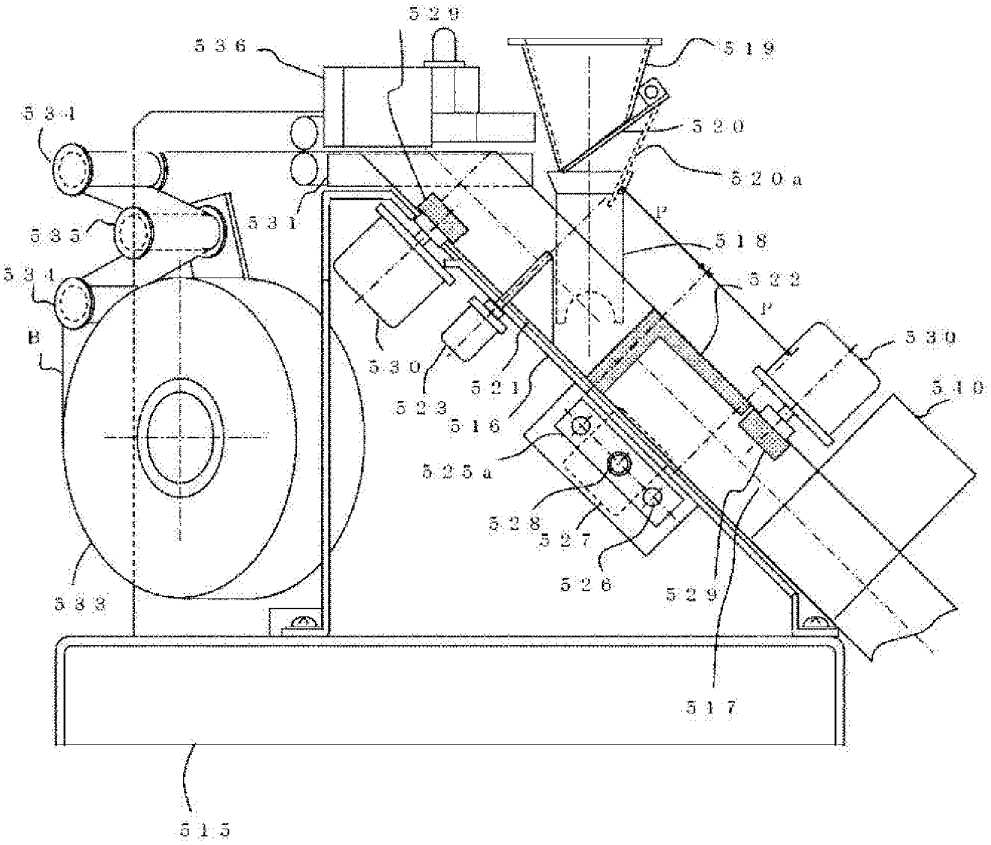
[Fig. 16]



[Fig. 17]



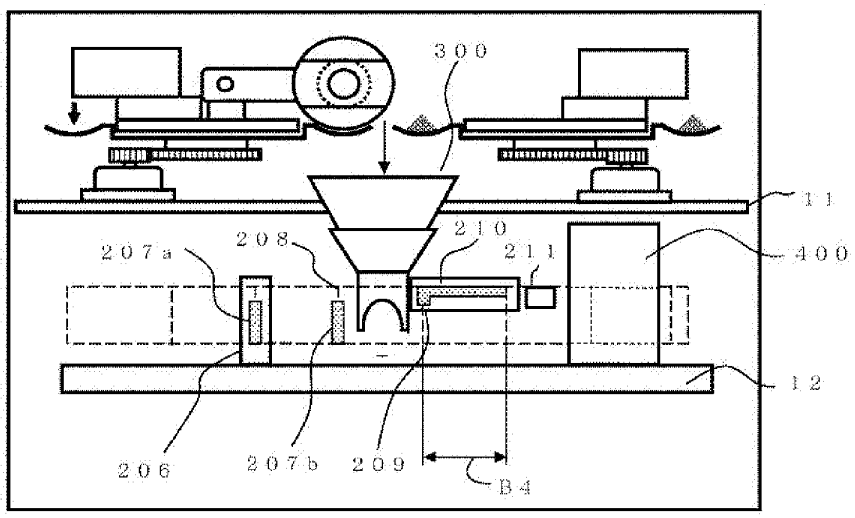
[Fig. 18]



drawing	open	—

Representative drawing | 1 | 2 | 3 | Four | Five | 6 | 7 | 8 | 9 | ...

Magnify and Rotate



Representative drawing

1 / 1 display

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Espacenet

Bibliographic data: JP2020000340 (A) — 2020-01-09

MEDICINE DISPENSING/PACKAGING DEVICE AND PRODUCTION METHOD OF DISPENSING/PACKAGING MEDICINE

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Classification: **- international:** ***A61J3/00; B65B61/00***
- cooperative:

Application number: JP20180120789 20180626 Global Dossier

Priority number(s): JP20180120789 20180626

Abstract of JP2020000340 (A)

To provide a medicine dispensing/packaging device that is never cut in a perforation portion of the dispensing/packaging paper during conveyance, and provide a production method of the dispensing/packaging medicine.SOLUTION: A medicine dispensing/packaging device has: a dispensing/packaging paper storage part where the V-folded dispensing/packaging paper is wound; a conveyance path for drawing the dispensing/packaging paper out of the dispensing/packaging paper storage part, and conveying it; a heat seal part provided in the middle of the conveyance path, and forming a heat seal to divide a dispensing/packaging paper into one package at a time; a medicine supplying part provided in the middle of the conveyance path, and supplying medicine by one package at a time between the dispensing/packaging papers; a drive roller for holding the dispensing/packaging paper where the medicine supplied by the medicine supplying part is stored, and performing conveyance drive; and a perforation making part provided at a conveyance direction down-stream of the dispensing/packaging paper from the drive roller, and forming the perforation in a portion heat-sealed by the heat seal part.SELECTED DRAWING: Figure 4

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B26F	1/18	(2006.01)	B26F	1/18		4C047

審査請求 未請求　請求項の数 7　OL　（全 15 頁）

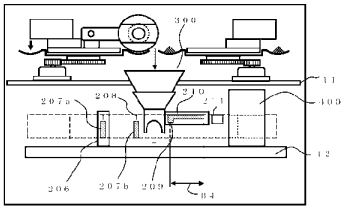
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最終頁に続く

(54)【発明の名称】薬剤分包装置及び分包薬剤の製造方法

【要約】
【課題】搬送中に分包用紙のミシン目部分で切れることの無い薬剤分包装置及び分包薬剤の製造方法を提供する。
【解決手段】Ｖ字折りされた分包用紙が巻回された分包用紙収納部と、前記分包用紙収納部から分包用紙を引出して搬送する搬送路と、前記搬送路の途中に設けられ、前記分包用紙を１個包分ずつに区分するヒートシールを形成するヒートシール部と、前記搬送路の途中に設けられ、前記分包用紙間に薬剤を１包分ずつ供給する薬剤供給部と、前記薬剤供給部によって供給された薬剤が収納された分包用紙を挟持して搬送駆動する駆動ローラと、前記駆動ローラよりも前記分包用紙の搬送方向下流に設けられ、前記ヒートシール部によってヒートシールされた部分にミシン目を形成するミシン目作成部と、を有する。
【選択図】図４



【特許請求の範囲】
【請求項１】
Ｖ字折りされた分包用紙が巻回された分包用紙収納部と、
前記分包用紙収納部から分包用紙を引出して搬送する搬送路と、
前記搬送路の途中に設けられ、前記分包用紙を１個包分ずつに区分するヒートシールを形成するヒートシール部と、
前記搬送路の途中に設けられ、前記分包用紙間に薬剤を１包分ずつ供給する薬剤供給部と、
前記薬剤供給部によって供給された薬剤が収納された分包用紙を挟持して搬送駆動する駆動ローラと、
前記駆動ローラよりも前記分包用紙の搬送方向下流に設けられ、前記ヒートシール部によってヒートシールされた部分にミシン目を形成するミシン目作成部と、
を有する薬剤分包装置。
【請求項２】
前記ミシン目作成部は、
前記分包用紙の搬送路の一方の面側に設けられ、ミシン刃が突没自在に収納された刃収納部と、
前記分包用紙の搬送路の他方の面側に、前記刃収納部と対向して設けられ、前記刃収納部から突出した前記ミシン刃との間で前記分包用紙にミシン目を形成する刃受け部と、
前記刃収納部と前記刃受け部とをそれぞれ前記分包用紙側に移動させて分包用紙を挟持するように駆動する第１の駆動部と、
前記刃収納部と前記刃受け部とによって前記分包用紙を挟持した状態で、前記刃収納部のミシン刃を前記刃受け部側に突出するように駆動することにより前記分包用紙にミシン目を形成する第２の駆動部と、
を有する請求項１記載の薬剤分包装置。
【請求項３】
前記ミシン刃は、
基部と、
前記基部から突出して設けられ、先端に山形の刃先が形成された複数の刃片が、隣接する刃片との間に所定の間隔を設けて形成された刃先部と、を有し、
前記第２の駆動部は、
前記ミシン刃の刃片の途中まで前記刃受け部側に突出させることにより、前記分包用紙にミシン目を形成し、
前記ミシン刃の基部まで前記刃受け部側に突出させることにより、前記分包用紙を切断する、
ことを特徴とする請求項２記載の薬剤分包装置。
【請求項４】
前記ミシン刃は、
前記分包用紙の搬送方向と直交する方向の両端部の刃片の刃の幅が内側の刃片の刃の幅よりも大きく形成され、これら両端部の刃片により分包用紙の搬送方向と直交する方向の両端部に切断開始部を形成する、
ことを特徴とする請求項３記載の薬剤分包装置。
【請求項５】
前記ミシン刃は、
前記それぞれの刃片が、中央部の刃片の基部からの長さが最も長く、端部に行くにつれて長さが徐々に短くなるように形成された、
ことを特徴とする請求項３又は請求項４記載の薬剤分包装置。
【請求項６】
前記ミシン刃は、
前記複数の刃片と刃片との間に、前記刃片の厚さよりも刃幅の広い横刃片を挿入するこ

とにより、十字状の刃を複数形成し、この十字状の刃により分包用紙に形成されるミシン目に、ミシン目に沿って分離されたときの切断開始部を形成する、
ことを特徴とする請求項３乃至請求項５のいずれか１項記載の薬剤分包装置。
【請求項７】
予め収納されたＶ字折りされた分包用紙を搬送路に引出し、
前記引出された分包用紙に１個包分ずつに区分するヒートシール部を形成し、
前記ヒートシール部が形成された分包用紙間に薬剤を１個包分ずつ供給して収納し、
前記薬剤が収納された分包用紙を駆動ローラにより挟持して１個包分ずつ搬送駆動し、
前記駆動ローラよりも前記分包用紙の搬送方向の下流側で、前記分包用紙のヒートシールされた部分にミシン目を形成する、
分包薬剤の製造方法。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は、薬剤を１個包分ずつ供給して分包する薬剤分包装置及び分包薬剤の製造方法に関する。
【背景技術】
【０００２】
薬剤調剤業務の自動化のために薬剤分包装置が開発され実用に供している。このような薬剤分包装置の例として特許文献１記載のものがある。
【０００３】
すなわち、Ｖ字折りされた分包用紙が巻回されたロールから、分包用紙の端部が引出され、複数の支持軸を介して搬送方向に向かって下方に傾斜した搬送路に沿って搬送され、漏斗状の薬剤ホッパ部に供給される。薬剤ホッパよりも下流側には、熱圧接部が設けられており、この熱圧接部にはヒートシール及びミシン目形成部が設けられている。そして、ヒートシールによって１個包を分離するＴ字形状のヒートシールが成されるとともに、各個包に分離するためのミシン目が形成される。ヒートシールが成された後に１個包分の薬剤が薬剤ホッパから分包用紙間に供給される。
【０００４】
薬剤が供給されると、熱圧接部よりも下流側に設けられた駆動ローラによって分包用紙が挟持されて１個包分の長さだけ引き出されて、次の個包のためのヒートシールとミシン目の作成が行われる。このような個包化動作を繰返すことによって１処方分の分包薬剤が作成される。
【先行技術文献】
【特許文献】
【０００５】
【特許文献１】特開２０１２－１３１５５１号公報
【発明の概要】
【発明が解決しようとする課題】
【０００６】
特許文献１記載の装置では、分包用紙を搬送する駆動ローラがミシン目作成部よりも下流側に設けられている。このため、駆動ローラによって分包用紙を引出した際に、分包用紙に過大な負荷が掛かるとミシン目部分で分包用紙が切れてしまうという虞があった。また、分包用紙間の下部には薬剤が封入されているので駆動ローラは必然的に分包用紙の上方を挟持して搬送する必要がある。搬送中に分包用紙が切れないようにするためには、分包用紙の上端にはミシン目（カット）を入れることができない。その結果、老人や筋力の衰えた人は上端側からミシン目に沿って切り取ることが困難であるという問題もあった。
【０００７】
そこで従来の分包機では、用紙の下端にミシン目（カット）を入れて、下側から切り取るようにする場合もあったが、これでは都度分包用紙を逆さにする必要があり、そのとき

に印字の向きが逆になって視認性が悪く、さらに切り取った後、もう一度逆さに元の状態にして、手で横方向に切って開封する必要があり、その不便さが指摘されていた。
【０００８】
本発明が解決しようとする課題は、搬送中に分包用紙のミシン目（カット）部分で切れることの無いようにした薬剤分包装置及び分包薬剤の製造方法を提供することを目的とする。また、第２の課題は、服用者が１個包をミシン目に沿って切断するのが容易なように分包用紙の上端部側にミシン目（カット）が入れられることのできる服用者にとって利便性の高い薬剤分包装置及び分包薬剤の製造方法を提供することを目的とする。
【０００９】
さらに、副次的な効果としては、このように分包用紙の上下端にミシン目（カット）を設けることで、長い分包用紙を例えば１日３包（朝・昼・晩）ごとに折りたたんで保管するような場合に、その折り目がしっかり付けやすいので、全て折りたたんだときの外観がきちんとしているという点も上げておきたい。
【課題を解決するための手段】
【００１０】
本発明の薬剤分包装置は、Ｖ字折りされた分包用紙が巻回された分包用紙収納部と、前記分包用紙収納部から分包用紙を引出して搬送する搬送路と、前記搬送路の途中に設けられ、前記分包用紙を１個包分ずつに区分するヒートシールを形成するヒートシール部と、前記搬送路の途中に設けられ、前記分包用紙間に薬剤を１包分ずつ供給する薬剤供給部と、前記薬剤供給部によって供給された薬剤が収納された分包用紙を挟持して搬送駆動する駆動ローラと、前記駆動ローラよりも前記分包用紙の搬送方向下流に設けられ、前記ヒートシール部によってヒートシールされた部分にミシン目を形成するミシン目作成部と、を有する。
【００１１】
また、本発明の分包薬剤の製造方法は、予め収納されたＶ字折りされた分包用紙を搬送路に引出し、前記引出された分包用紙に１個包分ずつに区分するヒートシール部を形成し、前記ヒートシール部が形成された分包用紙間に薬剤を１個包分ずつ供給して収納し、前記薬剤が収納された分包用紙を駆動ローラにより挟持して１個包分ずつ搬送駆動し、前記駆動ローラよりも前記分包用紙の搬送方向の下流側で、前記分包用紙のヒートシールされた部分にミシン目を形成する。
【図面の簡単な説明】
【００１２】
【図１】実施形態の散薬自動分包機の円盤配分部の平面の断面図。
【図２】実施形態の散薬自動分包機の落下ホッパの上昇位置を示す正面の断面図。
【図３】落下ホッパの構造と動作概要を示す図。
【図４】実施形態の散薬自動分包機の落下ホッパの下降位置を示す正面の断面図。
【図５】実施形態の散薬自動分包機の印刷包装機部の平面の断面図。
【図６】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが開いた状態を示す図。
【図７】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部との間に分包用紙が搬送されている状態を示す図。
【図８】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが開いた状態で刃収納部のカバーを外した図。
【図９】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが閉じてミシン目を作成している状態を示す図。
【図１０】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが閉じてミシン目を作成している状態の刃収納部のカバーを外した図。
【図１１】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが閉じて分包用紙を切断している状態を示す図。
【図１２】実施形態のミシン目作成装置の斜視図で、刃収納部と刃受け部とが閉じて分包

用紙を切断している状態の刃収納部のカバーを外した図。
【図１３】実施形態のミシン目作成装置のミシン刃の形状と移動距離を説明するための図。
【図１４】実施形態のミシン目作成装置のミシン刃の形状を説明するための図。
【図１５】実施形態のミシン目作成装置のミシン刃の形状と分包用紙との関係を説明するための図。
【図１６】実施形態の散薬自動分包機で製造された分包薬剤の例を示す図。
【図１７】第２の実施形態の印刷包装機を説明するための平面図。
【図１８】第２の実施形態の印刷包装機を説明するための正面図。
【発明を実施するための形態】
【００１３】
以下、実施形態に係る散薬自動分包機を、図面を用いて説明する。
以下の説明では散薬自動分包機を例にとって説明するが、本発明は散薬自動分包機に限定されるものではなく、錠剤自動分包機にも適用可能である。また、特許第６２５５５２８号公報や特開２０００－２４０８７号公報に記載されたような複数の薬剤を１つの個包に分包する薬剤分包装置にも適用可能なことは勿論である。
【００１４】
図１は本実施形態の散薬自動分包機の平面図、図２は散薬自動分包機の正面図である。筐体１０の中間台１１の上部には薬剤供給部である円盤配分部１００、中間台１１の下部には、薬剤包装部である印刷包装機２００が配置されている。また３００は落下ホッパであって、円盤配分部１００から放出される散薬をこの落下ホッパ３００の内面側を通して、印刷包装機２００側に導入する働きをなすものである。
【００１５】
円盤配分部１００には２組の配分部が設けられている。円盤配分部１００において、１０１は着脱自在な散薬カセットで、事前に別の場所で、当該処方に必要な分量の散薬が装填され、係員の手動操作か、図示しないロボットアーム等の自動装置によって、別の棚から振動台１０２に載置される。振動台１０２は、図示しない電磁石などによって振動を発生させ、この振動力を散薬カセット１０１に伝達させることで、散薬カセット１０１内の散薬を振動輸送し、矢印１０３の方向に散薬を少量ずつ落下させるものである。
【００１６】
１０４は水平に配置された配分円盤で、大きな円輪がステッピング・モータ１０５によって、歯車１０６を介して矢印１０４ａ方向に回転させられるようになっている。さらに配分円盤１０４の外周方向の上面には円弧状凹面１０７を形成していている。ここで、ステッピング・モータ１０５を連続的に回転しながら、振動台１０２を駆動すると、散薬が配分円盤１０４の円弧状凹面１０７に少量ずつ落下して、ドーナツ状の散薬の山Ｐ１を形成することができる。この動作を「円周撒き動作」と呼ぶこととする。
【００１７】
また、１０８は掻き出しディスク部で、レバー１０８ａが軸１０９を中心にして上下に回動できる。このレバー１０８ａの先端には、その円周外周がシリコンゴム製のディスク１１０が取り付けられ、モータ１１１で矢印１１０ａ方向に回転可能である。このディスク１１０は２枚の円板の間に羽根が設けられた水車状の形状である。なお、このディスク１１０の円板の直径は、円弧状凹面１０７の凹面の直径と同一である。
【００１８】
先の「円周撒き動作」の場合は、このディスク１１０は上方に回動して待避していて、ドーナツ状の散薬の山Ｐ１の形成を妨げない。次に「１包分配分動作」時は、掻き出しディスク部１０８のディスク１１０が下方に回動して、ディスク１１０が、円弧状凹面１０７に隙間なく密着する。この状態で、モータ１１１を駆動するとディスク１１０の円板に設けられた羽根によって円弧状凹面１０７の上の散薬が落下ホッパ３００に掻き落とされる。そして、ステッピング・モータ１０５を所定角度Ｒだけ回転させると、その角度分の散薬の量が、落下ホッパ３００側に払出される。ここで、先の所定角度Ｒとは、別に処方

箋から指定される１個包に包装すべき用量分の角度である。
【００１９】
例えば、処方箋で、ある散薬を１個包あたり１ｇで３６個包作成する場合にあっては、事前に散薬カセット１０１に３６ｇの散薬を装填しておき、これを「円周撒き動作」で、全量をドーナツ状に均一に撒く。次に「１包分配分動作」で、ディスク１１０を回転させながら、ステッピング・モータ１０５を１０度回転させると、正しく１個包分の１ｇの散薬が落下ホッパ３００に払出させることができるものである。このような円盤配分部１００と落下ホッパ３００で薬剤供給部を構成する。
【００２０】
円盤配分部１００には、左右に対称形に、２組の円盤部１１２ａと１１２ｂが配置しているが、これは、一方の円盤部１１２ａで「円周撒き動作」しているときは、他方の円盤部１１２ｂが「１包分配分動作」を出来るようにして、複数の連続する処方において無駄時間がなく、連続的に分包できるようにするためのものである。
【００２１】
図３は落下ホッパ３００の形状と動作の概要を示すものである。落下ホッパ３００は上ホッパ３０１と下ホッパ３０２の二重構造となっており、上ホッパ３０１の下開放部３０３を開閉自在なシャッタ３０４で閉鎖している。上ホッパ３０１の上端は、円盤配分部１００からの散薬を受け入れる上開口部３００ａが形成されている。下ホッパ３０２の下端部は図３（ａ）（ｂ）に示すように楔状に形成され、両端に突部である爪部３０５ａ、３０５ｂが形成され、その間に散薬を払出す刃部（下開口部）３０５ｃが形成されている。この落下ホッパ３００は全体として上下移動できるようになっている。そして、「１包分配分動作」で、円盤配分部１００から散薬を払出すタイミングでは、図３（ａ）（ｂ）の上位置に位置する。この時、シャッタ３０４は図３（ｂ）の側面図に示すように閉鎖しているので、落下した散薬は一旦このシャッタ３０４上に保持される。
【００２２】
このとき落下ホッパ３００の下端の左右の爪部３０５ａと３０５ｂは、搬送される谷折り状に二つ折された分包用紙Ｂの開放端Ｂ１にその先端を入れ込んでいる。
【００２３】
散薬の放出時は図３（ｃ）のように、落下ホッパ３００全体を下方に移動するが、左右の爪部３０５ａ、３０５ｂｃ楔状の形状が、落下ホッパ３００が分包用紙Ｂ間に進入するときのガイドの働きをしている。この状態でシャッタを３０４ａのように開くと、散薬は分包用紙Ｂの内部に収納されるものである。その後、落下ホッパ３００は図３（ｂ）の位置まで上昇する。
【００２４】
次に、図４と図５を用いて印刷包装機２００の構成と動作を説明する。図４は散薬分包機の正面の断面図であって、図２で上方に位置していた落下ホッパ３００は、下方に移動した状態を示している。図５は印刷包装機２００の上面の断面図である。２０１は分包用紙収納部としての分包用紙ロールであって、熱接着性を持つ二つ折りした用紙が谷折側を下にして、リールに巻き上げたものであり、下段台１２の上に設置されている。リールの外周側の用紙先端から引き出された分包用紙は、一点鎖線Ｂ２からＢ３のような経路で搬送路を搬送されるようになっている。２０２は印刷部で、インクリボン２０３、感熱印刷ヘッド２０４、プラテンローラ２０５等によって構成され、分包用紙Ｂの表面に、１包分ずつの処方情報を印字するものである。
【００２５】
２０６は下段台１２上に設けられたヒートシール部である縦シール機構で、分包用紙Ｂを前後（図５では上下）から熱板によって圧接することで、２０７ａのように縦方向のシールが行われることで１個包分ずつに区分する。１包分移動した位置での縦シールを２０７ｂに示すが、分包用紙Ｂの上開放端２０８はシールしないようになっている。これは、図３（ａ）のように、落下ホッパ３００の爪部３０５ａ、３０５ｂが、分包用紙Ｂ間に挿入した状態で、分包用紙Ｂを搬送できるようにするためである。次に配置される落下ホッ

パ３００の奥側には落下ホッパ洗浄装置３１０が取り付けられている。この落下ホッパ洗浄装置３１０については、本発明と直接関係しないので詳細な説明は省略する。
【００２６】
次の２０９は横シール機構で、分包用紙Ｂを前後から熱板によって圧接することで、２１０のように横方向と縦方向の未シール部分とのシールが行われる。先の縦シール２０７と横シール２１０とによって、分包用紙Ｂは１個包としてシールされるものである。なお、図では省略しているが、縦シール７はミシン目が形成される部分をシールせずに、ミシン目形成部を挟んだ両側をシールするようになっており、詳細は後述する。
【００２７】
２１１は駆動ローラであって、印刷部２０２のプラテンローラ２０５と同期駆動され、分包用紙Ｂの上端部分を両面から挟持して回転することにより、１個包分ピッチＢ４の距離を、１工程として駆動される。４００はミシン目作成装置で、縦シールされた部分の中間に設けられた非シール部に、縦方向のミシン目を形成することにより、服薬者が１個包ずつに分離しやすくなっている。なお、図２及び図４に示す縦方向の破線はミシン目ではなく、１個包の境目を示したものである。また、図２及び図４においては、説明を判りやすくするために落下ホッパ３００より下流側の縦シールの記載は省略している。
【００２８】
なお、落下ホッパ洗浄装置３１０の補機として、集塵ブロア３２０と、圧縮空気発生コンプレッサ３３０が、筐体後方に配置されて、それぞれ、落下ホッパ洗浄装置３１０の空気源として利用される。
【００２９】
以下、図６～図１５を用いてミシン目作成装置４００の構成と動作について説明する。図６はミシン目作成装置の斜視図であり、刃収納部４０２と刃受け部４０４とが開いている待機状態を示す図で、図７は刃収納部４０２と刃受け部４０４との間に分包用紙Ｂを挿入した状態を示す図である。分包用紙Ｂは刃収納部４０２と刃受け部４０４との中間に位置するように刃収納部４０２と刃受け部４０４とが配置されている。図８は刃収納部４０２のカバーを外した状態を示す図である。
【００３０】
図４及び図５に記載された下段台１２にはモータ用ベース４０６が固定され、このモータ用ベース４０６にはステッピング・モータ４０８が固定されている。また、下段台１２にはミシン刃ユニット４０１のベース４１０が固定されている。
【００３１】
ミシン刃ユニット４０１のベース４１０には刃収納部４０２が固定された支持部４２８が摺動自在に設けられている。また、ベース４１０には刃受け部４０４が固定された支持部４２４が摺動自在に設けられ、支持部４２４に固定されたスライド軸４２２と一体になって摺動するものである。そして、支持部４２４と支持部４２８とは互いに接離する方向に摺動自在である。これら支持部４２４と支持部４２８との間にはスプリング４２６が設けられ、互いに離間する方向に付勢されている。
【００３２】
刃収納部４０２の支持部４２８の内部にはシャフト４３４がスライド自在に設けられ、このシャフト４３４の左端にはミシン刃４３２が固定されている。そして、ミシン刃４３２は刃収納部４０２の２枚のカバーの間に、ミシン刃４３２が刃収納部４０２から突没する方向にスライド自在に設けられている。
【００３３】
ステッピング・モータ４０８の図示しない軸とカムシャフト４１２に固定されたプーリ４１４との間にはタイミングベルトが掛け渡され、ステッピング・モータ４０８が回転することによりカムシャフト４１２が回転するようになっている。
【００３４】
また、カムシャフト４１２には３つのカム板４１６，４１８，４２０が固定されている。最下段の第１のカム板４１６は刃受け部４０４を駆動するもので、第１のカム板４１６

を回転することで図示しないカムフォロワによってスライド軸４２２を図中右方向に引き寄せる。スライド軸４２２には刃受け部４０４が固定された支持部４２４が接続されているので、刃受け部４０４も図中右方向に引き寄せられる。

【００３５】

下から２段目の第２のカム板４１８は刃収納部４０２を駆動するもので、カム板４１８を回転することにより刃収納部４０２が固定された支持部４２８に取付けられたカムフォロワ４３０を図中、左方向に駆動するものである。したがって、ステッピング・モータ４０８を回転することによって刃収納部４０２と刃受け部４０４とが互いに接触する方向に移動して分包用紙Ｂを挟持する。カム板４１６と４１８の形状はそれ以上回転しても刃収納部４０２と刃受け部４０４とは分包用紙Ｂを挟持したままである。このようにカム板４１６による刃受け部４０４の駆動機構、及びカム板４１８による刃収納部４０２の駆動機構で第１の駆動部を構成している。

【００３６】

さらに最上段の第３のカム板４２０はミシン刃４３２駆動用のもので、シャフト４３４に固定されたカムフォロワ４３６が第３のカム板４２０に接触している。そして、ステッピング・モータ４０８が回転することによって第３のカム板４２０が回転し、カムフォロワ４３６を押すことによりシャフト４３４を図中左側に駆動する。その結果、シャフト４３４に固定されたミシン刃４３２が刃収納部４０２から刃受け部４０４側に突出して、分包用紙Ｂにミシン目を形成するものである。カム板４２０によるミシン刃の駆動機構が第２の駆動部を構成する。

【００３７】

ミシン刃ユニット４０１の待機状態を図８に示す。図８（ａ）に示すようにミシン刃ユニット４０１の待機状態ではミシン刃４３２は刃収納部４０２のカバー内に没した状態である。このときのカム板４２０とカムフォロワ４３６の状態を図８（ｂ）に示すが、カムフォロワ４３６がカムシャフト４１２に最も近い位置にある。

【００３８】

次に、ステッピング・モータ４０８が回転して分包用紙Ｂにミシン目を形成している状態を図９及び図１０に示す。図９及び図１０に示すように第１のカム板４１６及び第２のカム板４１８が回転することにより、刃収納部４０２と刃受け部４０４とは接触して分包用紙Ｂを挟持した状態となる。なお、図９及び図１０では分包用紙Ｂの記載は省略している。分包用紙Ｂにミシン目を形成する状態ではカム板４２０は図９（ｂ）に示すようにカムノォロワ４３６を押し込んでおり、図１０に示すようにミシン刃４３２の先端が刃受け部４０４内に突出した状態となる。

【００３９】

分包用紙Ｂにミシン目を形成した後は、ステッピング・モータ４０８が逆転することにより、カム板４２０が図９（ｂ）の状態から逆転して図８（ｂ）に示す待機位置に戻る。このような動作によって分包用紙Ｂにミシン目を形成すると、次の個包を形成するために駆動ローラ２１１によって分包用紙Ｂの搬送が行われる。なお、ミシン目の形成と同期して縦シールの形成、薬剤の供給、横シールの形成が行われる。これは、ミシン目の形成時には分包用紙Ｂが停止した状態にあり、分包用紙Ｂの停止した状態での作業である縦シールの形成、薬剤の供給、横シールの形成が行われるものである。以上の動作で１個包分のサイクルが終了する。

【００４０】

ここで、薬剤の処方は服薬者に対して、例えば朝昼晩で２週間分４２回分を処方する。１人の服薬者に対する４２回分の個包の間はミシン目を入れ、１人の服薬者に対する個包が完了した段階ではミシン目ではなく、分包用紙Ｂを切断することにより処方薬を放出する必要がある。

【００４１】

このため、本実施の形態では、ミシン目作成装置４００によって分包用紙Ｂの切断も行うようになっている。図１１及び図１２に示すように、カム板４２０が図９（ｂ）のミシ

ン目を形成する状態を越えて、ステッピング・モータ４０８をさらに回転させ、カム板４２０を図１１（ｂ）に示す位置まで回転させる。すると、カムフォロワ４３６はカムシャフト４１２から最も離れた位置まで押される。これによりミシン刃４３２がさらに突出してミシン刃４３２の基部まで刃受け部４０４内に突出する。これにより、分包用紙Ｂはミシン刃４３２により切断されることになる。なお、分包用紙Ｂの切断時はカムシャフト４１２の回転を戻すことなく、１回転させるのみでよい。

【００４２】

次に、ミシン刃４３２の形状と移動量とを図１３に示す。

ミシン刃４３２はシャフト４３４への固定部４３２ａ、刃の基部４３２ｂ、及び刃の基部４３２ｂから突出して設けられた刃先部４３２ｃとからなる。刃先部４３２ｃの先端に山形の刃先が形成された複数の刃片４３２ｄが、隣接する刃片４３２ｄとの間に所定の間隔を設けて形成されている。刃片４３２ｄと刃片４３２ｄとの間には３箇所に、刃先部の厚さｔよりも刃幅の広い横刃片が設けられているが、図１３（ａ）、（ｂ）では省略している。そして各刃片４３２ｄの先端までの長さは中央部の刃片が最も長く、端部に行くにつれて徐々に長さが短くなっている。各刃片４３２ｄの先端を結ぶ直線Ｌ１と基部の先端に平行な直線Ｌ２とのなす角度θは約４度の角度が設けられている。これにより、分包用紙Ｂにミシン目を形成する際は、カット部が中央の刃片４３２ｄから徐々に端部の刃片４３２ｄへと移るので、ミシン刃４３２の移動に要する駆動力も小さいもので済む。

【００４３】

また、ミシン刃４３２の長さ方向の端部、すなわち分包用紙Ｂの搬送方向に直交する方向の端部の刃片４３２ｅ、４３２ｅの刃幅は内側の刃片４３２ｄの刃幅よりも大きく形成されている。そして分包用紙Ｂの幅は図１３（ｂ）に記号Ｗと記載したように、分包用紙Ｂの端部が、ミシン刃４３２の端部の刃片４３２ｅ、４３２ｅの位置になるように構成されている。従って、分包用紙Ｂの搬送位置がずれても、分包用紙Ｂの端部に、服薬者が個包を切り離すときの切断開始部（カット）を確実に形成でき、服薬者が容易に分包を切り離すことができる。

【００４４】

図１３（ｂ）にミシン刃４３２によるミシン目形成と分包用紙Ｂの切断のときのミシン刃４３２の突出距離を示す。ミシン目形成時にはミシン刃４３２の刃先部４３２ｃの中間部であるＭの位置まで刃受け部４０４にミシン刃４３２が突出する。また、分包用紙Ｂの切断時は刃先部４３２ｃの位置を越えた刃の基部４３２ｂの位置Ｃまで刃受け部４０４にミシン刃４３２が突出する。このように構成することによって分包用紙Ｂの個包間へのミシン目の形成と、１処方間の分包用紙Ｂの切断とがミシン刃４３２の突出量を変えることによって達成することができるものである。

【００４５】

次に、ミシン刃４３２の刃片４３２ｄ間に横刃片を挿入することによる、十字カット刃について図１４及び図１５を参照して説明する。図１４（ａ）は斜視図、（ｂ）は左側面図、（ｃ）は正面図、（ｄ）は上面図をそれぞれ示している。

【００４６】

すなわち、ミシン刃４３２の、図１４で上から５枚目と６枚目の間、８枚目と９枚目の間、及び１１枚目と１２枚目の間の３箇所には、横刃４３２ｇが挿入されている。この横刃片４３２ｇは刃片４３２ｄの厚さｔよりも刃の幅が広く形成されており、各刃片４３２ｄの間に圧入されるとともに、横刃４３２ｆの基部側に設けられた溝部にミシン刃４３２の基部４３２ｂが圧入されることにより保持されている。このように構成されたミシン刃４３２とすることにより、ミシン目が形成されるとともに、分包用紙Ｂが各個包に分離されたときに各個包を開封するときの切断開始部（カット）を形成するものである。

【００４７】

横刃４３２ｇの挿入位置と枚数は上述の例に限定されるものではなく、刃片４３２ｄの間であればどの位置にも挿入できるものである。特に各個包に収納される散薬の量が少ないときは、各個方の下のほうの十字カット位置で開封したほうが飲み残しの量が少なくな

るので、それを考慮して挿入する位置、枚数を選択することができる。
【００４８】
図１５（ａ）にミシン刃４３２と分包用紙との関係を例示する。図１５（ａ）に示すように、分包用紙のシール部（斜線部）は、縦シール機構２０６によって、ミシン目形成部（非シール部）を例えば４ｍｍ残して形成され、ミシン目はこの非シール部に形成される。そして、例えば、分包用紙Ｂの幅、すなわち、搬送方向と直交する方向の幅が例えば７０ｍｍであると仮定すると、ミシン刃４３２の長さを分包用紙Ｂの幅よりも大きい７５ｍｍとする。これにより、分包用紙Ｂの端部はミシン刃４３２の端部の刃片４３２ｅに対向するようにでき、その結果、分包用紙Ｂの両端部に切断開始部（カット）Ｂ１を形成することができる。
【００４９】
また、図１５（ｂ）に示すように、横刃の刃幅をミシン刃４３２の厚さｔ＝１ｍｍよりも大きい４ｍｍ程度とすることにより、分包用紙Ｂの非シール部の幅４ｍｍに亘って十字カット部Ｂ２を形成することができ、個包の開封のときの切断開始部となる。よって、患者・利用者による開封が容易な分包薬剤を提供できるものである。
【００５０】
なお、図１６は製造された分包薬剤の断面図の例を示すもので、例えば、上端から２０ｍｍの位置から、９ｍｍ間隔で３個の十字カット部形成した例を示している。
【００５１】
なお、第１の実施形態では、分包用紙Ｂを水平方向に搬送し、搬送方向に沿って、縦シール部２０６、薬剤供給部である落下ホッパ３００、横シール部２０９、搬送ローラ２１１及びミシン目作成部４００を配置したが、分包用紙Ｂを搬送方向に向かって下方に傾斜した搬送路に沿って搬送するように構成すれば、縦シール部は薬剤供給部の下流側に設けることも可能である。
【００５２】
次に図１７及び図１８を用いて第２の実施形態の印刷包装機５００について説明する。図１７は平面図、図１８は、同じく正面図である。ベース板５１５にはＶ字折りされた分包用紙Ｂをロール状に巻回した分包用紙収納部５３３が設けられ、この分包用紙収納部５３３から１端を引出された分包用紙Ｂは、複数の支持ロール５３４，５３５を介して上方へ搬送され、ひねりローラ５３１によって搬送方向が変換され、搬送方向に沿って下方に４５度傾斜した搬送経路に搬送される。
【００５３】
ベース板５１５の上面には水平面に対して４５度の傾きを有する分包用紙Ｂの搬送ベース５１６が設けられ、この４５度平面に平行な中心線５１７に沿って立位の分包用紙Ｂの搬送経路にそって搬送される。この搬送経路の中央部には谷折りした分包用紙Ｂの上部開口側から下出口を侵入させた落下ホッパ５１８がほぼ垂直に設けられ、さらにその上部に薬剤供給ホッパ５１９が設けられる。薬剤供給ホッパ５１９の下部は開口していて、この開口を遮るシャッタ機構５２０は、一つの分包に入れるべき薬剤を一旦保持し、図示しないアクチュエータによって５２０ａのように開放することで、薬剤を下の落下ホッパ５１８を介して、谷折りした分包用紙Ｂの内部空間に薬剤を落下させて供給する。
【００５４】
この空間は左上の搬送上流に配置された紙押さえ板５２１と、下流側右下に配置された逆Ｌ字型ヒートシール部５２２によって左右を遮られている。紙押さえ板５２１は回動アクチュエータ５２３によって開閉動作し、分包用紙Ｂが搬送されているときは開き、停止している時は閉じるように制御される。ヒートシール部５２２は、面発熱体５２４をキャリッジ５２５ａに保持されている。キャリッジ５２５ａはガイドロッド５２６に軸支され、モータ５２７に直結された送りネジ５２８によって前進後退可能なごとくに構成される。キャリッジ５２５ａが前進すると、分包用紙Ｂの上端横方向と縦方向とが、受け板５２５ｂに圧接され、加熱によって、分包用紙Ｂはシールされるように構成される。
【００５５】

分包用紙Ｂが静止した状態で、キャリッジ５２５ａを所定時間前進させた状態で、かつ紙押さえ板５２１を閉じたタイミングで、シャッタ機構５２０を５２０ａのように開くと、薬剤が分包用紙Ｂ内に落下する。次に分包用紙Ｂを所定間隔Ｐ搬送して、再度キャリッジ５２５ａを前進させると、先ほど落下した薬剤の収納部分が一括してシールされる。この動作を繰り返すことで、分包用紙Ｂが連続的にシールされるが、この時、順次投入する薬剤の種類と量を処方箋に従って、服用順序に従って制御すれば、例えば２週間分の服用薬剤が、一回の服用分は一包毎に分割されて完成する。なお、ゴムローラ対５２９は分包用紙Ｂを挟持して搬送する手段であり、連続する分包用紙Ｂの複数箇所に設置することによって、用紙をたるみなく搬送できるようになっている。駆動ローラ対５２９はパルスモータ５３０によって、所定距離の搬送停止制御ができるようになっている。

【００５６】

下流側の駆動ローラ５２９の下流には第１の実施形態として説明したミシン目作成装置４００と同様のミシン目作成装置５４０が設けられている。

【００５７】

薬剤の分包を作成する動作は、搬送される分包用紙Ｂをヒートシール部５２２によって１包分を区分する縦シールを行う。なお、このとき前の個包に対して横シールも同時に成される。次に薬剤供給５１９から落下ホッパ５１８を介して１包分の薬剤を分包用紙Ｂ間に供給する。薬剤が供給された分包用紙Ｂは駆動ローラ５２９によって１個包分の長さ分搬送される。

【００５８】

次に２包目の薬剤が分包用紙Ｂ間に供給されて、さらに駆動ローラ５２９によって分包用紙Ｂが搬送される。この段階で最初の縦シール部がミシン目作成装置５４０の部分に来るので、ミシン目作成装置５４０によって縦シール部の中央部にミシン目が形成される。以下、この動作を繰返して１処方分の分包薬剤が完成したら、ミシン目作成装置５４０によって縦シール部をミシン目作成装置５４０によって切断することにより分包薬剤を製造するものである。

【００５９】

このように、ヒートシール部の位置は薬剤供給部の上流に限定されず、薬剤供給部の下流側であっても良いものである。

【００６０】

本発明のいくつかの実施形態、変形例を説明したが、これらの実施形態、変形例は、例として提示したものであり、発明の範囲を限定することは意図していない。これら新規な実施形態、変形例は、その他の様々な形態で実施されることが可能であり、発明の要旨を逸脱しない範囲で、種々の省略、置き換え、変更を行うことができる。これら実施形態やその変形は、発明の範囲や要旨に含まれるとともに、特許請求の範囲に記載された発明とその均等の範囲に含まれる。

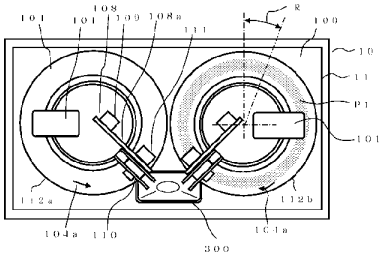
【符号の説明】

【００６１】

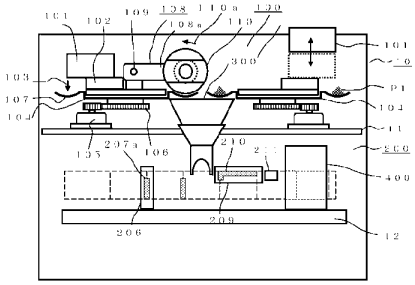
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２００・・・印刷包装機
２０１・・・分包用紙ロール（分包用紙収納部）
２０６・・・縦シール機構
２０９・・・横シール機構
２１１・・・駆動ローラ
３００・・・落下ホッパ（薬剤供給部）
４００・・・ミシン目作成装置
４０２・・・刃収納部
４０４・・・刃受け部
４１６，４１８・・・カム板
４２０・・・カム板

４３２・・・ミシン刃
４３２ｂ・・・ミシン刃の基部
４３２ｃ・・・ミシン刃の刃先
Ｂ・・・分包用紙
Ｂ２，Ｂ３・・・搬送経路（搬送路）

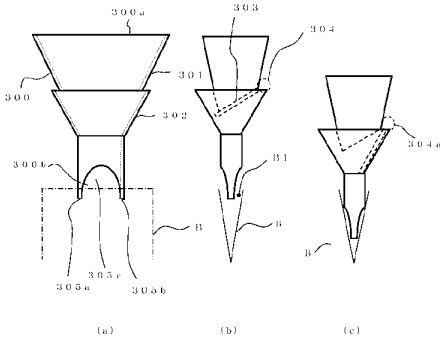
【図１】



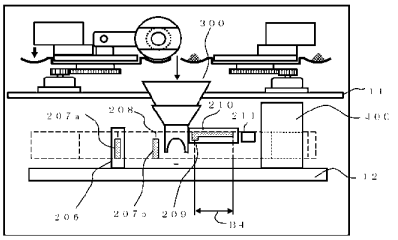
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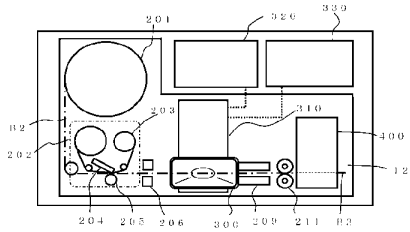
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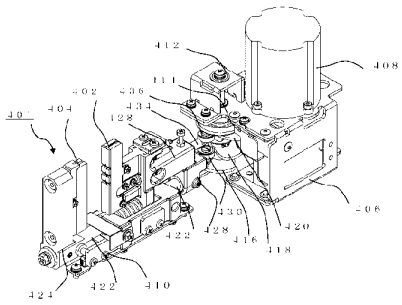
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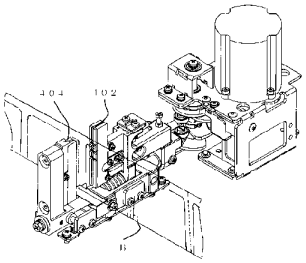
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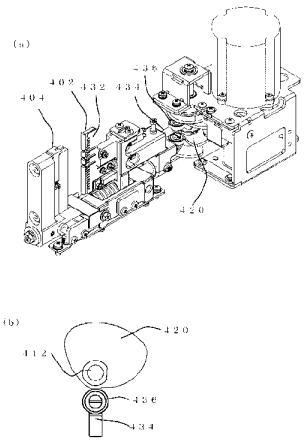
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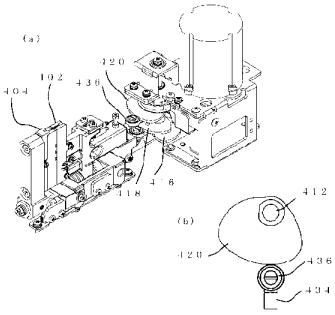
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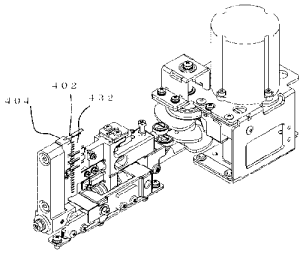
【図８】



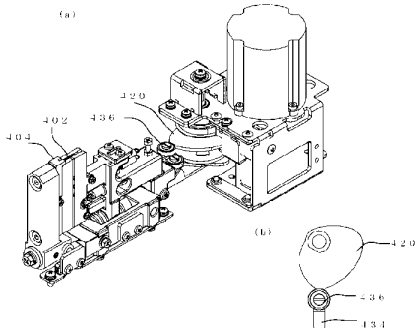
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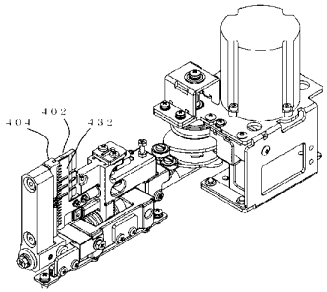
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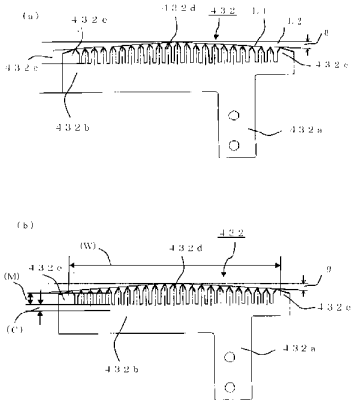
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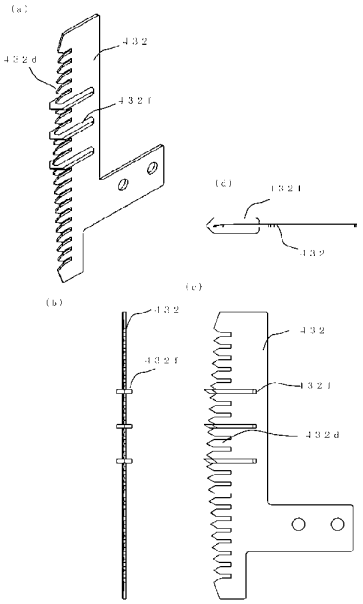
【図１２】



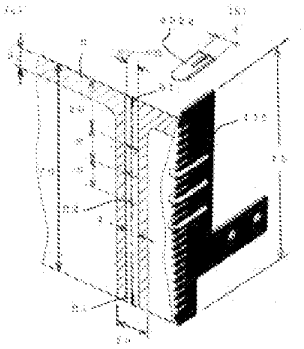
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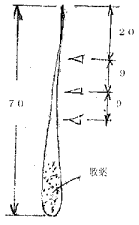
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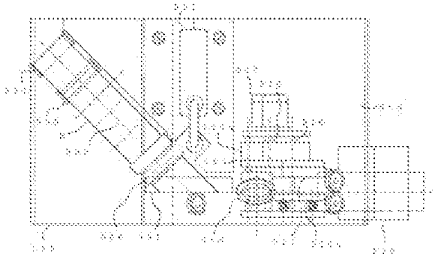
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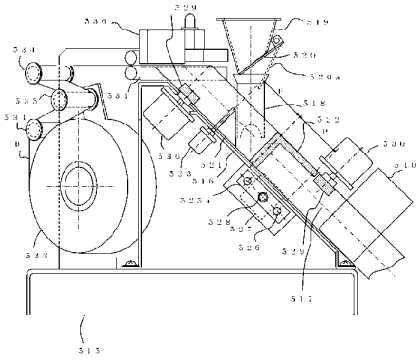
【図１６】



【図１７】



【図１８】



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(51) [International Patent Classification]
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B01F 1/00 (2006.01)
B01F 5/06 (2006.01)
B01F 15/06 (2006.01)
[FI]
B01F 3/04 A
B01F 1/00 A
B01F 1/00 B
B01F 1/00 G

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B01F 15/06 Z

[Number of claims] 35

[Total number of pages] 47

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Judge: Toyohide Watanabe
Judge: Tsuyoshi Kumakura
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[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 CO_2 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 embodiment 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 the open section.

[0010]

In one embodiment, between a process microchannel and a heat source and/or heat sink, between a second fluid stream channel and a heat source and/or heat sink, or between a process microchannel and a second fluid stream channel. and heat sources and/or heat sinks. Heat sources and/or heat sinks may be used for heating, cooling, or both cooling and heating. The heat source may include heat exchange channels and/or heating elements. The heat sink may include 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 channel, 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 second fluid stream channel, but not into the process microchannel and/or the second fluid stream channel or into the process microchannel. It should be sufficiently close to the process microchannel 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 microchannels, the second fluid stream channels and the heat exchange channels, the process microchannels and the heat exchange channels. One or more footers or manifolds are used to provide 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 between 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 sink and at least a portion of the process microchannel upstream of the mixing zone. In one embodiment, heat is exchanged between the heat source and/or heat sink and at least a portion of 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 microchannels and the second fluid stream channels are formed from parallel spaced apart sheets and/or plates, the process microchannels and the second fluid stream channels being adjacent to each other and alternating side by side. Arranged in the form of planes or alternating planes stacked 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 streams 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 properties.

In one embodiment

, the process is carried out in a microchannel mixer, the microchannel mixer comprising at least 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 embodiment at least about 1000 process microchannels.

[0021]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mixer comprising a plurality of process microchannels connected to at least one first fluid flow manifold, the first Fluid streams flow through at least one first fluid stream manifold to the process microchannels. In one embodiment, the process microchannel is adjacent to a second fluid flow channel, the microchannel mixer further comprising at least one second fluid flow manifold connected to the second fluid flow channel, the second Fluid flows through at least one second fluid flow manifold to the second fluid flow channels. In one embodiment, the process microchannels and/or liquid channels are adjacent to heat exchange channels, and the microchannel mixer further comprises at least one heat exchange manifold connected to the heat exchange 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 through an open section into the process microchannel, the process microchannel and liquid channel comprising concentric annular tubes.

[0023]

In one embodiment, the process is carried out in a microchannel mixer, the microchannel mixer comprising a plurality of process microchannels, with separate multiphase mixtures formed in each of the process microchannels. , the multiphase mixtures formed in at least two of the 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

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Natural oils include animal and vegetable oils (eg castor oil, lard oil) and liquid petroleum oils. and mineral oils such as solvent-treated or acid-treated mineral oils of the paraffinic, naphthenic or mixed paraffinic-naphthenic type. Natural oils include oils derived from coal or shale. The oil may be a saponifiable oil from the triglyceride family, such as soybean oil, sesame seed oil, cottonseed oil, safflower oil and the like. The oil may be a silicone oil (eg, cyclomethicone, silicone methicones, etc.). The oil may be an aliphatic or naphthenic hydrocarbon such as petrolatum, squalane, squalene or one or more dialkylcyclohexanes, or mixtures of two or more thereof. Synthetic oils include polymerized and intermolecularly reacted olefins (e.g. polybutylenes, polypropylenes, propylene isobutylene copolymers, etc.), poly(1-hexenes), poly(1-octenes), poly(1-decenes).) and mixtures thereof, alkylbenzenes (e.g. dodecylbenzenes, tetradecylbenzenes, dinonylbenzenes, di-(2-ethylhexyl)benzenes, etc.), polyphenyls (e.g. biphenyls, terphenyls, alkylated polyphenyls, etc.), alkylated diphenyl ethers and alkylated diphenyl sulfides and their derivatives, analogs and homologues and likes. Alkylene oxide polymers and copolymers and derivatives thereof in which the terminal hydroxyl groups have been modified by esterification, etherification, etc. are synthetic oils that can be used. Synthetic oils may include p

oly-alpha-olefins or Fischer-Tropsch synthetic hydrocarbons.

The liquid

may comprise a normally liquid hydrocarbon fuel, for example a distillate fuel such as motor gasoline as defined in ASTM standard D439, or a diesel fuel or heavy oil as defined in ASTM st andard D396.

[0088]

The liquid may comprise fatty alcohols, fatty acid esters or mixtures thereof. The fatty alcoh ol may be Guerbet alcohol. The fatty alcohol may contain from about 6 to about 22 carbon ato ms, in one embodiment from about 6 to about 18 carbon atoms, and in one embodiment from about 8 to about 12 carbon atoms. Fatty acid esters are esters of straight chain fatty acids of about 6 to about 22 carbon atoms with straight or branched chain fatty alcohols of about 6 to about 22 carbon atoms; It can also be an ester of a branched carboxylic acid of 1 atom with a straight or branched chain fatty alcohol of from about 6 to about 22 carbon atoms, or mixture s thereof. Examples are myristyl myristate, myristyl palmitate, myristyl stearate, myristyl isos tearate, myristyl oleate, myristyl behenate, myristyl erucate, cetyl myristate, cetyl palmitate, cetyl stearate, cetyl isostearate, cetyl oleate. , cetyl behenate, cetyl erucate, stearyl myristat e, stearyl palmitate, stearyl stearate, stearyl isostearate, stearyl oleate, stearyl behenate, ste aryl erucinate, isostearyl myristate, isostearyl palmitate, iso-stearate Stearyl, isostearyl isoste arate, isostearyl oleate, isostearyl behenate, isostearyl oleate, oleyl myristate, oleyl palmitate, oleyl stearate, oleyl isostearate, oleyl oleate, oleyl behenate, oleyl erucate, behenyl myristate, behenyl palmitate, behenyl stearate, behenyl isostearate, behenyl oleate, behenyl behenate, behenyl erucate, erucyl myristate, erucyl palmitate, erucyl stearate, erucyl isostearate, erucyl oleate, behenic acid Includes erucyl and erucyl erucate. fatty acid
mixtures of mono-, di-, and/or triglycerides made up of one or more fatty acids of about 18 c arbon atoms; one with one or more fatty alcohols and/or Guerbet alcohols of about 6 to about 22 carbon atoms; esters with one or more aromatic carboxylic acids (e.g., benzoic acid); one or more dicarboxylic acids of 2 to about 12 carbon atoms and one or more linear chains of 1 t o about 22 carbon atoms; or esters with branched alcohols, one or more polyols containing 2 to about 10 carbon atoms and 2 to about 6 hydroxyl groups, or mixtures of such alcohols and polyols, 2 to about 12 esters of one or more dicarboxylic acids (e.g. phthalic acid) of 1 to 22 c arbon atoms with one or more alcohols (e.g. butyl alcohol, hexyl alcohol) of 1 to 22 carbon at oms, benzoic acid and from about 6 It may also include esters with linear and/or branched alc ohols of about 22 carbon atoms, or mixtures of two or more thereof. The liquid is one or mor e branched primary alcohols of about 6 to about 22 carbon atoms, one or more linear and/or branched aliphatic alcohols of about 6 to about 22 carbon atoms

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carbonates, one or more Guerbet carbonates made from one or more aliphatic alcohols of fro m about 6 to about 22 carbon atoms, one or more of which each alkyl group contains from 1 t o about 12 carbon atoms; dialkyl (e.g. diethylhexyl) naphthalate, one or more linear or branc

hed, symmetrical or asymmetrical dialkyl ethers containing from about 6 to about 22 carbon a toms per alkyl group, from about 6 to about 22 carbon atoms Epoxidized fatty acid esters and one or more ring-opening products of polyols containing 2 to 10 carbon atoms and 2 to 6 hydr oxyl groups, or mixtures of two or more thereof. good.

[0090]

Water may be obtained from any convenient source. Water may be deionized or purified usin g osmotic or distillation methods. The microbody-forming material may include any microbod y-forming material

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The microbody-forming material may be in the form of a liquid or solid melt. Microbody-formi ng materials may include glass, eg, glass microbody (eg, microsphere)-forming materials, pol ymeric, eg, polymeric microbody (eg, polymeric microsphere)-forming materials. The polymer ic microbody-forming material is one or more of acrylic resins, silicone resins, urethane resin s, vinyl acetate resins, Teflon resins, polyamide resins, vinyl chloride resins, styrene-based res ins, phenolic resins, epoxy resins, styrene resins. -butadiene-styrene block copolymer resin, s tyrene-ethylene-butylene-styrene block copolymer resin, styrene-isoprene-styrene block copol ymer resin, n-butyl rubber, chloroprene rubber, natural rubber or two or more thereof It may also include combinations. In one embodiment, the polymeric microbody-forming material ma y comprise (meth)acrylic acid esters of alcohols of 1 to about 14 carbon atoms. In one embod iment, the polymeric microbody-forming material may comprise at least one alkyl (meth)acryl ate.

[0092]

In one or more embodiments of the present invention, emulsifiers and/or surfactants are not required, although one or more emulsifiers and/or surfactants may be used in forming the mu ltiphase mixture prepared by the process of the present invention. may be used. Emulsifiers a nd/or surfactants may be premixed with the liquid. The emulsifiers and/or surfactants are ioni c or non-ionic with a Hydrophilic-Lipophilic Balance (HLB) in the Griffin system ranging from 0 to about 18, in one embodiment from about 0.01 to about 18. may contain a chemical compo und. Ionic compounds may be cationic or amphoteric compounds. Examples include those disc losed in "McCutcheons Surfactants and Detergents", 1998 Edition, North American and Intern ational Editions. Pages 1-235 of the North American version and pages 1-199 of the Internatio nal version are hereby incorporated by reference in part for their disclosure of such emulsifier s. Emulsifiers and/or surfactants that can be used are

, alkylene oxide repeat units, carboxylated alcohol ethoxylates, ethoxylated alcohols, ethoxyla ted alkylphenols, ethoxylated amines and amides, ethoxylated fatty acids, ethoxylated fatty a cid esters and oils, fatty acid esters, fatty acid amides, glycerol esters , glycol esters, sorbitan esters, imidazoline derivatives, lecithin and derivatives, lignin and derivatives, monoglycerides and derivatives, olefin sulfonate esters, phosphate esters and derivatives, propoxylated and et hoxylated fatty acids or alcohols or alkylphenols, sorbitan derivatives, Sucrose esters and deri

vatives, sulfates or alcohols or ethoxylated alcohols or fatty acid esters, dodecylbenzenes and tridecylbenzenes or condensed naphthalenes or petroleum sulfonates, sulfosuccinates and der ivatives, tridecylbenzene and dodecyl Contains benzenesulfonic acid. Emulsifiers and/or surfac tants include one or more polyalkylene glycols, glycerol or sorbitan and one or more partial es ters of fatty acids containing from about 12 to about 22 carbon atoms, or mixtures thereof. m ay contain. Emulsifying agents and/or surfactants may include pharmaceutically acceptable m aterials such as lecithin. The concentration of these emulsifiers and/or surfactants in the multi phasic mixture made by the process of the present invention is up to about 20% by weight of the multiphasic mixture, and in one embodiment from about 0.01 to about 5% by weight. It may be in the range, in one embodiment from about 0.01 to about 2% by weight. In one emb odiment, this concentration may be up to about 2% by weight, in one embodiment up to abou t 1% by weight, and in one embodiment up to about 0.5% by weight.

[0093]

In one embodiment, the first fluid stream comprises a liquid stream and the second fluid str eam comprises air.

[0094]

In one embodiment, the first fluid stream comprises a liquid waste stream and the second fl uid stream comprises air. In one embodiment, the first fluid stream contains the hazardous li quid waste stream and the second fluid stream contains air

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[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

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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 embodime nt 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 pro vide 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 u sing conventional processing equipment such as mixing tanks. a temperature difference betwe en 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 mic rochannel 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 t hird fluid stream liquid channels can employ temperature zones along the length of such chan nels. 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 secon d zone near the end of the process microchannel. A cooling or quench zone may be incorporat ed into the process microchannels to rapidly cool and stabilize the multiphase mixture. Optim al along the length of the process microchannel, including the possibility of sections both befo re and/or after the mixing zone within the process microchannel that heat and/or cool the fee dstock 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 abo ut 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 ran ge from about 25 to about 10,000, and in one embodiment from about 250 to about 5000. Th e 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 o ne 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, 4 30, 530, 540) and the third fluid flow through the third fluid flow channels (440, 450) Flow rat es 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 abou t 100 m/s, and in one embodiment from about 0.1 m/s to about 10 m/s. The Reynolds numbe r of the second and third fluid streams may range from about 50 to about 5000, and in one e mbodiment from about 50 to about 500. The temperature of the second fluid stream entering

the second fluid stream channel and the third fluid stream entering the third fluid stream chan nel are from about -10°C to about 650°C, in one embodiment from about 25°C to about 450° C. °C. The absolute pressure within the second and third fluid flow channels may range from a bout 1 to about 25 atmospheres, and in one embodiment from about 1 to about 5 atmosphere s. Apertures (244, 244a, 313, 323, 333, 34
3, 416, 426, 436, 446) is in the range of about 0.005 to about 0.5 atmospheres, and in one e mbodiment about 0.05 to about 0.1 atmospheres. good. A schematic of the formation of bub bles or microbodies by the process of the present invention is shown in FIG
.
Referring to FIG. 21, gas bubbles or microbodies 650 emerge from openings 652 in microchan nels 654 and disperse into first fluid stream 656 . The bubble or microbody may grow in size while attached to the gas or microbody-forming material base 658 within the opening 652, for example, about ten times the size of the opening or more. Ultimately, shear forces at the bas e of the gas or microbody-forming material base 658 separate the bubbles or microbodies fro m the openings, dispersing the bubbles or microbodies into the first fluid stream 656 . In one embodiment, a relatively high open section pressure drop or, correspondingly, a high flow velo city of the second fluid stream through the second fluid stream channel results in a second flui d stream within the first fluid stream. may not be necessary to achieve the distribution of The lower pressure drop or lower flow velocity results in a lower inertia of the second fluid stream flowing through the apertured section, reducing bubble or microbody growth before the bubbl e or microbody separates from the aperture. can give rise to smaller bubbles or microbodies.
The multiphase mixture exiting the process microchannels (210, 210a, 310, 320, 330, 340, 410, 520) has a temperature of about 10°C to about 600°C, in one embodiment about 25°C t o about 450°C
.
It should be within the temperature range.
[0141]
The heat exchange fluid entering the heat exchange channels (290, 370, 380, 590) may be at a temperature ranging from about -40°C to about 300°C, and in one embodiment from abo ut 25°C to about 100°C. The heat exchange fluid exiting the heat transfer channels may have a temperature in the range of about -30°C to about 550°C, and in one embodiment about 30° C to about 200°C. The pressure drop of the heat exchange fluid as it flows through the heat e xchange channels may range from about 0.005 to about 5 atmospheres, and in one embodim ent from about 0.05 to about 1 atmosphere. The Reynolds number of the heat exchange fluid stream flowing through the heat exchange channels is up to about 10,000, in one embodimen t up to about 5000, in one embodiment in the range of about 100 to about 5000, in one embo diment from about 500 to about It should be in the range of 2000. The fluid stream may be preheated in the microchannel mixer or prior to entering the microchannel mixer using any ty pe of heat transfer device including microchannel heaters or heat pipes

.

In one embodiment, the first fluid stream may be preheated in a non-apertured region of the process microchannel upstream of the mixing zone. The multiphase mixture produced in the microchannel mixer is cooled in the microchannel mixer or after exiting the microchannel mix er using any type of heat exchange device including a microchannel heat exchanger. good too. In one embodiment, the multiphase mixture may be quenched to stabilize or remain stable. I n one embodiment, the multiphase mixture may be quenched in non-apertured regions of the process microchannel downstream of the mixing zone. In one embodiment, the multiphase mi xture may be cooled to room temperature or quenched within a time period ranging from abo ut 0.01 to about 100 seconds, in one embodiment from about 0.01 to about 10 seconds. goo d.

[0143]

Using the process of the present invention, a multiphase mixture can be produced at a rate of at least about 0.01 liter per minute, and in one embodiment at least about 1 liter per minut e. In one embodiment, the process can be used to create a multiphase mixture at a rate of at least about 10 liters per second. In one embodiment, optical or thermo-optical properties ma y be adjusted within the process microchannel

.

Examples of techniques for measuring and/or adjusting these optical or thermo-optical proper ties are in-line LSD (laser scattering diffraction) detection for multiphase mixture quality contr ol and analysis, including mean droplet size and span; Viscosity to assess product viscosity an d solids content

holographic imaging and similar methods including interferometry by modulating the propertie s of multiphase mixtures, optical measurements using photometry for bubble or microsphere size measurement.

Example 1 A multiphase microchannel containing an acrylic process microchannel having a r ectangular cross section and internal dimensions of 0.040 x 1.25 x 3 inches (1.02 x 31.75 x 7 6.2 mm)

.

A mixing device is constructed. A process microchannel has an open section in one of its side walls. The open section has a nominal aperture or pore size of 0.1 microns and dimensions of 0.010 x 1 x 1.5 inches (0.254 x 25.4 x 38.1 mm). The aperture section is constructed of stain less steel 316L and is supplied by Mott Corporation of Farmington, Conn. under catalog numb er 1110-12-12-018-01-A. The open section is connected to a gas distribution plenum and tubi ng to allow gas flow through the open section and into the process microchannel. The process microchannels are connected to plumbing to allow liquid flow through the process microchann els. Gas enters the process microchannel through the open section and contacts the liquid flo wing through the process microchannel. Bubbles form in the process microchannel as the gas flows through the openings in the open section. The process is carried out using air as the gas

and deionized water as the liquid. The air flow rate varies between 2 and 20 standard cubic ce ntimeters per minute (SCCM) and the water flow rate varies between 10 and 80 milliliters per minute (ml/min). Bubbles are formed with diameters in the range of 5 to 15 microns.

Example

2

The process described in Example 1 is carried out using a gas flow rate of 2 SCCM and a liqui d flow rate of 60 ml/min.

EXAMPLE 3 The process described in Example 1 is carried out using hydrogen as the gas and 1-hexene as the liquid

. Example 4 A high velocity gas (flow rate greater than 1 SLPM) and liquid (flow rate greater than 0.1 liters per minute) are mixed near the inlet of a process microchannel and then subje cted to surface feature regions. flows through The surface feature area has features with a de pth of 0.01 inch and an angle of 45 degrees on one side of the wall. The bulk flow path within the surface features is 0.0065 inches. A foam is produced having uniform cells with an averag e diameter of less than 25 microns. The stream length is 1.5 inches and the channel width or span is 0.5 inches. The process microchannels are near room temperature and ambient press ure. Very small bubbles are observed on and throughout the surface feature area. Example 5

The addition of surface features to the two sides of a microchannel that induces a change fro m laminar flow in the channel to strongly mixed flow in the channel was performed using Flue nt™ . studied by dynamics (CFD) simulations. For the simulation, the properties of the fluid w ere assumed constant, with a density of 5.067 kg/m ^{3} and a viscosity of 3.62e $^{-5}$

kg/m-sec. Boundary conditions were a uniform inlet velocity of 12.13 m/sec and no slip flow on all walls. A grid size of 315,174 cells is used. The geometry assumed is 4.06 mm wide, 0. 318 mm high and 63.5

mm

Rectangular cross-section of a continuous channel with a length of . The section 0 to 3.5 mm downstream of the inlet and the section 0 to 5.0 mm upstream of the outlet contain no mixing surface features (simple rectangular microchannels). Mixing surface features (or grooves) are cut into two opposing walls, each feature being generally rectangular in cross section. The mid dle section of the microchannel (3.5 mm to 58.5 mm downstream of the inlet) contains a mixi ng surface feature. A surface feature diagonally spans one of the channel walls at an angle of 63° from the direction of the mean bulk laminar flow, as shown in FIGS. Each surface feature

is approximately 0.25 mm deep, 0.48 mm wide and 9 mm long. The surface features are arra nged parallel to each other with a spacing of 0.48 mm between the features. The surface feat ures on the opposite wall are the same as the surface features on the first wall, rotated 180° around the channel centerline (the channel geometry is the center point of the inlet face is sy mmetrical about the axis of flow extending from to the center point of the exit face).

[0151]

FIG. 27 shows a plan view of the geometry of surface features simulated by CFD. Both the t op wall and bottom wall mixing components are superimposed. FIG. 28 is an isometric view of a microchannel with mixing components simulated by CFD, showing the direction of flow enter ing the channel. FIG. 29 shows a typical flow path line initiated along the horizontal centerline of the inlet face (drawn between arrows), looking down the flow axis from the inlet face. In cl assical laminar flow, the path line runs in a straight line between the inlet and outlet planes (i n the diagram shown in FIG. 29, the classical laminar flow path line deviates from the center li ne between the arrows). considered not to). In FIG. 30 a side view of the same path line of fl ow initiated along the horizontal centerline of the inlet face is shown (arrows indicate direction of flow). In FIG. 30, the divergence of the flow path lines from the centerline and swirling mot ion among the surface features show improved mixing and reduced heat and mass transport r esistance compared to laminar flow. FIG. 31 shows the flow path line initiated along the vertic al centerline of the inlet face (drawn between the arrows), looking down the flow axis from th e inlet face. In FIG. 31, the swirling motion of the flow suggests improved mixing and reduced heat and mass transfer resistance compared to classical laminar flow. Results from CFD simu lations show that, unlike laminar flow in microchannels, the mixing surface features twist and swirl the flow path in continuous channels, which is expected for laminar flow

.

Push outwards toward the wall faster than you can. The calculated pressure drop is 5.2 kPa.

[0153]

Addition of a gas or a second fluid stream to a microchannel containing surface features crea tes a flow pattern whereby the multiphase mixture is expected to approach laminar flow and b ubbles to be small and well dispersed. A small bubble may be defined as less than 25% of the microchannel gap. Although the invention has been described in connection with specific em bodiments, it is understood that various modifications of these embodiments will become app arent to those skilled in the art upon reading the specification

.

It is therefore intended that the invention disclosed herein encompass such modifications as f all within the scope of the appended claims.

BRIEF DESCRIPTION OF THE FIGURES

[0155]

FIG. 1 is a schematic representation of a microchannel that can be useful in the process of the invention.

FIG. 2 is a flowsheet showing an example of a particular form of the process of the invention i n which a microchannel mixer is used to form a multiphase mixture;

FIG. 3 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention; A first fluid stream flows through the process microchannel and from an adjacent second fluid stream channel through an open section in the process microchannel to the process microchannel.

It mixes with the second fluid stream entering the channel.

FIG. 4 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 5 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 6 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 7 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 8 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 9 is a flowsheet showing an example of a multi-phase mixture forming unit used in the p rocess of the invention;

FIG. 10 is a schematic representation of a dual multiphase mixture;

FIG. 11 is a schematic diagram of a microchannel air blowing unit that can be used in accorda nce with the process of the present invention;

12 is a schematic diagram of a microchannel multiphase mixture forming unit that can be use d in the air blowing unit illustrated in FIG. 11; FIG.

FIG. 13 is an SEM image of a porous stainless steel substrate before heat treatment;

14 is a SEM image of the substrate shown in FIG. 8 after being heat treated; FIG.

FIG. 15 is an SEM image of a specialized porous substrate useful in the process of the inventio n;

FIG. 16 is a plan view of an apertured sheet useful in making the apertured sections of proces s microchannels used in the process of the present invention;

FIG. 17 is a plan view of an apertured sheet or plate useful in making the apertured section of the process microchannels used in the process of the invention;

FIG. 18 is an illustration of a relatively thin apertured sheet overlying a relatively thick apertur ed sheet or plate useful in creating the apertured section of the process microchannels used in the process of the present invention;

FIG. 19 shows an example of a relatively thin apertured sheet overlying a relatively thick aper tured sheet or plate useful in creating the apertured sections of process microchannels used in the process of the present invention.

FIG. 20 shows examples of alternative embodiments of apertures that can be used in the aper

tured section of process microchannels used in the process of the present invention; The aperture has a coating partially filling the aperture and overlying the sidewalls of the aperture.

FIG. 21 is a schematic diagram showing the formation of gas bubbles or microbodies during operation of the process of the invention;

FIG. 22 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 23 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 24 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 25 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 26 is a schematic representation of surface features that can be provided within a microchannel used in the process of the invention;

FIG. 27 is a plan view of the surface feature geometry simulated by computational fluid dynamics (CFD) as described in Example 5; The surface elements above the upper and lower walls are visible.

FIG. 28 shows surface elements simulated by CFD as described in Example 5;

1 is an isometric view of a microchannel with

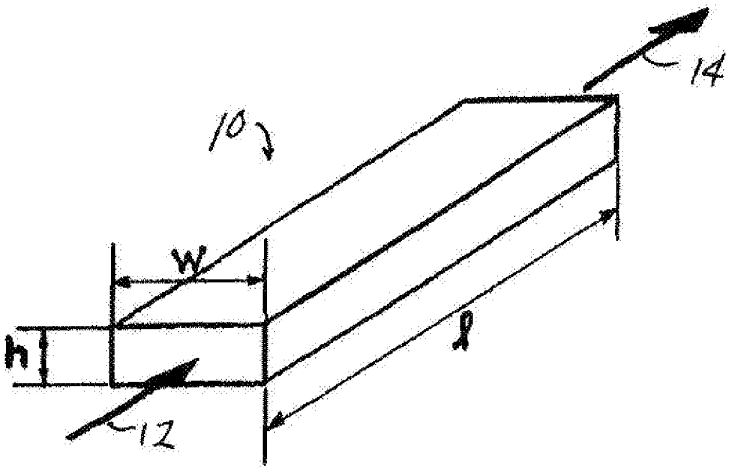
FIG. 29 shows examples of flow pathlines in microchannels initiated along the horizontal centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

FIG. 30 shows flow pathlines (arrows indicate direction of flow) in microchannels initiated along the horizontal centerline of the inlet face. Viewed from the side, as described in Example 5.

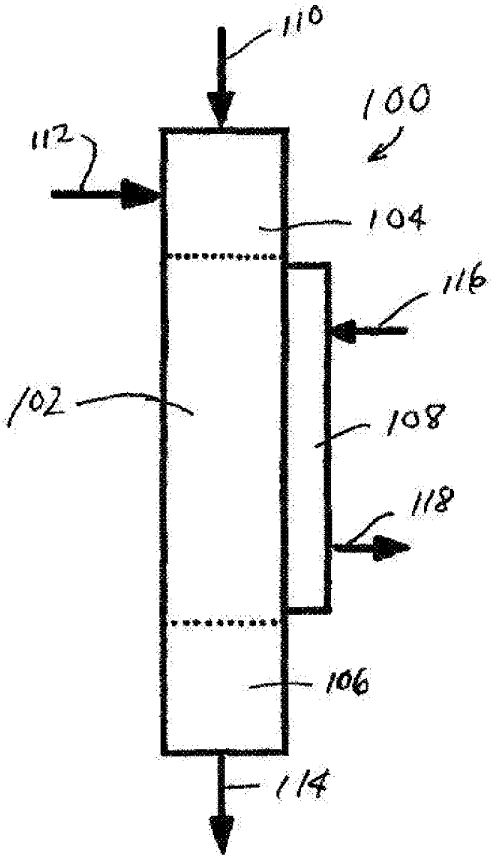
Figure 31 shows flow pathlines in the microchannel initiated along the vertical centerline of the inlet face (drawn between arrows). Looking down the flow axis from the inlet face as described in Example 5.

drawing open —

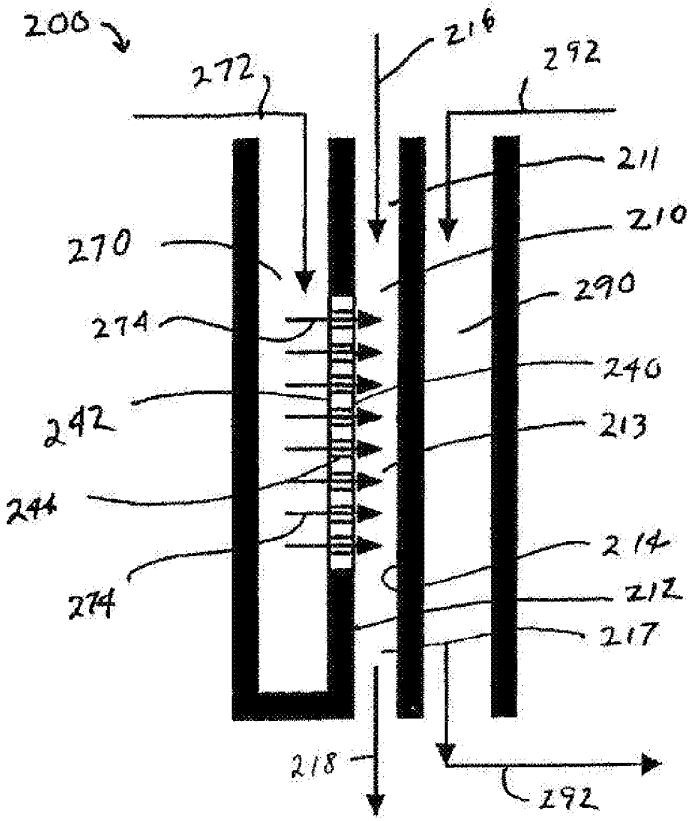
[Fig. 1]



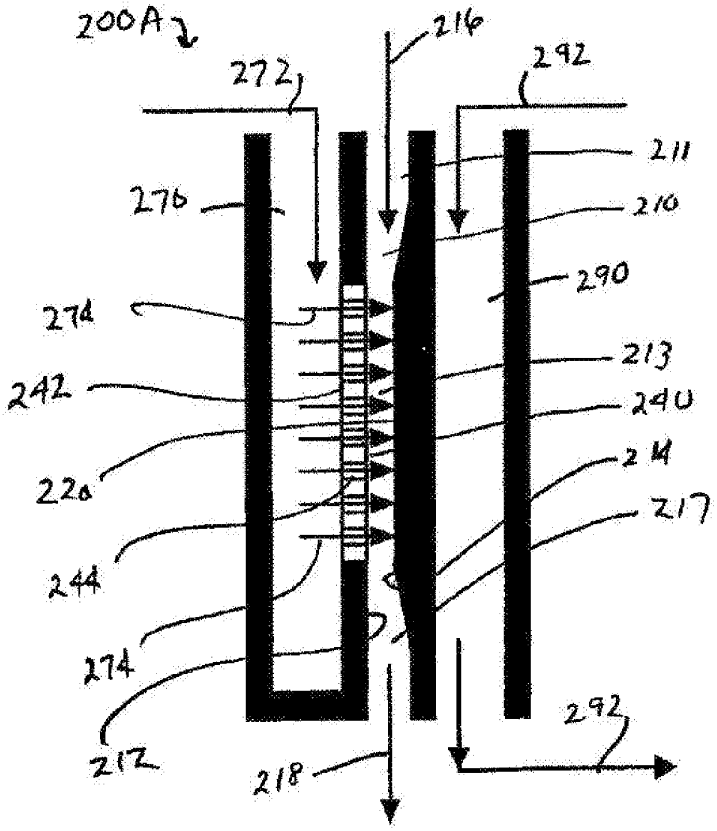
[Figure 2]



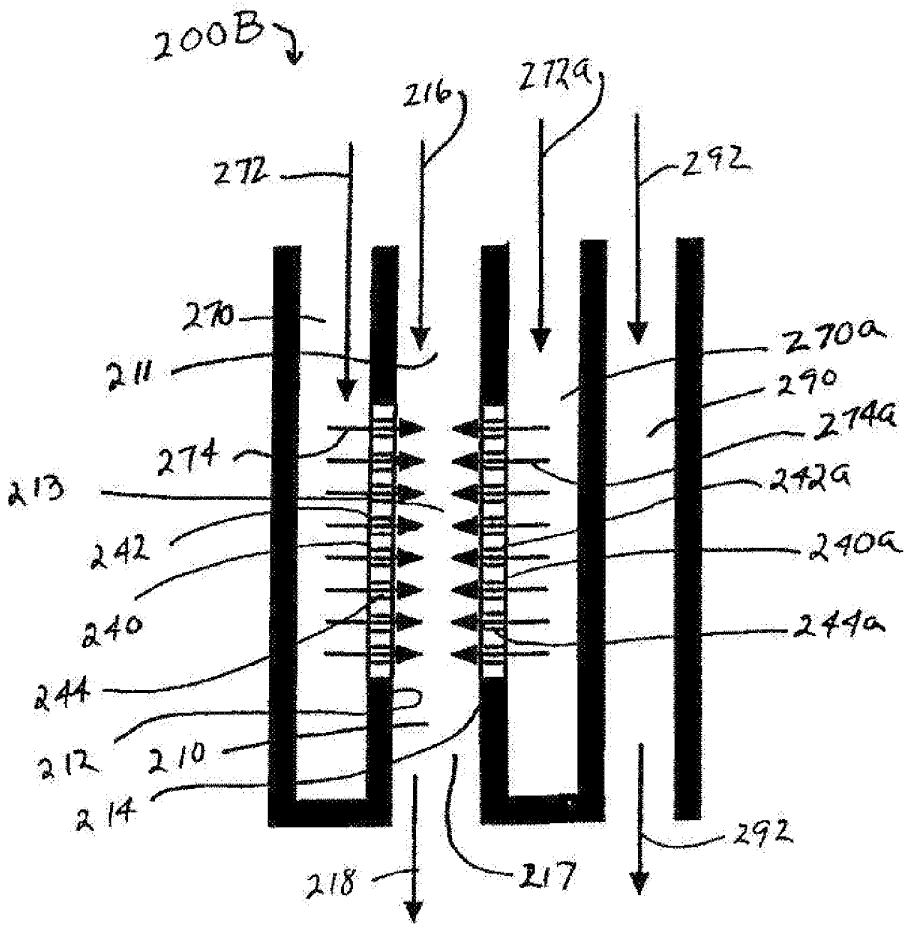
[Figure 3]


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

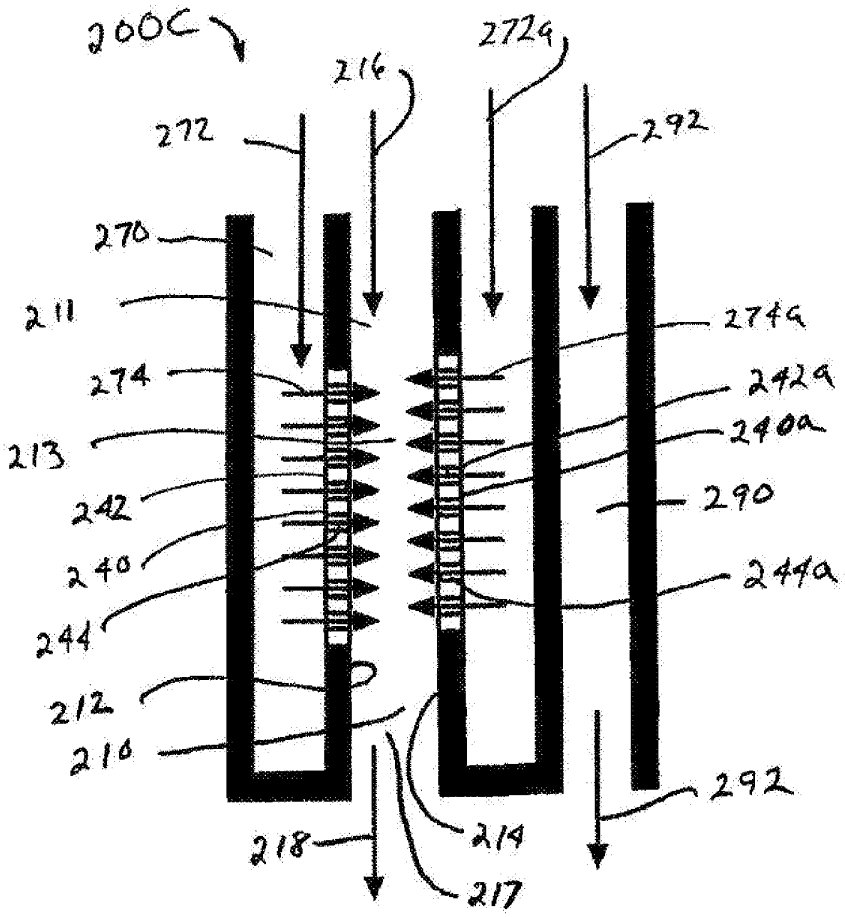
[Figure 4]


200A
216
272
292
211
276
210
290
274
213
242
240
220
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212
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292

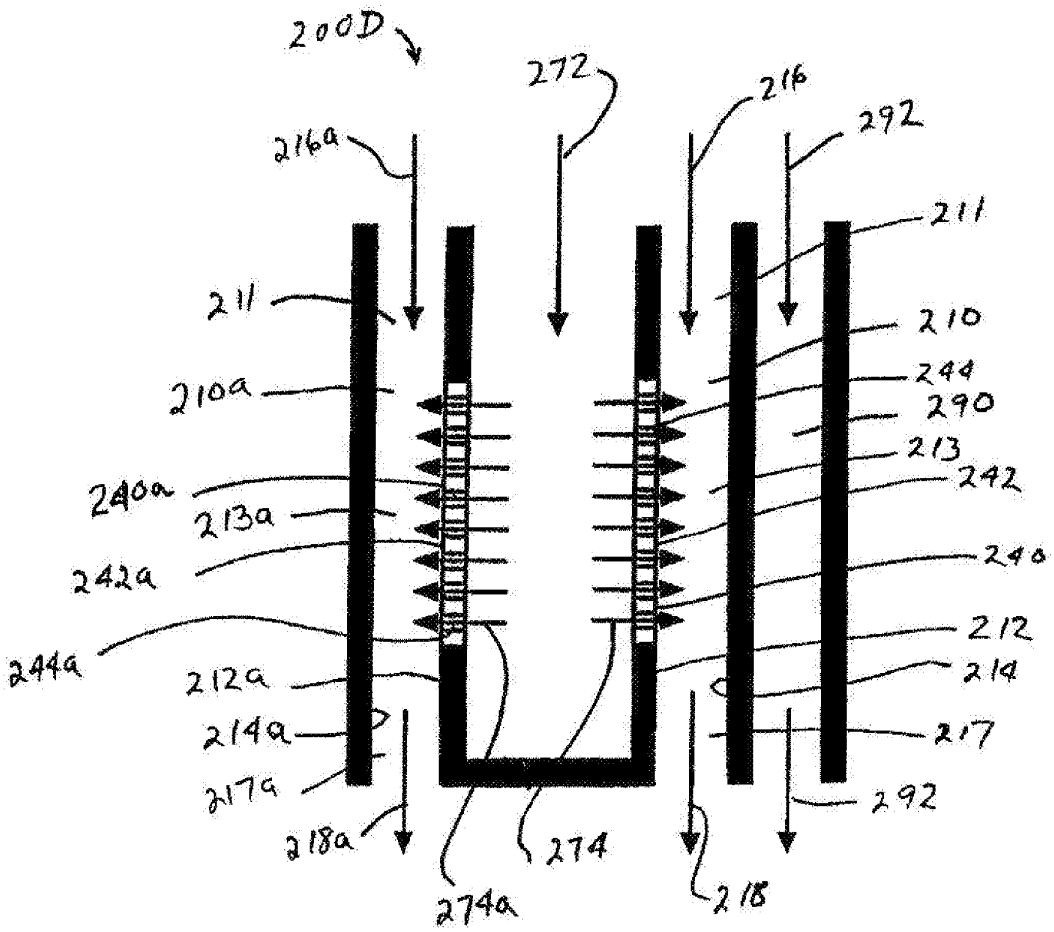
[Figure 5]


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

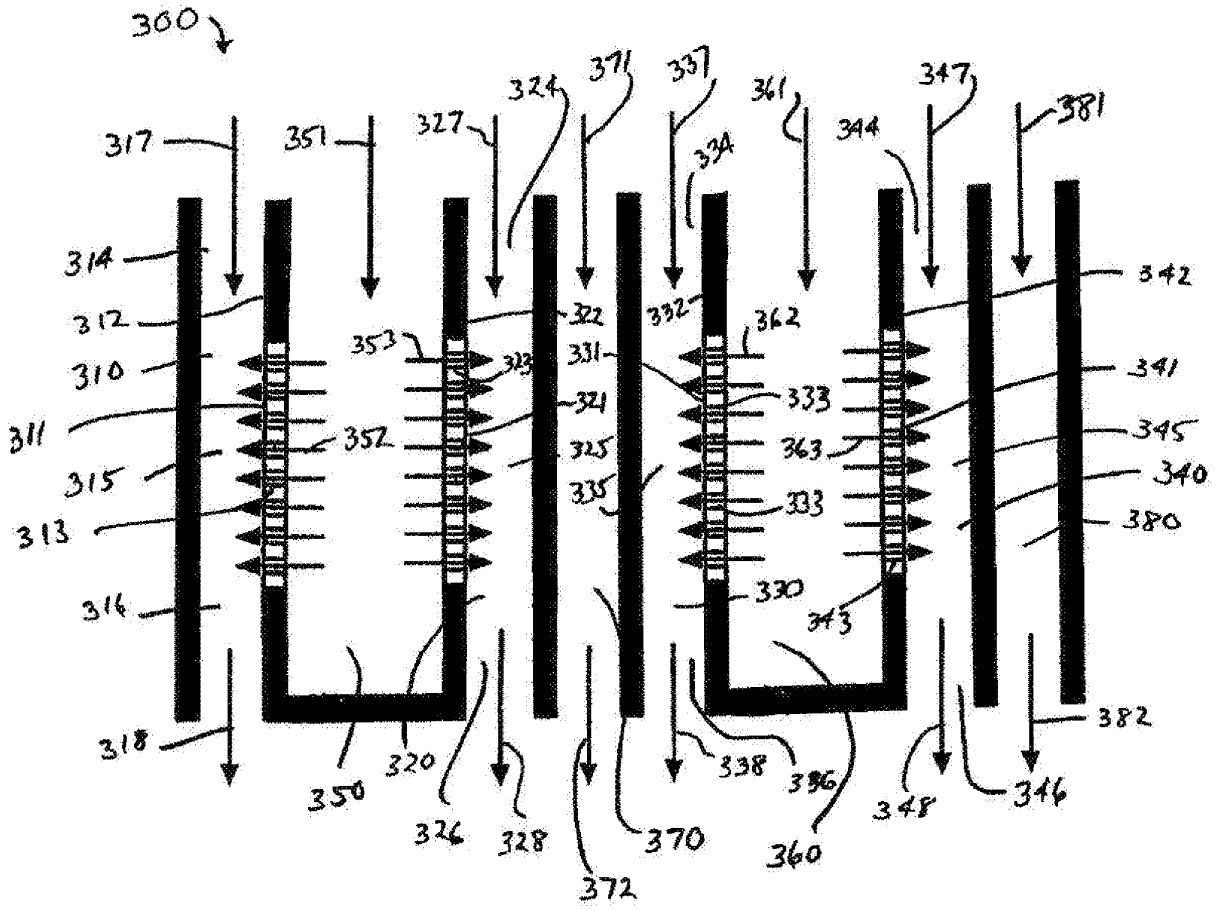
[Fig. 6]


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

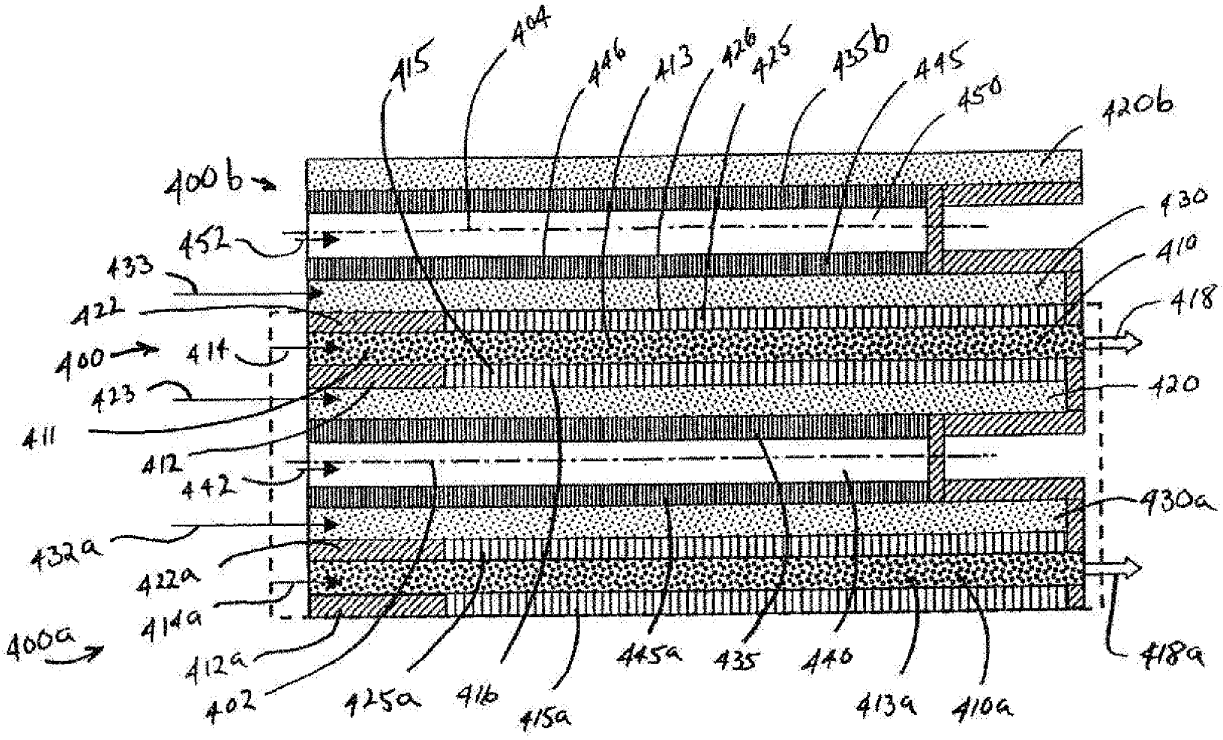
[Fig. 7]


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

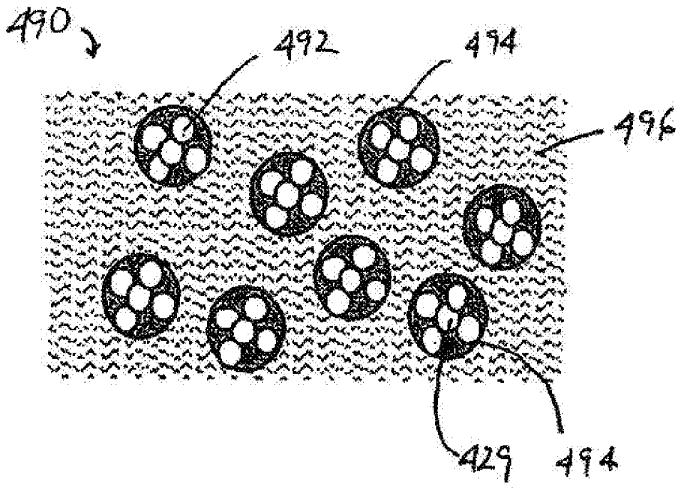
[Fig. 8]


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
325
335
332
362
333
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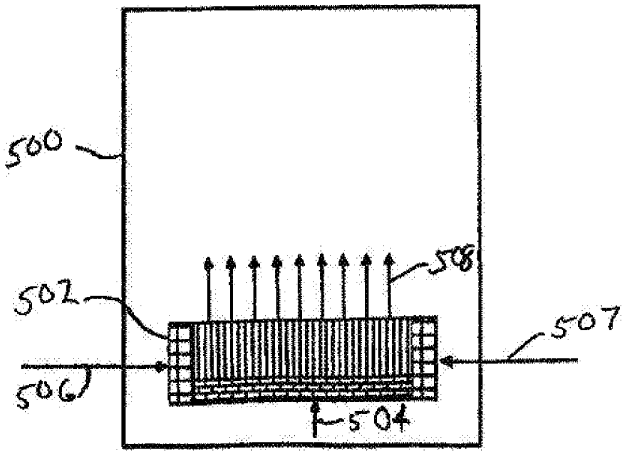
[Fig. 9]


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

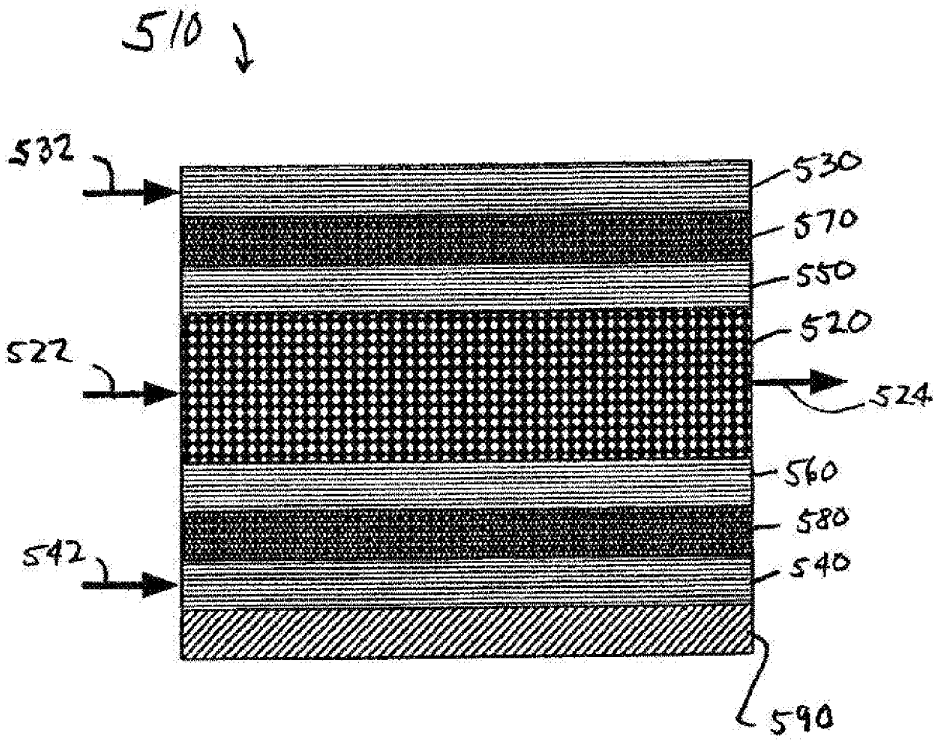
[Fig. 10]



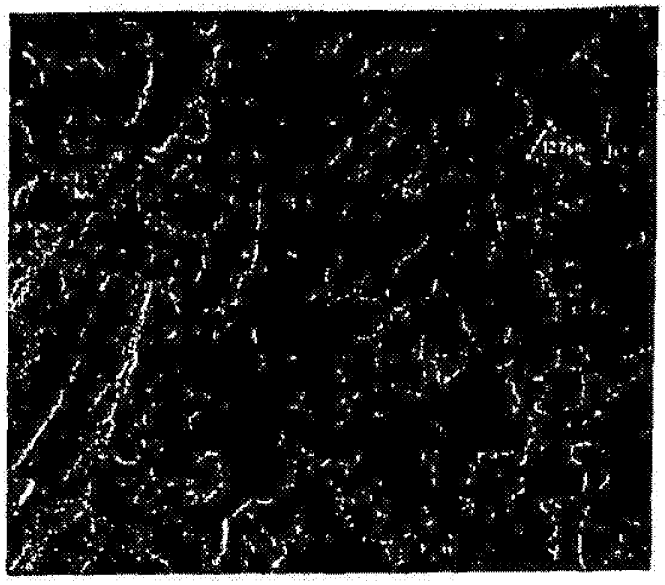
[Fig. 11]



[Fig. 12]



[Fig. 13]



[Fig. 14]